

Case Report

Morel's laminar sclerosis showing apraxia of speech: Distribution of cortical lesions in an autopsy case

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A 57-year old man with chronic alcoholism presented with apraxia of speech and disturbance of consciousness. He had a history of gastrectomy and had been drinking alcohol. The symptoms improved with administration of thiamine, but he later developed diarrhea and delirium, and died approximately 40 days after the onset. Autopsy findings were consistent with Wernicke's encephalopathy and pellagra encephalopathy. Furthermore, laminar cortical necrosis with vacuoles and astrocytosis was found in the second and third layers of the bilateral frontal cortices, suggesting Morel's laminar sclerosis. The lesions were mainly located in the bilateral primary motor cortices. Involvement of the lower part of the left primary motor cortex may be associated with apraxia of speech in our case.

Key words: apraxia of speech, Morel's laminar sclerosis, pellagra encephalopathy, primary motor cortex, Wernicke's encephalopathy.

INTRODUCTION

A brief summary of the clinicopathological features of this case was previously reported in this journal as "Neuropathology Education" by Tsuchiya, one of the authors of this

paper.¹ This time, we have added the description of the clinical course, pathological findings, distribution of the cortical lesions, and review of the literature regarding Morel's laminar sclerosis, and discuss matters related to clinical practice.

The term Morel's laminar sclerosis was derived from the publication by Morel in 1939 describing unusual pathological changes in four alcoholics, taking the form of spongiform change and gliosis of the cerebral cortex, mostly confined to the third layer.² Although some reports described patients with Morel's laminar sclerosis,^{3–6} the information regarding clinical and pathological findings has been limited.

Apraxia of speech (AOS) is caused by disturbance of motor programming of articulation, and is classically distinguished from Broca's aphasia by the preservation of the ability to write language.⁷ Here, we report a patient presenting with AOS, and having histological findings indicating Morel's laminar sclerosis, as well as Wernicke's encephalopathy and pellagra encephalopathy.

CASE REPORT

The patient was a 57-year-old Japanese man, who had been living alone. After the publication of the previous paper,¹ we found that the patient had been drinking 80–100 g of alcohol per day (The duration was unclear.). Past history included diabetes mellitus, foot necrosis, angina pectoris, and gastric cancer. Because of these diseases, coronary artery bypass graft (at age 51), digital amputation (at age 55), and total gastrectomy (at age 55) were performed. Five

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days before admission, his brother had contact with the patient by telephone, and the patient had been normal. On the day of admission, an acquaintance visited him and found him lying near his bed. He opened his eyes, but could not speak. On admission, body temperature was 36.0°C, blood pressure 136/115 mmHg, and heart rate 101 beats/min. General examination showed severe emaciation and surgical scars on the chest and abdomen. The palpebral conjunctiva was anemic. The second and third digits of the right foot had been amputated. On neurological examination, consciousness disturbance (easy arousal after normal calling), and hyporeflexia in the four extremities were demonstrated. He could not speak, but comprehension of spoken language was normal. Tongue protrusion was impossible. External ocular movement was normal. There was no motor paralysis in the face or limbs. Ataxia of the upper limbs was not apparent, while that of the lower limbs and trunk could not be examined. Blood test showed a white blood cell (WBC) of $7100/\text{mm}^3$ (normal range: 4000–9000), red blood cell (RBC) $237 \times 10^4/\text{mm}^3$ (normal range: $430\text{--}570 \times 10^4$), platelet count (Plt) $14.9 \times 10^4/\text{mm}^3$ (normal range: $15\text{--}35 \times 10^4$), total protein 6.3 g/dL (normal range: 6.5–8.0), urea nitrogen 41.6 mg/dL (normal range 8–20), creatinine 0.7 mg/dL (normal range: 0.6–1.2), aspartate aminotransferase (AST) 58 IU/L (normal range: < 35), alanine aminotransferase (ALT) 45 IU/L (normal range: < 40), blood sugar 180 mg/dL, and C-reactive protein 0.9 mg/dL. Brain CT demonstrated mild atrophy at the bilateral frontal and temporal lobes. Although blood thiamine was not measured, the diagnosis of Wernicke's encephalopathy was suspected based on the history of gastrectomy and drinking alcohol. Hydration with administration of thiamine was initiated, but niacin was not given. Consciousness disturbance gradually improved, but anterograde and retrograde amnesia, and time disorientation became evident. At that time, we found that his written language was normal, although the disturbance in speech output was not completely resolved. Diarrhea was also seen after the initiation of oral intake, but he was transferred to another hospital 30 days after admission. Thereafter, he developed delirium and convulsion, and was transferred back to our hospital 6 days later. He died on the same day. Artificial ventilation was not administered throughout the course. Autopsy was limited to the brain.

