References

1. Ross ED: The aprosodias: Functional anatomic organization of the affective components of language in the right hemisphere. *Arch Neurol* 1981;38:561-569.
2. Ross ED, Mesulam M-M: Dominant language functions of the right hemisphere?: Prosody and emotional gesturing. *Arch Neurol* 1979; 36:144-148.
3. Heilman KM, Scholes R, Watson RT: Auditory affective agnosia: Disturbed comprehension of affective speech. *J Neurol Neurosurg Psychiatry* 1975;38:69-72.
4. Tucker DM, Watson RT, Heilman KM: Discrimination and evocation of affectively intoned speech in patients with right parietal disease. *Neurology* 1977;27:947-950.
5. Larsen B, Skinhøj E, Lassen NA: Variations in regional cortical blood flow in the right and left hemispheres during automatic speech. *Brain* 1978;101:193-209.
6. Ross ED: Modulation of affect and nonverbal communication by the right hemisphere, in Mesulam M-M (ed): *Principles of Behavioral Neurology.* Philadelphia, FA Davis Co Publishers, 1985, chap 6.
7. Hughes CP, Chan JL, Su MS: Aprosodia in Chinese patients with right cerebral hemisphere lesions. *Arch Neurol* 1983;40:732-736.
8. Gorelick PB, Ross ED: The aprosodias: Further functional-anatomic evidence for the organization of affective language in the right hemisphere. *J Neurol Neurosurg Psychiatry,* in press.
9. Fisher CM: The pathologic and clinical aspects of thalamic hemorrhage. *Trans Am Neurol Assoc* 1959;84:56-59.
10. Bugiani O, Conforto C, Sacco G: Aphasia in thalamic hemorrhage. *Lancet* 1969;1:1052.
11. Samarel A, Wright TL, Sergay S, et al: Thalamic hemorrhage with speech disorder. *Trans Am Neurol Assoc* 1976;101:283-285.
12. Reynolds AF, Harris AB, Ojemann GA, et al: Aphasia and left thalamic hemorrhage. *J Neurosurg* 1978;48:570-574.
13. Reynolds AF, Turner PT, Harris AB, et al: Left thalamic hemorrhage with dysphasia: A report of five cases. *Brain Lang* 1979;7:62-73.
14. Cappa SF, Vignolo LA: 'Transcortical' features of aphasia following left thalamic hemorrhage. *Cortex* 1979;15:121-130.
15. Alexander MP, LoVerme SR: Aphasia after left hemispheric intracerebral hemorrhage. *Neurology* 1980;30:1193-1202.
16. Demeurisse G, Derouck M, Coekaerts MJ, et al: Study of two cases of aphasia by infarction of the left thalamus without cortical lesion. *Acta Neurol Belg* 1979;79:450-459.
17. Cohen JA, Gelfer CE, Sweet RE: Thalamic infarction producing aphasia. *Mt Sinai J Med* 1980;47:398-404.
18. Gorelick PB, Hier DB, Benevento L, et al: Aphasia after left thalamic infarction. *Arch Neurol* 1984;41:1296-1298.
19. McFarling D, Rothi LJ, Heilman KM: Transcortical aphasia from ischemic infarcts of the thalamus: A report of two cases. *J Neurol Neurosurg Psychiatry* 1982;45:107-112.
20. Smyth GE, Stern K: Tumors of the thalamus: A clinico-pathological study. *Brain* 1938; 61:339-374.
21. Damasio AR, Damasio H, Rizzo M, et al: Aphasia with nonhemorrhagic lesions in the basal ganglia and internal capsule. *Arch Neurol* 1982;39:15-20.
22. Naeser MA, Alexander MP, Helm-Estabrooks N, et al: Aphasia with predominantly subcortical lesion sites: Description of three capsular/putaminal aphasia syndromes. *Arch Neurol* 1982;39:2-14.
23. Cappa SF, Cavalotti G, Guidotti M, et al: Subcortical aphasia: Two clinical CT scan correlation studies. *Cortex* 1983;19:227-241.
24. Wallesch C-W: Two syndromes of aphasia occurring with ischemic lesions involving the left basal ganglia. *Brain Lang* 1985;25:357-361.
25. Tanridag O, Kirshner HS: Aphasia and agraphia in lesions of the posterior internal capsule and putamen. *Neurology* 1985;35:1797-1801.
26. Ross ED, Harvey JH, deLacoste-Utamsing C, et al: How the brain integrates affective and propositional language into a unified behavioral function. *Arch Neurol* 1981;38:745-748.
27. Benson DF: *Aphasia, Alexia and Agraphia.* New York, Churchill Livingstone Inc, 1979.
28. Ross ED, Edmondson JA, Seibert GB, et al: Acoustic analysis of affective prosody during right-sided Wada Test: A within-subjects verification of the right hemisphere's role in language. *Brain Lang,* in press.
29. Ross ED, Holzapfel D, Freeman F: Assessment of affective behavior in brain-damaged patients using quantitative acoustical-phonetic and gestural measurements. *Neurology* 1983; 33(suppl 2):219-220.
30. Geschwind N: Discussion of cerebral connectionism and brain function, in Millikan CH, Darly FL (eds): *Brain Mechanisms Underlying Speech and Language.* New York, Grune & Stratton, 1967, pp 71-72.
31. McKissock W, Paine KWE: Primary tumors of the thalamus. *Brain* 1958;81:41-63.

