

## Hyperventilation and vomiting due to posterior circulation stroke

Braj B. Pandey, MD; Tuan C. Dang, MD; and John F. Healy, MD

Central neurogenic hyperventilation has been reported in brainstem infiltration by tumors<sup>1</sup> but seldom with acute posterior stroke. Vomiting is frequent with such strokes<sup>2</sup> but usually not associated with hyperventilation. We describe a patient with acute occlusive posterior stroke in whom the combination of hyperventilation and vomiting delayed diagnosis.

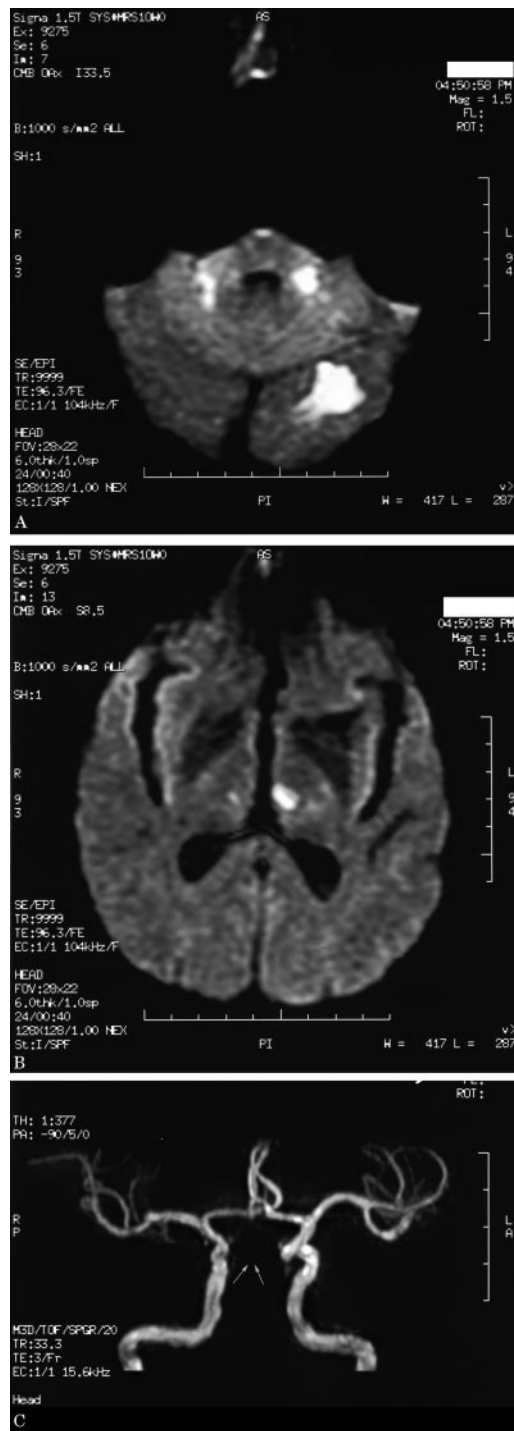
**Case report.** A 54-year-old man with diabetes mellitus and hypertension had nausea and vomiting for 1 day. Clinical examination was normal except for elevation of blood pressure (189/95 mm Hg) and respiratory rate (20/min). Laboratory tests showed blood glucose level of 213 mg/dL and white blood count of 15,800/mm<sup>3</sup> with 83% neutrophils. Chest and abdominal radiographs were negative. He was given IV saline and sent home with a diagnosis of gastroenteritis.

The patient returned the next day with persistent vomiting, difficulty breathing, blurred vision, fever, and malaise. His respiration was 26/min. He was mentally alert but dysarthric. He had normal cranial nerves, normal motor examination, diminished pedal sensation and slowed hand coordination. Laboratory tests showed white cell count of 14,800/mm<sup>3</sup> with a left shift, blood glucose level of 185 mg/dL, bicarbonate level of 16 mmol/L, anion gap of 22, arterial blood pH of 7.61, P<sub>a</sub>O<sub>2</sub> of 113 mm Hg, and P<sub>a</sub>CO<sub>2</sub> of 15 mm Hg. The prime suspects were sepsis, salicylate poisoning, drug overdose, CNS disease, and hyperventilation syndrome. The serum salicylate level, urine toxicology screen, CT scans of the head, CSF tests, and blood cultures were negative. On re-evaluation the next morning, the patient displayed severe dysarthria, poor coordination, trunk ataxia, and hyperventilation. A clinical diagnosis of central hyperventilation from cerebellar/brainstem stroke was made. Diffusion-weighted MRI of the brain revealed large infarcts in the left occipital lobe and bilateral cerebellar peduncles in the region of the vestibular nucleus (figure, A), thalamus (figure, B), and midbrain. Time-of-flight MR angiogram revealed no flow in the vertebrobasilar system (see the figure, C).