The brain weighed 1130 g after fixation. Macroscopically, bilateral mamillary bodies and inferior colliculi appeared gray. There were no abnormalities in the thalamus or cerebral cortex (Fig. 1). Atherosclerotic changes of the middle cerebral arteries and basilar artery were mild. Brain tissue samples were fixed post mortem with 10% formalin and embedded in paraffin. Ten- μm -thick hemispheric sections were prepared at the plane of the left frontal lobe (the most

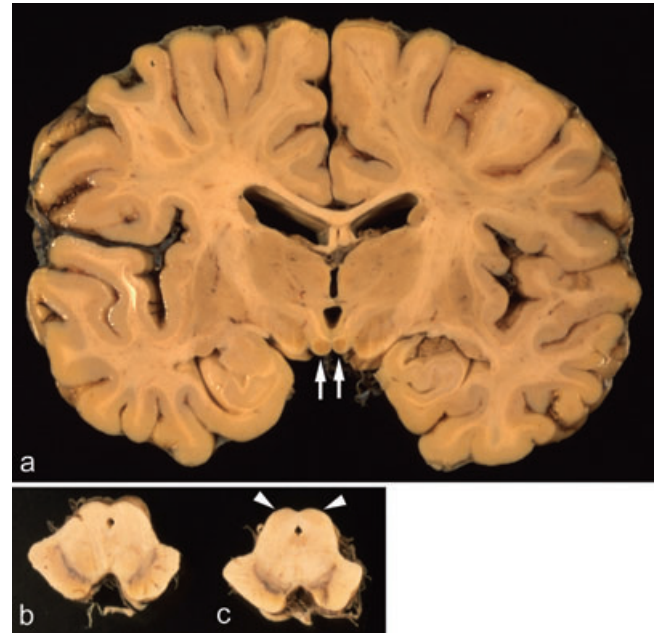


Fig. 1 (a,c) Grayish discoloration in the bilateral mamillary bodies (a, arrows) and inferior colliculi (c, arrowheads). (b) At the level of the upper midbrain. There are no macroscopic abnormalities in the periaqueductal gray matter, thalamus or cerebral cortex.

anterior section), left amygdala, bilateral mamillary bodies, left pulvinar nucleus, and right occipital lobe. The sections of upper and lower portions of the midbrain, upper and middle portions of the pons, upper, middle, and lower portions of the medulla oblongata, and bilateral cerebellum were also prepared. These sections were stained with HE, KB, Bodian, and Gallyas method, and anti-glial fibrillary acidic protein (GFAP) (rabbit, polyclonal, Dako, Glostrup, Denmark, 1:1000). Reticulin silver stain was also performed to visualize the capillaries.