Behavioral Manifestations of Central Pontine Myelinolysis

Bruce H. Price, MD, M.-Marsel Mesulam, MD

• A young woman with a clinical history and magnetic resonance imaging scan consistent with central pontine myelinolysis came to medical attention because of prominent behavioral symptoms. Marked clinical recovery occurred despite persistent radiologic abnormalities. Rapid correction of hyponatremia was probably related to the development of the central pontine myelinolysis. A normal computed tomographic scan and the absence of brain-stem signs delayed accurate diagnosis.

(*Arch Neurol* 1987;44:671-673)

Central pontine myelinolysis (CPM) was first described by Adams et al[1] in 1959. Early descriptions emphasized its grave prognosis.[2] More recent reports have documented survival and recovery.[3] Ventral pontine involvement with subacute onset of cerebellar, cranial nerve, and pyramidal tract dysfunction is the typical presentation.[4]

We describe a patient in whom reversible behavioral abnormalities constituted the major manifestation of CPM. One purpose of this article is to alert physicians to the possible behavioral presentation of CPM. Another is to reemphasize the relationship between rapid correction of hyponatremia and CPM. We also forward some thoughts on the pathophysiology of these behavioral changes.

Accepted for publication Dec 15, 1987.

From the Division of Neuroscience and Behavioral Neurology, Charles A. Dana Research Institute, Beth Israel Hospital, Boston.

