Abstract

We observed a 41-year-old woman with severe central pontine myelinolysis (CPM) and unusually extensive extrapontine myelinolysis (EPM), but without evidence of hyponatremia. Increased alcohol consumption in prior months was the main cause of her CPM/EPM. However, in general, EPM is a rare accompaniment in alcoholic patients with CPM without hyponatremia. With regard to our patient, the EPM was unusually widespread; magnetic resonance imaging (MRI) of her brain showed multiple hyperintense lesions on T2-weighted images distributed symmetrically in bilateral caudate nuclei, lentiform nuclei and thalami. Serial follow-up MRI revealed almost complete resolution of EPM after methylprednisolone pulse therapy. By contrast, marked cavitary hypointensity in the pons remained, but complete remission of neurological symptoms was achieved.

Key words: central pontine myelinolysis (CPM), extrapontine myelinolysis (EPM), magnetic resonance imaging (MRI), alcoholism, hypokalemia, methylprednisolone

Introduction

It is widely recognized that there is a close correlation between the occurrence of central pontine myelinolysis (CPM) and rapid correction of hyponatremia. The pontine base represents the most frequent lesion susceptible to this osmotic insult, although lesions can occur outside the pons; this is known as extrapontine myelinolysis (EPM). Extrapontine lesions can be found on the basal ganglia, thalami, cerebellum, lateral geniculate body, and cerebral cortex or subcortex. In addition to hyponatremia, however, chronic alcoholism is the most notable predisposing condition, as reported by Adams et al (1). With advances in imaging techniques, many clinically mild or asymptomatic cases have been observed among chronic alcoholics without evident history of rapidly corrected hyponatremia (2, 3). On MRI, these patients show varying extents of CPM, whereas extrapontine involvement is usually rare. Herein, we report a case of severe CPM accompanied by unusually extensive EPM in a chronic alcohol abuser without hyponatremia. Serial MRI was performed, and the imaging characteristics and treatment outcome with corticosteroids are discussed in relation to her clinical symptoms.

Case Report

A 41-year-old Japanese woman was referred to our hospital because of progressive neurological deterioration, including dysphagia, dysarthria and gait disturbance. The patient had been in her usual state of health until two weeks earlier, when she began to complain of general fatigue. She had been a habitual drinker throughout most of her adult life, and she noted that there had been a recent increase in her alcohol consumption; she had consumed more than 2 liters of beer daily for at least 3 months prior to presentation. She was initially seen by a primary care physician, and laboratory tests at that time revealed alcoholic liver dysfunction, as shown by the following findings: aspartate aminotransferase 182 IU/l (13-33 IU/l), alanine aminotransferase 179 IU/l (6-
Figure 1. Initial MR images with maximal neurological impairment. An axial FLAIR image at the level of the basal ganglia shows multiple extrapontine hyperintense lesions, including lesions in the caudate nuclei, lentiform nuclei, thalami and the tail of the left caudate nucleus (A). The image below is an image at the pontine level showing a round hyperintense area within the central basis pontis (B). Diffusion-weighted images also demonstrate high signal intensity in the corresponding regions (C and D). T1-weighted images show hypointense areas in the same lesions (E and F).

27 IU/l), γ-glutamyl transpeptidase 74 IU/l (6-46 IU/l), and total bilirubin 2.5 mg/dl (0.3-1.2 mg/dl). Hepatitis B surface antigen and hepatitis C virus antibody were negative. There was also a mildly elevated serum amylase of 413 IU/l (39-115 IU/l), but she did not suffer from abdominal pain and careful examination by abdominal ultrasound and computed-tomography yielded normal results. Serum electrolyte analysis revealed mild hypokalemia of 3.0 mEq/l (3.7-5.0 mEq/l), but a normal sodium level of 135 mEq/l (135-147 mEq/l) was noted. She was advised to avoid alcohol, and was given oral replacement to correct the hypokalemia. She received no intravenous sodium supplementation. Her food and water intake had been almost normal. However, one week before referral to our hospital, she began to complain of difficulty swallowing and speaking, accompanied by unsteadiness of gait and eventual inability to walk. Her serum sodium (138 mEq/l) at this time was also within the normal range.