Microscopic examination demonstrated necrotic foci with many vacuoles, accompanied by proliferation of macrophages and astrocytes, and capillary proliferation in the bilateral mamillary bodies and left inferior colliculi (Figs 2,3). Pinpoint hemorrhages were seen in the right mamillary body (Fig. 2c) and bilateral inferior colliculi. Neurons were relatively preserved in the lesion (Fig. 2d). Periaqueductal gray matter and oculomotor nucleus were not involved. In the thalamus, neuronal loss with astroglytosis was obvious in the bilateral mediodorsal nuclei, anterior nuclei (Fig. 3c), and left pulvinar nuclei. In the bilateral inferior olivary nucleus, patchy neuronal loss (Fig. 3d) with astroglytosis was evident. There were no abnormalities in the hypoglossal nucleus or cerebellum. These findings suggested the diagnosis of Wernicke's encephalopathy. In addition, central chromatolysis of the neurons without astrocytic or microglial changes was evident in the Betz

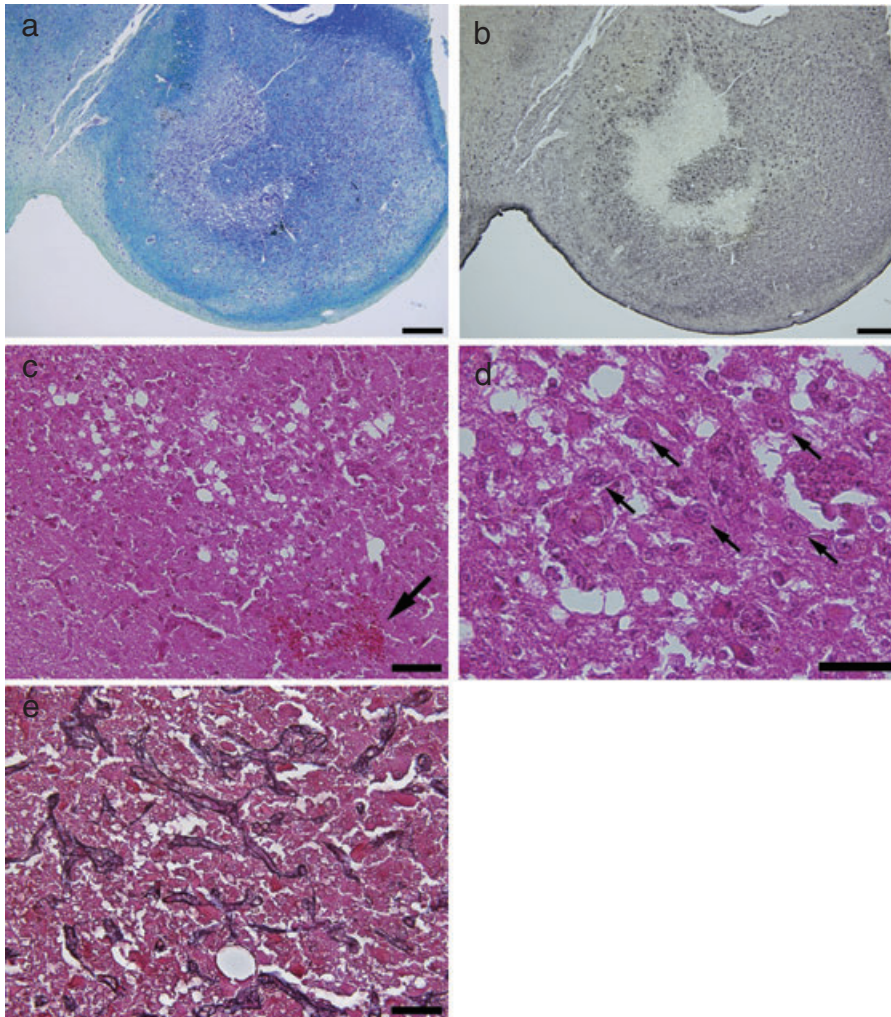


Fig. 2 (a) and (b) are serial sections. (a) Necrotic lesions in the right mamillary body. Bar = 500 μ m. (b) Astrocytosis and central necrosis. Bar = 500 μ m. (c) Many vacuoles and hemorrhages (arrow) in the right mamillary body. Bar = 100 μ m. (d) Relative preservation of the neurons (arrows) in the right mamillary body. Bar = 50 μ m. (e) Capillary proliferation in the right mamillary body. Bar = 50 μ m. (a) KB stain, (b) GFAP stain, (c, d) HE stain, (e) Reticulin silver stain.