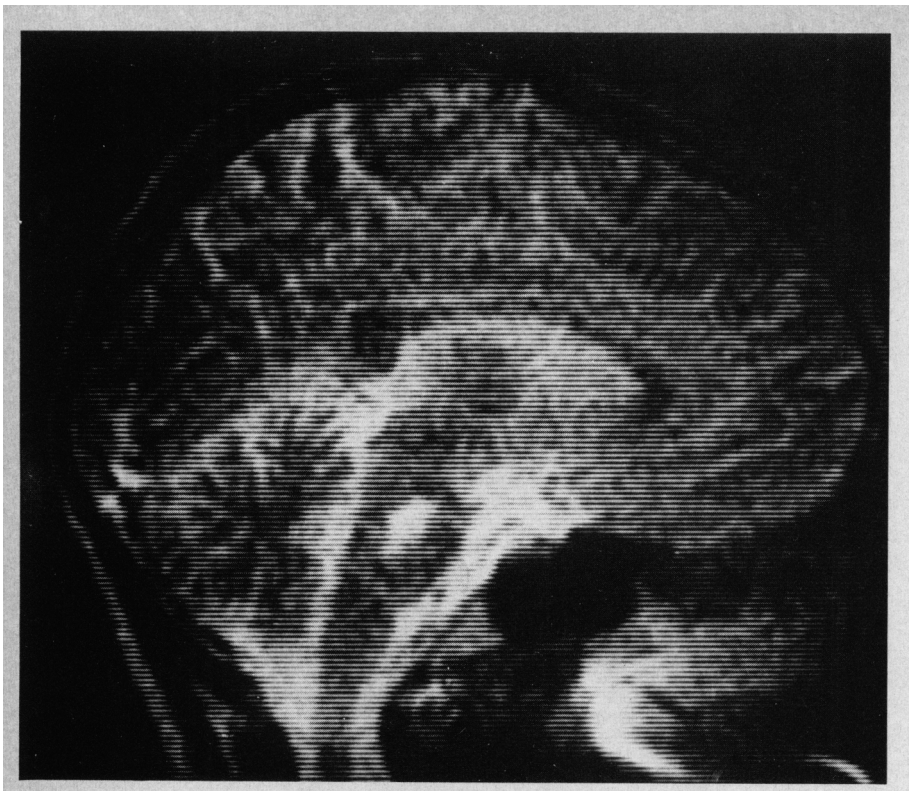
Reprint requests to Division of Neuroscience and Behavioral Neurology, Charles A. Dana Research Institute, Beth Israel Hospital, 330 Brookline Ave, Boston, MA 02215 (Dr Price).

REPORT OF A CASE

A 29-year-old right-handed professional woman was in excellent health until her return from Mexico. She developed intractable nausea, anorexia, and diarrhea for one week, leading to a 2.2-kg (5-lb) weight loss.

Results of a clinical examination at that time were normal, except for orthostatic hypotension. Laboratory test results disclosed the following values: serum sodium, 114 mEq/L (114 mmol/L); potassium, 1.9 mEq/L (1.9 mmol/L); arterial blood gases demonstrated respiratory alkalosis; her alanine aminotransferase level was elevated to 128 U/L; and aspartate aminotransferase, to 115 IU/L. *Campylobacter* was grown from her stools. There was no history of major psychiatric disease in the patient or her family.

She received 2 L of normal saline with potassium supplementation. Seventeen hours later, her sodium level was 133 mEq/L (133 mmol/L), and her potassium level was 4.2 mEq/L (4.2 mmol/L). She recov-



Magnetic resonance sagittal image demonstrating triangular area of increased signal intensity in upper, midportion of pons without associated mass effect.

ered uneventfully and was discharged after two days.

Six days after discharge, while on duty, her colleagues noted inappropriate, confused, and restless behavior. Neurologic examination disclosed an inattentive, agitated woman with pressured, tangential speech, mild dysarthria, word-finding difficulties, and right-hand clumsiness. Judgment and insight were markedly impaired. She kept circulating throughout the hospital despite admonishment to remain in her room, denied the importance of her illness, groomed herself publicly in the hallways, spoke of her difficulties to strangers, and inappropriately attempted to resume her professional activities. Other than occasional paraphasic errors, no cognitive deficits were apparent.

Results of laboratory tests, including a complete blood cell count, electrolytes, thyroid functions, vitamin B_{12} and folate levels, toxic screens, antinuclear antibody, hepatitis B surface antigen (HBsAg), and echocardiogram were unremarkable, as was a contrasted computed tomographic (CT) scan of the head. Her erythrocyte sedimentation rate was elevated to 37 mm/h. Cerebrospinal fluid analysis, including IgG and oligoclonal bands, was normal. Bilateral carotid angiogram and visual, auditory, median, and tibial somatosensory evoked potentials were normal. Electroencephalography (EEG) showed left anterior sylvian to midtemporal delta slowing and occasional biposterior generalized sharp waves. Magnetic resonance imaging (MRI) scanning using steady-state free procession and spin-echo sequences with sagittal and axial images demonstrated a triangular area of increased signal intensity in the midportion of the pons without mass effect (Fig 1).

