

Case Report

Portal-systemic shunt encephalopathy presenting with diffuse cerebral white matter lesion: An autopsy case

Noriyuki Kimura, Toshihide Kumamoto, Takuya Hanaoka, Kenichiro Nakamura, Yusuke Hazama and Ryuki Arakawa

Department of Neurology and Neuromuscular Disorders, Oita University, Faculty of Medicine, Oita, Japan

We report herein an autopsy case of portal-systemic encephalopathy (PSE) presenting with diffuse tissue rarefaction in the cerebral deep white matter. Clinically, the patient showed recurrent episodes of unconsciousness, abnormal behavior and urinary incontinence, as well as flapping tremor. Cognitive impairment and peripheral neuropathy developed following recurrent episodes. Although conventional arterial portography revealed a small portal-systemic collateral vessel of a left gastro-renal venous shunt, abdominal CT and liver biopsy showed no evidence of liver cirrhosis and serum ammonia level showed a mild increase. T2-weighted MRI demonstrated symmetrical signal hyperintensities in the deep white matter. Neuropathological findings showed Alzheimer type II astrocytes in the deep layers of the cerebral cortices and severe tissue rarefaction with no or slight reactive astrocytosis in the subcortical and deep white matter. These white matter changes have been reported infrequently in patients with PSE. The present case suggests that chronic PSE without liver cirrhosis may develop diffuse white matter lesions.

Key words: Alzheimer type II astrocyte, diffuse white matter lesion, gastro-renal shunt, peripheral neuropathy, portal-systemic encephalopathy.

INTRODUCTION

Portal-systemic shunt occurs due to liver cirrhosis or idiopathic portal hypertension, and plays an important role in

the etiology of recurrent hepatic encephalopathy.¹ In the 1950s, Sherlock *et al.* and White *et al.* emphasized the pathophysiological role of ammonia, which is generated in the intestine and flows directly into the systemic circulation through shunt vessels.^{2,3} This syndrome is thus referred to as portal-systemic encephalopathy (PSE) or Inose's type hepatocerebral degeneration.⁴ In general, PSE is clinically characterized by recurrent episodes of disturbed consciousness and other neurological symptoms such as flapping tremor of the outstretched hands, extrapyramidal symptoms, and hyper-reflexia during the non-episodic period.^{5,6} Hyperintensity in bilateral lenticular nuclei on T1-weighted MRI is the characteristic finding of PSE.⁷ Neuropathological findings show Alzheimer type II cells and spongiform changes in the gray matter.⁸ Some investigators have recently claimed to have observed PSE in patients without liver cirrhosis or portal hypertension.^{9–12} Although clinical and radiological findings were well described, neuropathological examinations of brain tissue from autopsy were limited in those cases.

We encountered an autopsy case of PSE due to congenital gastro-renal shunt without liver cirrhosis and portal hypertension. The patient had experienced recurrent episodes of unconsciousness accompanied by peripheral neuropathy and dementia. Interestingly, pathological findings showed diffuse tissue rarefaction due to severe loss of myelin and axons in the cerebral deep white matter, in addition to Alzheimer type II astrocytes in the cerebral cortex. Although some reports have described diffuse white matter lesions in hepatic encephalopathy, such changes are rare in PSE. We therefore describe the clinico-neuropathological findings of this patient with PSE, and discuss the correlations between MRI and pathological findings.

Correspondence: Noriyuki Kimura, MD, Department of Neurology and Neuromuscular Disorders, Oita University, Faculty of Medicine, Idaigaoka 1-1, Hasama, Yufu, Oita 879-5593, Japan. Email: noriyuki@med.oita-u.ac.jp

Received 5 December 2007; revised 9 January 2008 and accepted 10 January 2008.