cells (Fig. 3e), pontine nucleus (Fig. 3f), left abducens nucleus, and bilateral cuneate nucleus, indicating pellagra encephalopathy. Furthermore, laminar cortical necrosis with vacuoles and astrocytosis was found in the second and third layers of the bilateral frontal cortices (Fig. 4). The vacuoles were partly seen in the first layer. The distribution of cortical lesions is shown in Figure 5. The lesions were mainly located in the bilateral primary motor cortices. On the left side, the lower part of the primary motor cortex was involved. The deep layers of the cortex were preserved. Neither thrombi nor atherosclerotic changes were observed in the vessels adjacent to the lesions. Alzheimer's type-II astrocytes were absent in the cerebral cortex and basal ganglia. There were no ischemic changes in the hippocampal pyramidal cells or cerebellar Purkinje cells. The Braak stage of neurofibrillary tangles was stage I. There were no Lewy bodies or Pick bodies. In other words, cortical changes cannot be explained by ischemia, hypoxia, hepatocerebral degeneration, or neurodegenerative diseases.

DISCUSSION

Clinically, our patient presented with AOS that improved after the administration of thiamine. He also developed diarrhea and delirium probably associated with pellagra. At autopsy, the diagnosis of Wernicke's encephalopathy and pellagra encephalopathy was confirmed. Furthermore, laminar cortical necrosis with vacuoles and astrocytosis was found in the second and third layers of the bilateral frontal cortices, suggesting Morel's laminar sclerosis.

Thiamine deficiency, which is considered a cause of Wernicke's encephalopathy, damages the mamillary bodies, medial thalamus, and periaqueductal gray matter. Other areas that are sometimes affected include the corpora quadrigemina, reticular formation of the midbrain, pontine tegmentum, superior vermis of the cerebellum,⁸ and inferior olivary nucleus.⁹ Observed lesions include loosening of the neuropil and vascular changes such as hemorrhage, capillary proliferation/dilatation, and endothelial swelling in the mamillary bodies and the subependymal structures

