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Acute necrotizing encephalopathy with widespread edematous lesions of symmetrical distribution

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Summary. A 67-year-old Japanese woman with liver cirrhosis was affected by an unusual acute progressive encephalopathy, presenting mental confusion and slurred speech as its initial symptoms. She died in profound coma, following the entire course of 17 days. Autopsy disclosed bilateral symmetrical, widespread, edematous and necrotic lesions, their centers being located in the basal ganglia, diencephalon and midbrain, and their peripheries expanding into the cerebral white matter, cerebellum, pons and medulla. Diapedesis of erythrocytes and serum plasma was conspicuous, in contrast to paucity of capillary proliferation. Although the lesions were somewhat similar to those of Wernicke's and Leigh's encephalopathies, they were considered to be representative of a more acute metabolic disorder distinct from the latter conditions.

Key words: Acute encephalopathy – Leigh's encephalopathy – Wernicke's encephalopathy – Liver cirrhosis

A number of metabolic or toxic encephalopathies are known to present bilateral symmetrical necrotic lesions, the topography and nature of which characterize each condition. Here we present an autopsy case of acute encephalopathy, showing bilateral symmetrical involvement with particular pathological features which differentiate the case from any of the known categories.

Case report

Clinical findings

A 67-year-old female with posthepatitic liver cirrhosis was noticed to be inattentive and dysarthric on March 12, 1986, in the hospital to which she had been admitted because of ascites and rupture of the rectal varix. She had no history of alcohol drinking. In the hospital course, she had been taking sufficient amount of dietary thiamine.

Neurological examination revealed impaired attention, slurred speech, saccadic eye movement with nystagmus, weakness and ataxia of the extremities, dysesthesia and painful paresthesia. Memory, comprehension and orientation were fairly preserved. Flapping tremor was absent. Laboratory examination disclosed positive HBs antibody, abnormal liver functions, normal blood ammonia and respiratory alkalosis. Spinal tap yielded xanthochromic CSF with mildly increased protein. CT scan on March 17 showed bilateral low-density areas in the thalamus, brain stem and cerebellum.

Her condition rapidly deteriorated, and on March 19, she was comatose and dysphagic, with the arms rigidly extended. The pupils became mydriatic and unresponsive to light. Jaundice and severe hyponatremia developed. On CT scan on March 27, low-density areas were more exaggerated and extensive, involving the cerebral deep white matter and corpus callosum. Respiration became increasingly dysrhythmic, resulting in death on March 28.

Pathological findings

The cadaver (148 cm in height and 42 kg in weight) was icteric. Mesonodular, thin-septal cirrhosis of the liver, weighing 630 g, was accompanied by esophageal and rectal varices, splenomegaly, organizing portal thrombosis, and massive ascites.

The brain (weight 1,400 g) was swollen and soft. Sclerosis of the basal arteries was slight. On transverse sections (Fig. 1), bilateral symmetrical lesions showing softening and deep brown discoloration were distributed in the caudomedial part of lenticular nuclei, ventral part of ventrolateral and centromedian nuclei of thalamus, lateral and posterior nuclei of hypothalamus, subthalamic nuclei, red nuclei, inferior colliculi and substantia nigra. Patchy discoloration was seen also in the corpus callosum. Surrounding these, edematous lesions were distributed concentrically in the cerebral deep white matter, cerebellar dentate nuclei and dorsolateral tegmentum of the brain stem down to the level of inferior olivary nuclei. Many petechial or brushy hemorrhages were observed in the ventral thalamus, mammillary bodies, substantia nigra and periventricular region of brain stem.

On microscopic examination, the sharply demarcated lesions were markedly spongy with loosening of the neuropil (Fig. 2a). Axons were less severely affected. In the central zone of the lesions, most of the neurons were necrotic. In the peripher-