On admission to our hospital, she was apathetic, responded only to simple questions by nodding, and occasionally showed emotional incontinence with forced crying. She was of relatively short stature, but normally nourished; her body weight was 46 kg and her height was 150 cm (body mass index=20.4). The findings on general physical examination were unremarkable. Her cranial nerve examination revealed marked pseudobulbar palsy; dysarthria and dysphagia with hyperactive jaw jerk were observed, but there was no atrophy or fasciculation of her tongue. Her speech was totally aphasis, and complete dysphagia caused her to require a nasogastric tube feeding. During her motor examination, marked pyramidal spasticity and coexistent extrapyramidal rigidity were noted in both arms and legs, being greater in the lower than in the upper extremities. Both resting and positional tremor were seen in head and limbs. The weakness was mild in the upper extremity and moderate in the legs. The deep tendon reflexes were all brisk and symmetrical, and plantar responses were flexor. Findings on sensory examination were unremarkable. She could barely stand with support, and was unable to walk. Her laboratory data yielded a normal sodium level of 140 mEq/l and a potassium level of 4.7 mEq/l. Although she was found to have a slightly low level of serum albumin (3.5 g/dl, normal range: 3.9-4.9), other measures of nutritional status, including serum protein (6.9 g/dl, normal range: 6.5-8.0) and total cholesterol (260 mg/dl, normal range: 150-219), were almost within the normal range. Her liver function test at this time showed normal results. The results of other laboratory studies, including vitamin B1 (77.8 ng/ml, normal range: 21.3-81.9) and vitamin B12 (1,139 ng/ml, normal range: 233-914), were also normal. The result of her head MRI revealed striking abnormalities. T2-weighted and FLAIR images showed a round hyperintense area in the central portion of the pontine base and bilateral symmetric regions of hy-
perintensity in the caudate nucleus, lentiform nucleus and thalamus (Fig. 1A and B). There was also a small hyperintense lesion in the tail of the left caudate nucleus. Diffusion-weighted imaging (DWI) also allowed detection of the lesions, but the DWI signal was greater in the pontine lesion than in the extrapontine lesions (Fig. 1C and D). On the T1-weighted image, both pontine and extrapontine lesions appeared as areas of hypointensity (Fig. 1E and F). There was no abnormal signal intensity of the mammillary bodies, periaqueductal gray matter or corpus callosum. The pontine lesion did not show any extension into the midbrain and medulla (Fig. 2). T2* (T2 star) imaging showed no hypointensity in the affected lesions. Routine electroencephalography demonstrated a normal background alpha rhythm without slow wave activity. Brainstem auditory evoked potentials revealed abnormal prolongations in the I-VI interpeak latencies. Somatosensory evoked potentials, which were obtained by median nerve stimulation, showed that the N20 amplitudes were decreased, but that the N13 to N20 interpeak latencies were normal. Based on the imaging features coupled with her clinical presentation, the multiple supra-infratentorial lesions were strongly suggested to represent CPM with widespread EPM.

Since there were severe neurological abnormalities, no generally accepted therapies available, and few reports describing favorable effects of corticosteroids, we treated her with two courses of methylprednisolone pulse therapy (1,000 mg/day for 3 days). The first course of pulse therapy resulted in partial relief of her pseudobulbar palsy, and pulse therapy was repeated one week later, followed by 30 mg/day of oral prednisolone. The dosage was gradually tapered. Her neurological status gradually improved thereafter. Follow-up MRI performed on the 10th day of hospitalization showed partial improvement of her EPM: with T2/FLAIR hyperintensities in the extrapontine lesions slightly decreased (Fig. 3A). However, even more prominent hyperintensity in her pontine lesion was noted on T2/FLAIR images (Fig. 3B).

She only experienced mild pseudobulbar palsy and virtually no other residual neurological abnormalities at the time of discharge (the 42nd day of hospitalization). MRI reevaluation performed at this time revealed further decreases in the hyperintensities in the extrapontine lesions, but the hypointensity lesion in the tail of the left caudate nucleus remained (Fig. 3C). The T1-weighted image showed persistent, but only slight hypointensity in the same lesions. Although the time-course was initially different between her CPM and EPM, the pontine lesion also demonstrated decreased hyperintensities on T2/FLAIR images in conjunction with clinical improvement at the time of discharge (Fig. 3D). However, there was no significant difference in the area of hypointensity in her pontine lesion on the T1-weighted image.

MRI obtained at the 5 months follow-up showed almost complete resolution of her EPM (Fig. 3E). Only the tail of the left caudate nucleus showed residual small hyperintensity on T2/FLAIR images. A T1-weighted image demonstrated no abnormalities in her extrapontine lesions. By contrast, an area of cavitory hypointensity in her pontine lesion was seen on both T1- and T2-weighted/FLAIR images (Fig. 3F). Despite the persistent marked pontine lesion, her mental status and motor function had recovered completely at the 5 months follow-up; she was organizationally interactive with others in recreational activities, such as volleyball. She was successful at abstinence from alcohol.

### Discussion

It has recently been reported that CPM can occur in patients without hyponatremia (2-8). However, there have been only a few reports of EPM in patients without hyponatremia (6-8). Of note, two prospective studies of MR findings among large populations of chronic alcoholics showed that the CPM in this population was usually mild compared with the CPM in patients with rapidly corrected hyponatremia; none of the patients in these studies showed EPM (2, 3). Thus, EPM is a rare accompaniment in alcoholic patients with CPM without hyponatremia.