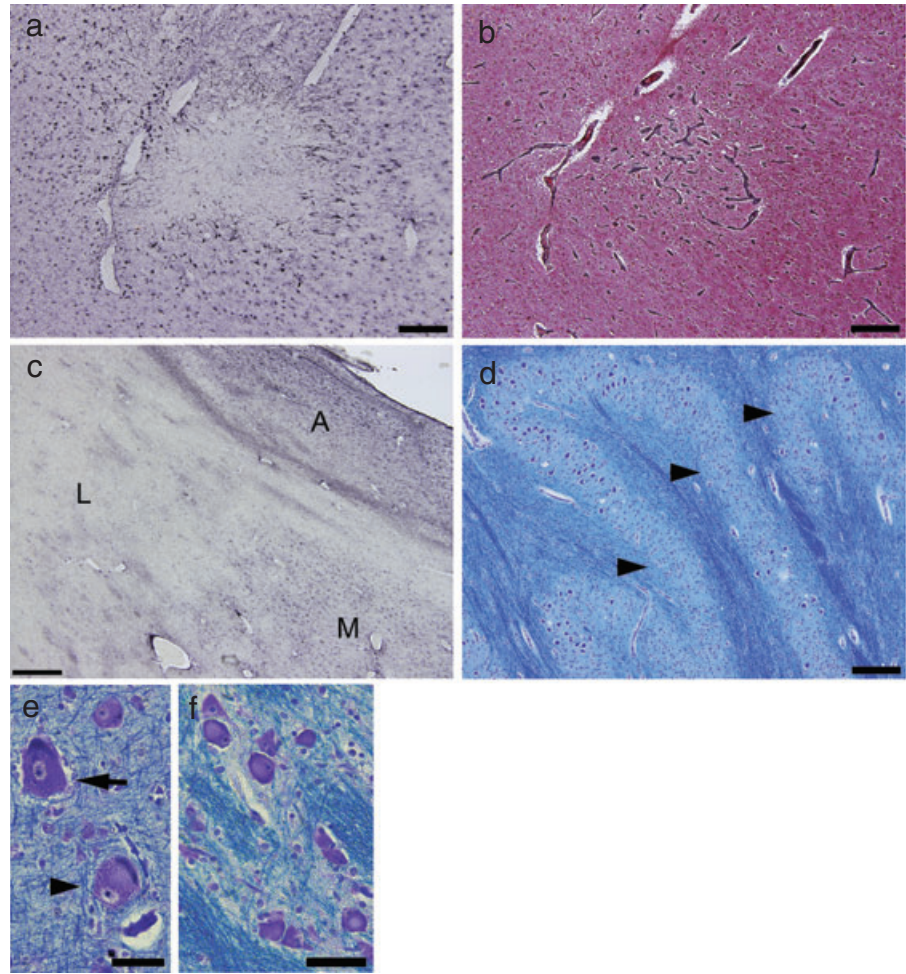


Fig. 3 (a) and (b) are serial sections. (a,b) Central necrosis with astrocytosis (a) and capillary proliferation (b) in the left inferior colliculi. Bar = 200 μ m. (c) Astrocytosis in the mediodorsal nucleus (indicated with M) and anterior nucleus (indicated with A) of the right thalamus, with sparing of the lateral nucleus (indicated with L). Bar = 500 μ m. (d) Patchy neuronal loss in the right inferior olivary nucleus (arrowhead). Bar = 200 μ m. (e) Central chromatolysis of the Betz cell (arrowhead) and a normal Betz cell (arrow). Bar = 50 μ m. (f) Central chromatolysis of the neurons in the pontine nucleus. Bar = 50 μ m. (a, c) GFAP stain, (b) Reticulin silver stain, (d–f) KB stain.

along the aqueduct and fourth ventricle.^{9,10} In the thalamus and inferior olivary nucleus, by contrast, neuronal loss is demonstrated with sparing of the neuropil and capillaries.⁹ The distribution of lesions is associated with abundant thiamine-related glucose and oxygen metabolism.¹¹ Most surgical procedures that include gastrectomy, gastrojejunostomy, colectomy, gastric bypass surgery are risk factors for the development of Wernicke's encephalopathy.⁸

Various CNS disorders are seen in patients with Wernicke's encephalopathy. They include Marchiafava-Bignami disease,⁶ pellagra encephalopathy,¹² and Morel's laminar sclerosis.⁵ To date, pathomechanisms of Marchiafava-Bignami disease or Morel's laminar sclerosis have not been fully understood, although direct intoxication of alcohol or thiamine deficiency is considered to cause these diseases, while pellagra is thought to be caused by niacin deficiency.

Pellagra is classically characterized by a triad of dermatitis, diarrhea and dementia (or derilium), but dermatitis and diarrhea are often lacking.¹³ Coexistence of Wernicke's encephalopathy or Marchiafava-Bignami disease makes

the diagnosis of pellagra difficult. Based on the alcoholic background, thiamine therapy is started in most patients, but niacin is rarely started. Furthermore, antagonism between thiamine and niacin had also been suggested. The metabolic demands from a relative excess of thiamine may increase the requirements for pyridine coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These require niacin as a cofactor. Serudaru *et al.* reported a case of a "late-onset" pellagra encephalopathy in an alcoholic patient who deteriorated after thiamine therapy.¹³ This case and our case suggested that multiple vitamin therapy should be started when treating undiagnosed encephalopathies in patients with chronic alcoholism.