It had been 72 hours since the symptom onset. The time limit for IV thrombolysis (<3 hours) and intra-arterial mechanical disruption of the clot or stent placement (6 to 12 hours) had passed. Additionally, the risk/benefit ratio of invasive procedures was considered unfavorable owing to completed infarctions. Treatment with IV heparin was started empirically. On hospital day 3, the patient became somnolent and developed unequal quadriparesis and right facial weakness. CT scan of the head was negative for hemorrhage. On day 5, he was poorly responsive and developed right eye lateral deviation with bilateral pupillary dilatation (right > left). The respiration rate was 22/min with pH of 7.5 and P<sub>a</sub>CO<sub>2</sub> of 21 mm Hg. Because of poor gag reflex, an endotracheal intubation was performed. He continued to overbreathe the ventilator. On day 7, he became fully comatose and would show decerebrate posturing spontaneously and in response to painful stimuli. There was no evidence of "locked-in" syndrome or dysautonomia. On day 8, he had no pupillary, corneal, or gag reflex. The mechanical ventilation, heparin, tube feeding, and IV fluids were discontinued per family wishes. His hyperventilation persisted. On day 9, his breathing and pulse slowed markedly, recovered, and finally stopped 22 hours after all support was withdrawn. The family denied an autopsy.

**Discussion.** Initiation and control of respiration are known to involve the lateral pontine and medullary tegmentum.<sup>3</sup> Bilateral medullary infarcts can cause hypoventilation.<sup>4</sup> Hyperventilation is reported in pontine infiltration<sup>1</sup> but not in pontine ischemia/infarction. We suspect our patient had ongoing pontine ischemia that could have caused hyperventilation. A search for hyperventilation in posterior strokes yielded two case reports. The first described chronic dyspnea and hyperventilation in an alert 79-year-old woman with old lacunar infarcts of the thalamus.<sup>5</sup> The second reported acute hemiparesthesias and hyperventilation in an alert 52-year-old woman with thalamic hemorrhage.<sup>6</sup> The authors of both reports blamed thalamic lesions for the hyperventilation.

Despite the clinical differences from these reported cases, thalamic infarcts could be the other reason for our patient's hyperventilation.



**Figure.** Diffusion-weighted MRI reveals bright signal consistent with acute infarcts in the left occipital lobe and both cerebellar peduncles in the region of vestibular nuclei (A) and bilateral thalami (B). Time-of-flight MR angiogram (C) reveals bright signal from blood flow in both carotid arteries. No flow is noted in the basilar artery (arrows).

The most likely cause of the vomiting was bilateral vestibular nucleus infarction. Top-of-the-basilar syndrome<sup>7</sup> resulted in the altered mental status, pupillary/gaze abnormalities, and infarction of the midbrain and thalamus. Proximal basilar artery occlusion could cause pontine infarction. Involvement of the medial pontine tegmentum could result in coma.<sup>3</sup> Care must be taken to differentiate it from the "locked-in" syndrome.<sup>3</sup> We suspect the patient died either from respiratory fatigue or from involvement of the dorsal motor nucleus of the vagus.

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## Effect of D-penicillamine on neuromuscular junction in patients with Wilson disease

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The clinical, serologic, and electrophysiologic features of myasthenia gravis (MG) associated with long-term use of D-penicillamine are indistinguishable from acquired autoimmune MG.<sup>1,2</sup> Most reports involve patients with rheumatoid arthritis (RA) who have underlying autoimmunity. We investigated the effect of D-penicillamine on the neuromuscular junction and the presence of acetylcholine receptor (AChR) antibody in the sera of patients with Wilson disease (WD).