The patient's behavior, speech, and dexterity returned to normal over a period of two weeks. In four weeks, she returned to her occupation full-time without difficulty. An EEG performed three months after discharge demonstrated high-voltage alpha bursts over the left anterior and midtemporal region, with brief paroxysmal generalized bifrontal theta. Her erythrocyte sedimentation rate returned to normal, electrolytes remained stable, and a repeat MRI scan performed 2½ months after onset showed no change in the appearance of the brain-stem lesion. Twelve months after onset, she continues to do well.

COMMENT

Patients who subsequently develop CPM characteristically arrive at the hospital in a debilitated state with a low serum sodium level.[5] There are many reports of intractable nausea, vomiting, and diarrhea prior to admission. Though frequently associated with Wernicke's encephalopathy and chronic alcoholism,[2] CPM may occur in the context of other conditions such as pneumonia, neoplasms, malnutrition, ataxia, weight loss, gastrointestinal bleeding, Wilson's disease, and renal transplantation.[6,7] The peak age of incidence is the fourth through seventh decades; however, CPM has been documented in children as well.[2,8] A low sodium level with rapid correction (or overcorrection) is a common feature, and may constitute an important factor in the cause of the myelinolysis.[5] A positive correlation between the severity of the sodium deficits, the rate of its correction, and the size of the lesion has been suggested.[9] The rapid correction of electrolytes and especially serum sodium in these patients is thought to lead first to improvement, and then, in three to ten days, to the pontine myelinolysis with associated cerebellar ataxia, cranial nerve dysfunction, and quadriparesis with respiratory difficulties.[5]

Emotional lability, especially crying, has been reported in CPM and thought to be secondary to corticobulbar lesions.[10] Confusion and disorientation have been noted in some patients, and may precede other signs or symptoms. However, the cause of these symptoms is unclear, given the associated diseases that can independently lead to a metabolic encephalopathy.[6] The behavioral changes described in CPM are almost always overshadowed by more prominent brain-stem signs. The maximal neurologic deficit usually emerges one to three weeks later, and, in severe cases, intercurrent illness causes death two to four weeks after onset.[9] In other instances, improvement and complete recovery have been reported.[3]

Cerebrospinal fluid analysis in CPM is usually normal. Brain-stem auditory evoked potentials may or may not demonstrate prolongation of wave I through V latencies.[11-13] The CT scan may demonstrate a nonenhancing, hypodense ventral-pontine lesion, but normal CT scans have also been reported.[13,14] The CT abnormality may last longer than clinical symptoms.[16] In one patient who completely recovered after six months, only partial CT resolution was apparent after 12 months, with complete CT resolution shown 22 months after onset.[17] The EEG is usually normal or nonspecific.[6] Magnetic resonance imaging scans have been reported to show an abnormal density signal in the ventral pons without mass effect.[13] Repeated MRI scans performed 15 weeks to eight months later may or may not demonstrate interval changes, despite clinical improvement.[18] A specific antemortem test for the diagnosis of CPM is currently unavailable.

In our patient, the diagnosis of CPM is suggested mostly by the MRI scan abnormality and the rapid correction

of hyponatremia eight days prior to the onset of symptoms. Albeit mild, the right-handed clumsiness, the dysarthria, and the rate of clinical resolution are consistent with this diagnosis. The marked behavioral abnormalities in the absence of prominent brain-stem signs and the setting of a young person in good underlying health are the unusual features. The EEG focality and language impairments are atypical in that they indicate a lesion in the left hemisphere, but they could be associated with extra pontine myelinolysis that has been reported in CPM.[9]