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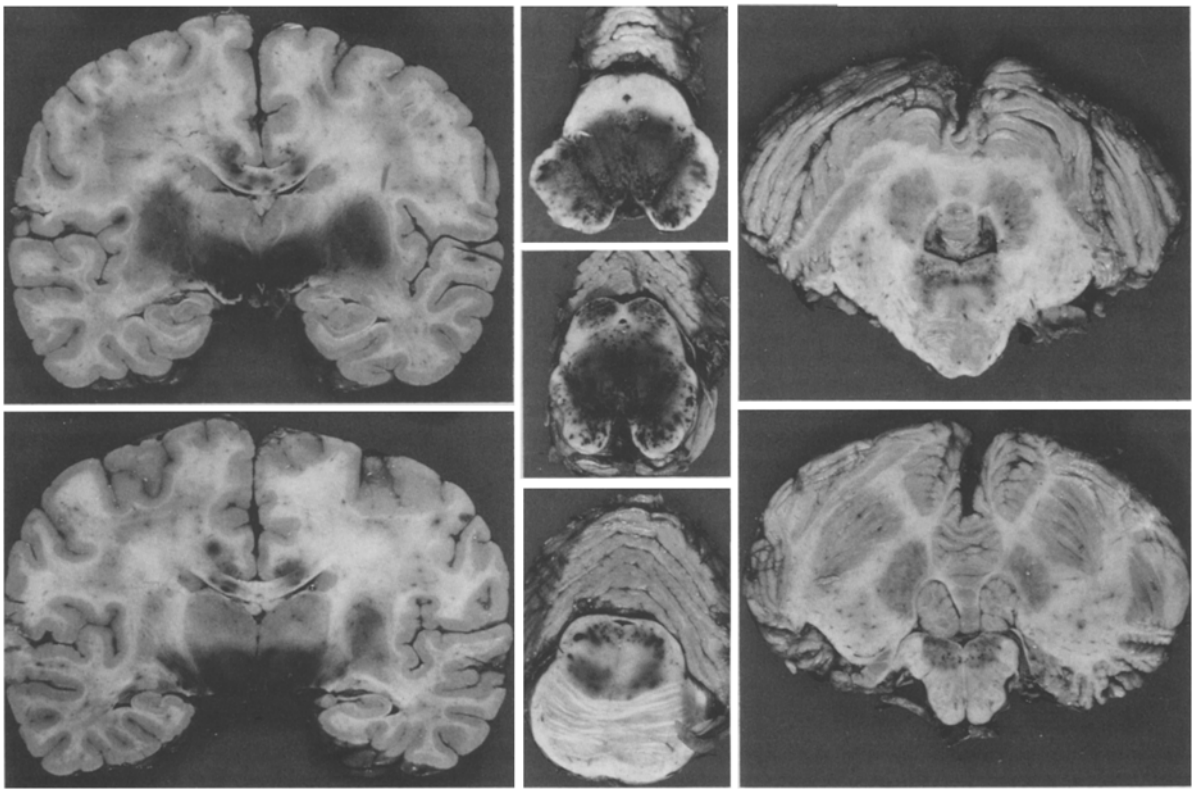

Fig. 1. Gross appearance of the brain. There are symmetrical central lesions with deep-brown discoloration in the basal ganglia, the diencephalon and the mesencephalon. Surrounding these are peripheral lesions with pale discoloration in the cerebral white matter, cerebellar dentate nuclei and lower brain stem tegmentum. Many petechiae are seen in the central zone

al zone, larger number of neurons survived, although often with ischemic changes. Frank necrosis of all tissue elements was restricted to some small areas such as ventromedial portions of the lenticular nuclei, accompanied by moderate phagocytic activity and capillary proliferation.

Except for these areas, vascularity was not increased (Fig. 2b). Veins and capillaries were often conspicuous due to an increase in size and number of their endothelial and adventitial cells (Fig. 2d). In the central zone, ring-shaped hemorrhages were frequently observed around venules or capillaries (Fig. 2b). Extravasation of fibrin was occasionally seen (Fig. 2c). Phagocytosis was noted only to a mild degree. In the peripheral zone, polymorphonuclear leucocytes and monocytes were often aggregated along the venous adventitia (Fig. 2d). Although some of them were extravasated, inflammatory or phagocytic activity was inconspicuous.

Activation of glia was unremarkable, except for presence of scattered astrocytes with swollen, pale nuclei.

Outside these lesions, mild ischemic changes were observed. Spinal cord, optic nerves and other cranial nerves were spared.

Discussion

In the present case, the topography of the lesions was bilaterally symmetrical and independent of the pattern of arterial supply or venous drainage. Because of the concentric pattern and irrelevance to normal structures, it seemed to be determined by radial diffusion of edema fluid. The lesions bore some similarity to those of certain metabolic encephalopathies such as Wernicke's and Leigh's encephalopathy.

The distribution resembled that of Wernicke's encephalopathy in that the mammillary bodies and the floor of the fourth ventricle were involved. However, there were some striking differences to Wernicke's cases. In the latter, the sites of most predilection are located along the ventricular system. In the thalamus, nuclei along the third ventricle, such as the medial dorsal nucleus and medial pulvinar nucleus, are most frequently involved [10, 15]. In the midbrain, the periaqueductal region at the level of the superior colliculi is frequently affected [1, 2, 10, 13, 15]. In our case, these nuclei and regions were spared. Instead, regions that were located more ventrally or laterally, such as lenticular nuclei and substantia nigra, were severely involved. These nuclei have been reported to be affected only rarely in Wernicke's encephalopathy [1, 2, 10, 13, 15].