Pellagra encephalopathy presents with various symptoms such as dementia (or derilium), hypertonus, and myoclonus.¹³ Serudaru *et al.* reported that hypertonus and myoclonus were associated with lesions of pontine nucleus and cerebellar dentate nucleus, respectively,¹³ but correlation between the symptoms and brain lesions has not been fully established. Histopathologically, pellagra

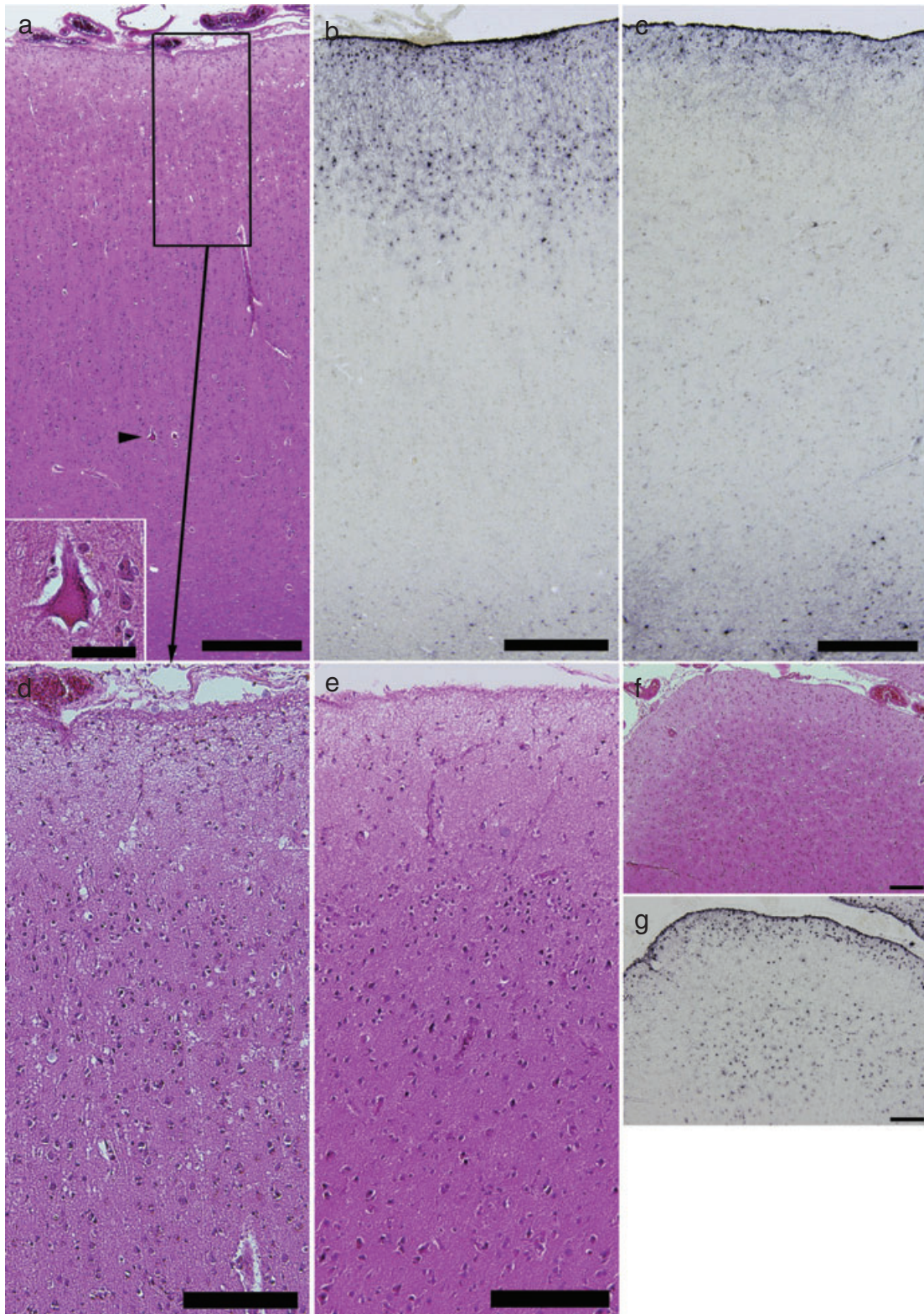


Fig. 4 (a) and (b) are serial sections. (a,b) Laminar cortical necrosis with vacuoles (a) and astrocytosis (b) in the second and third layers of the left primary motor cortex, with some vacuoles in the first layer (a). Bar = 500 μ m. The arrowhead in (a) indicates a Betz cell located in the fifth layer. *Inset* shows this Betz cell. Bar = 50 μ m. The area surrounded by the rectangle