PATHOANATOMIC STUDIES

Central pontine myelinolysis is a unique clinical pathologic entity, which involves median pontine structures and usually spreads in a centrifugal, symmetric fashion.[1] It may involve the corticospinal, corticobulbar, and pontocerebellar tracts, cranial nerves, and other ventral pontine structures.[1,6] Extensive involvement of the midbrain, pontine tegmentum, paramedian reticular area, sympathetic fibers, and sensory pathways may occur.[1,9,19] Approximately 10% of cases have associated extra pontine lesions in the spinal cord, medulla, mesencephalic tectum, basal ganglia, cerebellum, internal capsules and thalami, cerebral peduncles, optic radiations, lateral geniculate bodies, hemispheric white matter, and cerebral cortex.[9,20]

Incomplete demyelination and edema is seen with preservation of nerve cells, axis cylinders, and blood vessels. There are no signs of inflammation.[1] Central pontine myelinolysis as verified by postmortem examination may not be clinically obvious. Of the four cases originally reported by Adams et al,[1] two manifested no clinical symptoms. The small size of their lesions was the suggested explanation. Norenberg et al[5] and Wright et al[9] also reported CPM at postmortem examination, which may not have been clinically apparent.[9,5]

The exact pathophysiology of our patient's altered behavior remains obscure. Since the onset occurred eight days after correction of her electrolyte abnormalities, a metabolic derangement is unlikely. Instead, it is more plausible that these behavioral alterations were caused by the CPM. The location of the MRI abnormality suggests that the lesion may have interfered with the ascending projections of the raphe nuclei, pontomesencephalic reticular formation, and perhaps even those of the nucleus locus coeruleus. This would interfere with the cortical and thalamic supply of serotonin, acetylcholine, and norepinephrine, respectively. Considerable evidence indicates that alterations in these neurotransmitter pathways play a role in the modulation of mood and arousal.[21]

Behavioral abnormalities with other pontine lesions have been reported. In pediatric pontine tumors, profound mental status changes may precede other signs and symptoms.[22-24] These behavioral changes may range from restlessness, irritability, aggression, and rage, to apathy, lethargy, disorientation, and confusion.

Animal experiments suggest that hyponatremia rapidly corrected by hypertonic saline can induce demyelination, whereas hyponatremia alone or its slow correction does not.[25] Current indications are to reverse hyponatremia to prevent seizures and encephalopathy, but to do so slowly. If the serum sodium level is below 105 mEq/L (105 mmol/L), initial correction at 2 mEq/L/h (2 mmol/L/h) is recommended for the first 20 mEq/L (20 mmol/L). The serum sodium level should then be allowed to drift to normal range. If the serum sodium level is 105 mEq/L (105 mmol/L) or greater, it can be corrected at the same rate to a level of 125 to 130 mEq/L (125 to 130 mmol/L). Serum sodium levels above 120 mEq/L (120 mmol/L) usually do not require immediate correction.[26] Adherence to these guidelines could reduce the incidence of CPM.

This patient indicates that CPM should be included in the differential diagnosis of acute behavioral changes, especially if rapid correction of hyponatremia has occurred in the recent past. In fact, CPM may occur more frequently than clinically suspected, and MRI scanning may be essential for accurate diagnosis.

The preparation of this manuscript was supported in part by the Javits Neuroscience Investigator Award, National Institutes of Health, Washington, DC.

We wish to thank Mark Aronson, MD, for referring the patient, Donald Schomer, MD, for interpreting the electroencephalograms, Ferenc Jolesz, MD, for interpreting the magnetic resonance imaging scans, Nan Rubin, MS, for administering language examinations, and Loraine Karol for her secretarial assistance.

References

1. Adams R, Victor M, Mancall E: Central pontine myelinolysis: A hitherto undescribed disease occurring in alcoholic and malnourished patients. *Arch Neurol Psychiatry* 1959;81:154-172.

2. Bhagavan BS, Wagner JA, Juanteguy J: Central pontine myelinolysis and medullary myelinolysis. *Arch Pathol Lab Med* 1976;100:246-252.

3. Wiederholt WC, Nobayashi RM, Stockard JJ, et al: Central pontine myelinolysis: A clinical reappraisal. *Arch Neurol* 1977;34:220-223.