CLINICAL SUMMARY

A 61-year-old Japanese woman developed fever, pain in the upper extremity and confusional state, despite good health until November 1993. Symptoms lasted for 24 h, and then subsided without treatment. She had experienced the same episodes twice before admission. Episodes would vary in duration from 24 h to 2 weeks and did not correlate with dietary changes or any other specific factors. She was admitted to our hospital on April 24, 1996, due to recurrent episodes of disturbed consciousness, abnormal behavior and urinary incontinence. No history of alcohol or drug abuse or significant family history could be elicited. On admission, no signs of liver disease were apparent such as jaundice, hepatosplenomegaly or vascular spider, with the exception of mild palmar erythema. Neurological examination showed drowsy state, disorientation and abnormal behavior such as restlessness and loud crying. Cranial nerve signs and muscle strength were normal, but muscle tone and deep reflexes were decreased. Flapping tremor of bilateral hands appeared occasionally. She displayed severe painful paresthesia in the extremities. No other neurological signs were identified, such as dysarthria, incoordination or extrapyramidal signs.

Laboratory findings revealed normal blood count and mild liver dysfunction as follows: aspartate aminotransferase, 211 IU/L (normal, 13–33 IU/L); alanine aminotransferase, 257 IU/L (normal, 6–27 IU/L); γ -glutamyl transferase, 113 IU/L (normal, 10–47 IU/L). Serum ammonia level was mildly increased at 42 μ mol/L (normal, 9–33 μ mol/L). Molar ratio of branched-chain amino acids (leucine, isoleucine and valine) to aromatic amino acids (tyrosine and phenylalanine) had decreased to 2.25 (normal, 2.43–4.40). An indocyanine green test showed 15% retention at 15 min (normal, <10%). Serum copper and ceruloplasmin levels were normal. Hepatitis B surface antigen and antibody were both negative, as was a test for hepatitis C virus antibody. A test for antinuclear antibody was positive, but antimitochondrial antibody and antismooth muscle antibodies were negative. Serum and urinary amino acid analyses yielded normal results. Specific patterns of aminograms as in citrullinaemia and argininosuccinic aciduria, which usually accompany hyperammonaemia, were not identified. White blood lysosome enzyme assay showed normal results. Blood levels of very-long-chain fatty acids were within normal limits. Analysis of CSF was unremarkable for cells, protein and glucose. EEG showed a diffuse θ wave, but not triphasic waves. Brain MRI demonstrated symmetrical signal hyperintensities in the deep cerebral white matter on T2-weighted imaging, but no signal abnormalities in bilateral basal ganglia on T1-weighted imaging (Fig. 1a,b). Sonography and CT of the abdomen showed no abnormalities, including shunt

vessels. Endoscopic examination did not reveal esophageal or gastric varices or *Helicobacter pylori* infection. Ultrasound-guided fine needle liver biopsy showed mild lymphocytic infiltration without fibrosis in the portal tracts, indicating autoimmune hepatitis without liver cirrhosis. Conventional arterial portography disclosed a small portal-systemic collateral vessel of a left gastro-renal venous shunt (Fig. 1c). However, both the radiologist and gastroenterologist excluded the contribution of the shunt to recurrent episodes of unconsciousness because the size of the shunt vessel was insufficient to result in encephalopathy. Therefore the diagnosis of PSE could not be confirmed, and the hyperammonaemia might occur due to unknown causes. Conservative treatments such as administration of lactulose and infusion of branched-chain amino acid-enriched solution were performed for normalization of blood ammonia levels. The patient became free from episodes of loss of consciousness after several days of these treatments and was discharged on July 17.

The patient was subsequently admitted to our hospital with similar episodes twice over the next 3 years. Although neurological symptoms and laboratory data were almost the same as on first admission, cognitive function deteriorated (Mini-Mental State Examination, 21 points; revised Wechsler Adult Intelligence Scale, 80 points). In addition, a nerve conduction study revealed reduced conduction velocity of motor and sensory nerves in all extremities. Pathological findings of sural nerve biopsy revealed segmental demyelination and myelinated fiber loss without vascular inflammation (Fig. 2h). A density of the myelinated fibers revealed a decrease number of both large-diameter and small-diameter fibers. Teased-fiber analysis showed 53% were normal fibers, 43% had segmental demyelination and segmental remyelination, 1% had axonal degeneration, and 3% were unclassifiable.