in (a) is shown in (d). (c) Normally, astrocytes are present only in the first layer of the cerebral cortex (the left postcentral gyrus of the patient). Bar = 500 μ m. (d) Neuronal loss in the second and third layers. Bar = 200 μ m. (e) There are no abnormalities in the second and third layers of the left postcentral gyrus. Bar = 200 μ m. (f), (g) Another cortical lesion. Bar = 200 μ m. (a), (d-f) HE stain, (b, c, g) GFAP stain.

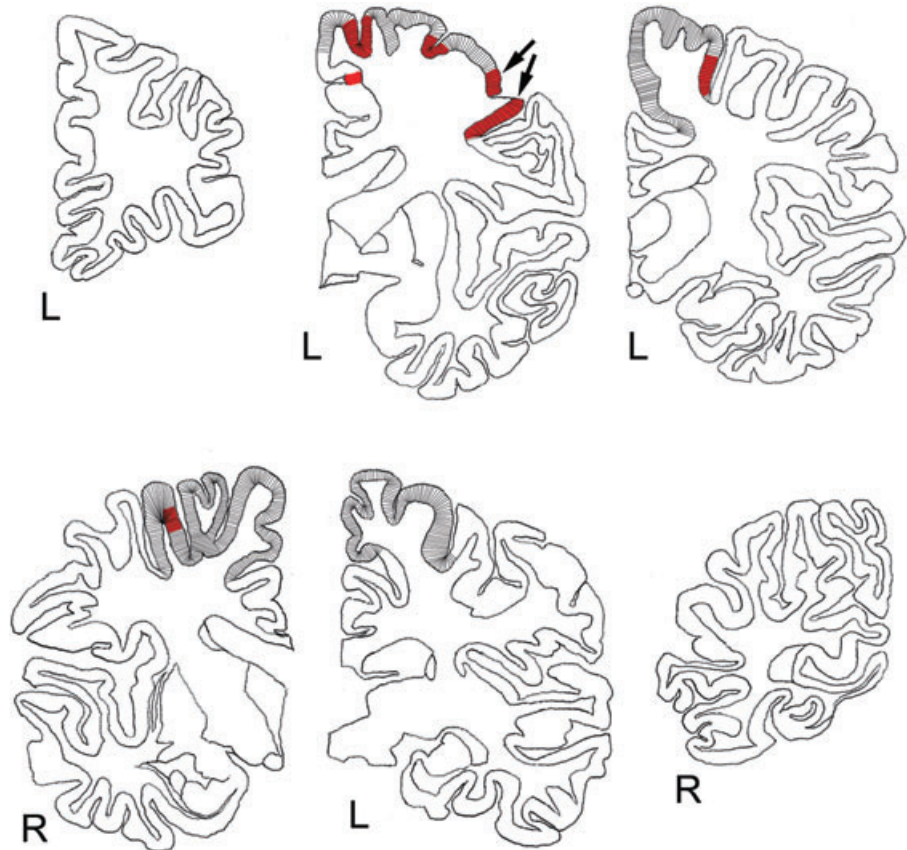


Fig. 5 The primary motor cortices where Betz cells were seen are depicted with lines. The distribution of laminar cortical necrosis with vacuoles and astrocytosis is shown in red. The lesions were mainly located in the bilateral primary motor cortices. On the left side, the lower part of the primary motor cortex was involved (arrows).