On the other hand, distribution of the present case resembled that of Leigh's encephalopathy in that basal ganglia and substantia nigra were involved. However, involvement of the mammillary bodies, which was present in our case, is absent in all the adult cases of

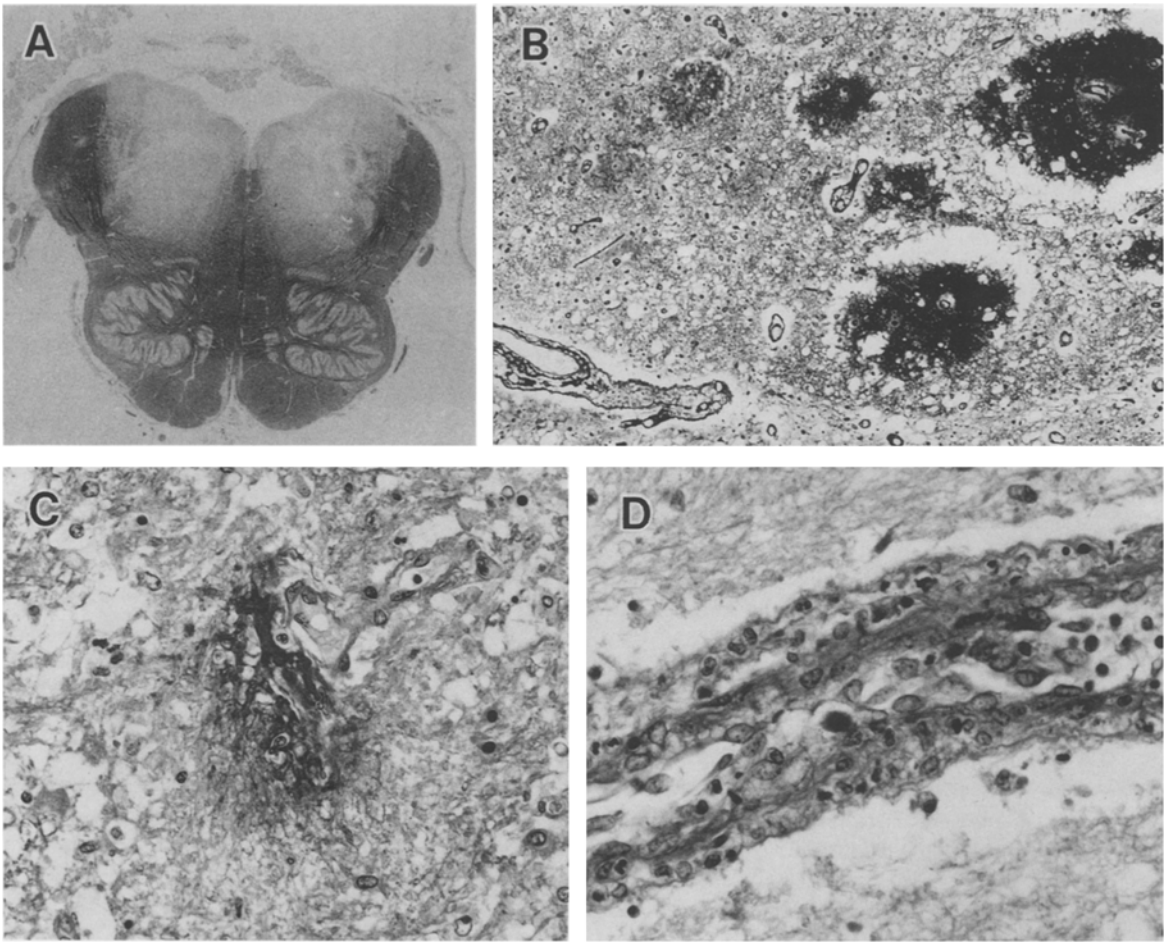

Fig. 2. A Medulla oblongata. Symmetrical lesions in the tegmentum, showing myelin pallor, are sharply demarcated. Klüver-Barrera, ×2.7. **B** Mammillary body. Florid capillary hemorrhage without significant increase in vascularity. Watanabe's method of silver stain, ×68. **C** Subthalamic nucleus. Extravasation of fibrin and a few macrophages from a capillary. The surrounding tissue is markedly spongy. H&E, ×273. **D** Cerebral white matter. The vein is prominent partially due to proliferation of its endothelial and adventitial cells, and partially due to presence of leucocytes and macrophages in the adventitia. H&E, ×27

Leigh's encephalopathy [4, 5, 7, 8, 11, 12, 14] except for the two cases reported by Feigin [3].

The most essential pathological feature of the present case was severe edema. In the central zone, diapedesis of serum and erythrocytes severely injured the neurons, while in the peripheral zone, diapedesis of less proteinaceous fluid provoked milder damage. There must have been "dysoria" [6], or breakdown of the blood-brain barrier. Although Wernicke's and Leigh's encephalopathies are prototypes of dysoric lesions, lesions in this case differed from those of the two conditions. The edematous gross appearance was unusual for the latter lesions [2, 9]. Diapedesis of erythrocytes was more florid, exceeding even the acute Wernicke lesions. Both vascular proliferation and glial reaction were not so prominent as in the latter lesions. Probably these contrasts reflect difference in the chronological course of pathological process, which would have been more acute in our case.

It was reasonable to assume that the pathological features of our case were the expression of some acute metabolic disorder. Biochemical abnormalities clinically recognized in this patient included nothing more than those frequently encountered in cirrhotic patients in the advanced stage. However, it seemed unlikely that hepatic failure was the single metabolic basis, for comparable cases of hepatic encephalopathy have never been reported. The possibility that another metabolic disorder, possibly an inherited one, became overt triggered by hepatic failure was strongly suspected, but failed to be elucidated biochemically.

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