4. Messert B, Orrison WM, Hawkins MJ, et al: Central pontine myelinolysis: Consideration on etiology, diagnosis, and treatment. *Neurology* 1979;29:147-160.

5. Norenberg MD, Leslie KO, Robertson AS: Association between rise in serum sodium and central pontine myelinolysis. *Ann Neurol* 1982; 11:128-135.

6. Goebel HH, Zur PH: Central pontine myelinolysis: A clinical and pathological study of ten cases. *Brain* 1972;95:495-504.

7. Schneck SA: Neuropathological features of human organ transplantation: II. Central pontine myelinolysis and neuroaxonal dystrophy. *J Neuropathol Exp Neurol* 1966;25:18-39.

8. Codman TE, Rorke LB: Central pontine myelinolysis in childhood and adolescence. *Arch Dis Child* 1969;44:342-350.

9. Wright DG, Laureno R, Victor M: Pontine and extra-pontine myelinolysis. *Brain* 1979; 102:301-385.

10. Poeck K: Pathophysiology of emotional disorders associated with brain damage, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology*. New York, North Holland Publishing Co, 1969, vol 3, pp 356-363.

11. Stockard JJ, Rossiter VS, Wiederholt WC, et al: Brain-stem auditory evoked potentials in suspected central pontine myelinolysis. *Arch Neurol* 1976;33:726-728.

12. Kandt RS, Heldrich FJ, Moser HW: Recovery from probable central pontine myelinolysis associated with Addison's disease. *Arch Neurol* 1983;40:118-119.

13. Takeda K, Sakuta M, Saeki F: Central pontine myelinolysis diagnosed by magnetic resonance imaging. *Ann Neurol* 1985;17:310-311.

14. Anderson TL, Moore RA, Grinnell VS, et al: Computerized tomography in central pontine myelinolysis. *Neurology* 1979;29:1527-1530.

15. Thompson DS, Hutton JT, Stears JC, et al: Computerized tomography in the diagnosis of central and extrapontine myelinolysis. *Arch Neurol* 1981;38:243-246.

16. Telfer RB, Miller EM: Central pontine myelinolysis following hyponatremia, demonstrated by computerized tomography. *Ann Neurol* 1979;6:455-456.

17. Gerber O, Geller M, Stiller J, et al: Central pontine myelinolysis: Resolution shown by computed tomography. *Arch Neurol* 1983;40:116-118.

18. DeWitt LD, Buonanno FS, Kistler JP, et al: Central pontine myelinolysis: Demonstration by nuclear magnetic resonance. *Neurology* 1984; 34:570-576.

19. Burcar PJ, Norenberg MD, Yarnell PR: Hyponatremia and central pontine myelinolysis. *Neurology* 1977;27:223-226.

20. Goldman JE, Horoupian DS: Demyelination of the lateral geniculate nucleus in central pontine myelinolysis. *Ann Neurol* 1981;9:185-189.

21. Risch SC, Kalin NH, Murphy DL: Neurochemical mechanisms in the affective disorders and neuroendocrine correlates. *J Clin Psychopharmacol* 1981;1:180-185.

22. Bray PF, Carter S, Taveras JM: Brain-stem tumors in children. *Neurology* 1958;8:1-7.

23. Lassman LP, Arjona VE: Pontine gliomas of childhood. *Lancet* 1967;1:913-915.

24. Cairns H: Mental disorders with tumors of the pons. *Folia Psychiatr Neurol Neurochir Neerl* 1950;53:193-203.

25. Kleinschmidt-De Masters BK, Norenberg MD: Neuropathologic observations in electrolyte-induced myelinolysis in the rat. *J Neuropathol Exp Neurol* 1982;41:67-80.

26. Ayus JC, Krothapalli RK, Arieff AI: Changing concepts in the treatment of severe symptomatic hyponatremia *Am J Med* 1985; 78:897-902.