encephalopathy is characterized by central chromatolysis of the neurons in the pontine nucleus, where they are constant, in the cerebellar dentate nuclei, nuclei of cranial nerves, gracile and cuneate nuclei, and Betz cells.¹⁴ The central chromatolysis in pellagra is thought to be not a retrograde change but a primary cytoplasmic change.¹⁴

Morel's laminar sclerosis was derived from the publication by Morel describing unusual pathological changes in four alcoholics, demonstrating spongiform change and astrocytosis seen extensively and symmetrically in the cerebral cortex, mostly confined to the third layer.² The review of Morel's laminar sclerosis published by Okeda *et al.* in 1976⁵ described 21 cases of Morel's laminar sclerosis, in which Marchiafava-Bignami disease was seen in 17 cases (81%), and Wernicke's encephalopathy was seen in six cases (30%). They reported that Morel's laminar sclerosis was not seen in the occipital lobe. In their own case, laminar astrocytosis was seen in the third layer of the frontal, parietal, and temporal cortex. Spongiform changes were observed in the adjacent second layer. The lesions were severe in the middle and inferior frontal gyri.⁵ Since 1976, three papers have reported patients with Morel's laminar sclerosis in the English language literature.^{3,4,6} Naeije *et al.* reported that the lesions selectively involved the third and fourth layers of the cortex. Characteristic

changes were neuronal loss, capillary proliferation with thickened endothelia, proliferation of microglial cells, and swollen astrocytes.³ Okeda *et al.* reported that the cerebral cortex presented extensive laminar astrocytosis and/or laminar neuronal loss accompanied by capillary proliferation in the middle layers of the frontal and parietal cortices in case 2.⁴ Sato *et al.* reported that the cerebral cortices showed mild neuronal loss and proliferation of astrocytes, particularly in the third layer.⁶

Recently, by application of MRI, cortical involvement in patients with Wernicke's encephalopathy or Marchiafava-Bignami disease has been increasingly reported.^{11,15-22} Interestingly, the primary motor cortex was involved in most of these cases while the description regarding focal neurological signs was absent. In other words, the regions around the primary motor cortex seem to be sometimes mildly involved in these diseases. Although these reports did not include detailed histological findings, the cortical lesions may reflect Morel's laminar sclerosis¹⁷ or hepato-cerebral degeneration.²³

To date, clinicopathological correlation in Morel's laminar sclerosis has rarely been reported, probably because consciousness disturbance due to concomitant Wernicke's encephalopathy or Marchiafava-Bignami disease masks the symptoms. In our case, spontaneous

speech was impossible on admission, but comprehension of spoken language was good. After the disappearance of consciousness disturbance, we found that the written language was normal, even though the disturbance in speech output was not completely resolved. Although neuropsychological tests were not performed in detail, we considered that his speech disturbance was AOS. The concept of AOS has been controversial and is sometimes called pure anarthria²⁴ or aphemia.^{7,25} AOS is caused by disturbance of motor programming of articulation, and is classically distinguished from Broca's aphasia by the preservation of ability to write language.⁷ The differentiation of AOS from dysarthria is also sometimes difficult. In our case, tongue protrusion was impossible, but speech disturbance was significantly worse than expected. Although AOS has been reported to be caused by brain lesions involving various areas,^{7,24–27} one of the responsible areas is the lower part of the left primary motor cortex.^{25,27}

In conclusion, we report a patient with Morel's laminar sclerosis in whom AOS was seen. Involvement of the lower part of the left primary motor cortex may be associated with AOS in our case.

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