Although we cannot exclude the possibility that our patient had suffered from minor fluctuations in serum sodium during the inter-measurement period, our patient had no evidence of hyponatremia based on the available data. Furthermore, there was no episode of rapid correction or over-correction of serum sodium level. The temporal relations among her increased alcohol consumption, alcoholic liver dysfunction and MRI findings indicated that chronic alcoholism was the principal causative factor. However, her MRI showed unusual extrapontine involvement. A possible explanation for this finding might be the presence of hypokalemia at initial presentation. Several reports have shown that underlying hypokalemia may predispose patients to more pro-

![Figure 2. A sagittal T1-weighted image. The pontine lesion did not show any extension into the midbrain and medulla, and the image demonstrated that the hypointensity lesion was limited to the pontine base.](Image 327x578 to 526x780)
Figure 3. Follow-up MR images. Serial FLAIR images captured on the 10th day of hospitalization (A and B), at the time of discharge (the 42nd day of hospitalization) (C and D), and at the 5 months follow-up (E and F). The pontine lesion showed temporary enlargement on the 10th day of hospitalization (B), followed by a gradual transition to a marked hypointense area (D and F). By contrast, the extrapontine lesions showed almost complete resolution, although some residual hyperintensity can be noted in the tail of the left caudate nucleus (E).

nounced myelin damage (8-12). In the present patient, although the hypokalemia was mild, we cannot deny the possibility that it may have had a pathological effect with regard to the unusual accompaniment of EPM in otherwise non-complicated alcoholism. However, given the MR finding of unusually extensive EPM in our patient, it seems feasible that there exist other distinctive mechanisms of pathogenesis. Since there are reports on concomitant autoimmune disorders (13, 14), reports about the favorable effects of intravenous immunoglobulin therapy (14, 15), and there was a benign outcome observed after methylprednisolone pulse therapy in our patient, it is possible that unknown immunological pathogeneses have contributed to the occurrence of her CPM/EPM. However, there are arguments against the immunopathogenesis of CPM/EPM, because occurrences of CPM have been reported in liver transplant patients who had been already treated with immunosuppressants, such as cyclosporine (16). In addition, as Marchiafava-Bignami disease, which is most notably a disease of demyelination in the corpus callosum, occurs predominantly in chronic alcoholics, it is more than probable that there also exists a direct correlation between the toxic effects of alcohol and the occurrence of CPM/EPM.

We carefully documented the radiological changes in CPM/EPM in three follow-up sessions. The clinical and MRI findings correlated well in the course of EPM, and almost complete resolution was confirmed at 5 months follow-up, whereas in the course of CPM, the dynamics of the lesion did not correlate well with her clinical improvement and outcome. Given the almost complete resolution of EPM after methylprednisolone pulse therapy, we suggest that the increased DWI signals in the extrapontine lesions indicate the contribution of a T2 “shine-through” effect in our patient; that is, principally vasogenic edema. By contrast, the increased DWI signal in the pontine lesion might be due to coexistent cytotoxic edema; an area of marked cavitary hypointensity persisted in the pontine lesion on both T1-weighted and T2-weighted images. On these grounds, it may be concluded that there are different types of pathologic findings between CPM and EPM. However, since we did not obtain apparent diffusion coefficient maps, the relative contribution of either cytotoxic edema or vasogenic edema to the CPM/EPM could not be specifically determined.

Although the favorable outcome of our patient might be attributed to the absence of severe metabolic derangement and spontaneous remission, as noted above, our case seems to indicate that the methylprednisolone pulse therapy may have contributed to her complete clinical remission and substantial resolution of the imaging characteristics, particularly of the EPM. Remarkably, there were virtually no clinical sequelae pertaining to the residual pontine lesion. There are only a few anecdotal case reports of beneficial effects of
corticosteroids in patients with CPM (6, 13, 17), but recent animal experiments have shown that the early administration of dexamethasone can prevent the development of CPM in the setting of rapidly corrected hyponatremia (18, 19). The reason for this favorable effect is postulated to be that the corticosteroids protect against the disruption of the blood-brain barrier following osmotic endothelial injury. Based on the findings on her serial follow-up MRI, we assume that the reversal of vasogenic edema due to methylprednisolone pulse therapy might also be a reasonable explanation for her favorable outcome, with nearly complete resolution of EPM.

To summarize, our case illustrated a case of severe CPM and unusually extensive EPM despite the absence of significant metabolic derangement. Our case may broaden the clinical spectrum of CPM/EPM and suggested that this clinical entity should be considered in various clinical settings.

References


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