**Subjects and methods.** Sixty prospective patients were recruited from a large cohort of WD patients from a university hospital of south India. These patients were on D-penicillamine for at least 6 months (Group I, n = 40) or drug-naïve (Group II, n = 20). D-Penicillamine was started among Group II patients, and they were re-evaluated after 6 months. Patients on drug(s) that could induce or aggravate MG were excluded.

Details regarding history and clinical features were noted. Bedside fatigability tests (ptosis, diplopia, sit-ups, arm abduction, voice fatigability) were carried out in all patients. Repetitive nerve stimulation test study was carried out from trapezius and abductor digiti minimi muscles at 34 °C. A decrement of >10% was considered as positive. Postexercise facilitation and postexercise exhaustion were studied immediately and after 3 to 4 minutes of isometric exercise.

AChR antibodies were estimated by direct and indirect ELISA by blinded coding,<sup>3,4</sup> and the test was considered to be positive only when both the assays were positive. Thirty healthy voluntary blood donors (age 20 to 35 years, mostly men) served as control subjects.

**Results.** Group I (n = 40, male/female 25:15). The mean age of patients on D-penicillamine was 21.5 ± 9.8 years and mean duration of symptoms was 111.5 ± 102.1 months. The mean duration of D-penicillamine intake (250 to 1,000 mg/day) was 95.9 ± 131.1 months. Thirty-five patients had the neurologic form of the disease, and the others had osseomuscular<sup>2</sup> and hepatic<sup>1</sup> forms. Two subjects were asymptomatic siblings. None of the patients had any clinical or electrophysiologic evidence of MG. AChR antibodies were positive in 10 patients (male/female 6:4).

Group II (n = 20, male/female 13:7). The mean age in drug-naïve patients was 15.4 ± 6.2 years and mean duration of symptoms 26.2 ± 42.2 months. Fourteen patients presented with neurologic symptoms, and four had the hepatic form. Two were asymptomatic siblings. None of them had clinical or electrophysiologic features of MG. AChR antibodies were positive in 6 of 20 patients (male/female 4:2) with neurologic (4) and hepatic (1) forms of the disease. One was an asymptomatic sibling.

Four patients (including one patient with positive titer) were

lost to follow-up. Repeat studies after 6 months of D-penicillamine therapy in the remaining 16 patients did not reveal any clinical or electrophysiologic evidence of MG. One seropositive patient was detected to be seronegative at follow-up, whereas the other four patients remained seropositive. Seronegative patients (n = 11) maintained their seronegative status.

There was no significant difference in age or duration of symptoms and treatment with D-penicillamine between seropositive and seronegative patients. Five sera among 30 controls (16.6%) also tested positive. Comparison of seropositivity by proportion test between controls and Group I (z = 0.409), between controls and Group II (z = 1.09), and between Groups I and II (z = 0.85) revealed no significant difference (table).

**Discussion.** It is not certain whether the occurrence of MG in patients with RA on D-penicillamine therapy is due to underlying autoimmunity or to drug therapy.<sup>2</sup> We addressed this question by selecting a cohort of patients with WD wherein there is no confounding effect of autoimmunity. None of these patients had clinical or electrophysiologic evidence of MG despite prolonged treatment with D-penicillamine (6 to 571 months).

D-Penicillamine-induced MG may appear from <2 to 5 years after the initiation of therapy<sup>5</sup> and is often associated with elevated AChR antibody titers. It is completely reversible, and antibody titers fall by 50% within 35 to 60 days after D-penicillamine withdrawal.<sup>6</sup> In our study, AChR antibody positivity was about 25% in drug-naïve and slightly higher in D-penicillamine-treated WD subjects, whereas in the control subjects, it was 16.6%. Others<sup>6</sup> had a similar observation and concluded that D-penicillamine induces low levels of AChR antibody in genetically susceptible individuals. An earlier study from the same center had reported 10% AChR positivity in controls by ELISA.<sup>4</sup> It appears from the

**Table** AChR antibodies in patients with Wilson disease and controls

Study group	AChR antibodies	
	Positive (%)	Negative (%)
Group I: baseline, n = 40	10 (25)	30 (75)
Group II: baseline, n = 20	6* (30)	14 (70)
6 mo after treatment, n = 16	4† (25)	12 (75)
Control, n = 30	5 (16.6)	25 (83.4)

\* Three patients (Group II) lost to follow-up and one dead.

† One patient (Group II) lost to follow-up and one became negative.

AChR = acetylcholine receptor.

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