Follow-up MRI demonstrated that cerebral white matter lesions extended from deep to subcortical white matter. Disturbance of consciousness was also improved for a few days with antihyperammonaemia therapy, but neurological symptoms including cognitive impairment continued to worsen and the patient died of pulmonary embolism in November 2001. Total duration from onset of the first episode to death was 8 years.

PATHOLOGICAL FINDINGS

Macroscopic findings

The brain, weighing 1100 g after fixation, showed slight cerebral atrophy. Coronal sections revealed moderate atrophy of cerebral white matter with dilatation of the lateral ventricle. Tissue softening was observed diffusely in the white matter. Multiple small lesions with greyish dis-

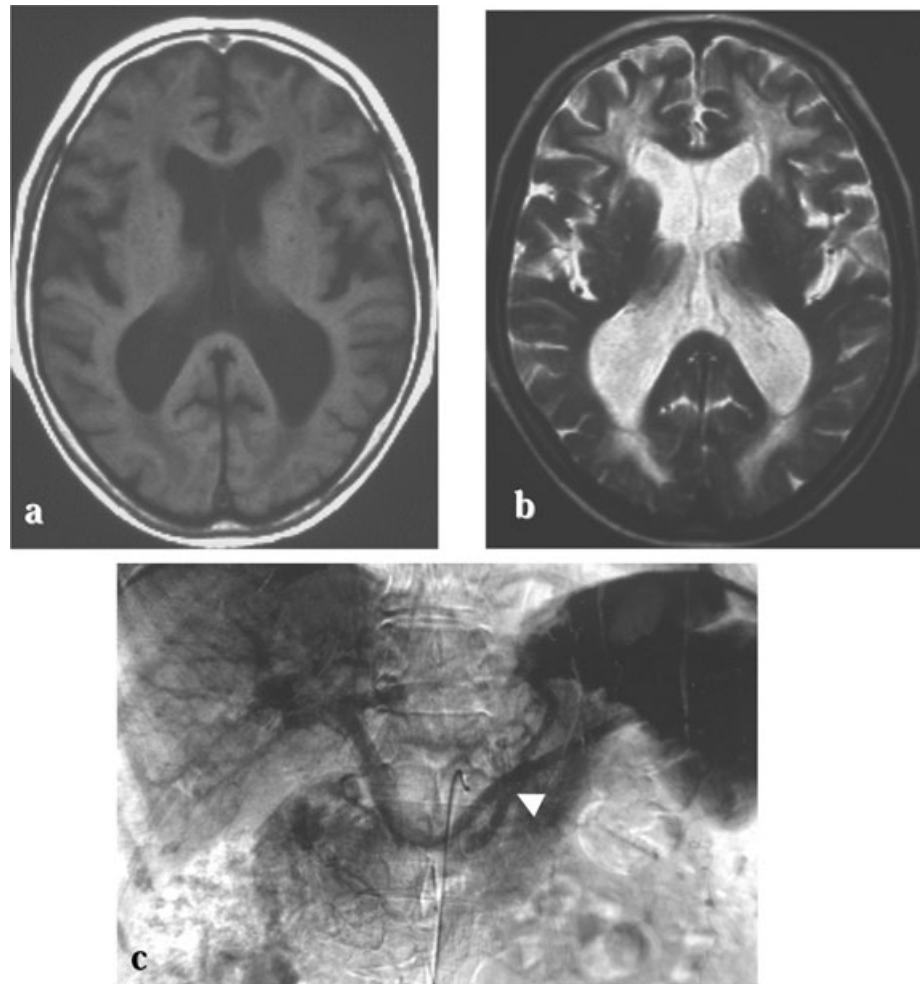


Fig. 1 T1- and T2-weighted MRI and conventional arterial portography. (a) T1-weighted MRI shows no abnormal signals in bilateral basal ganglia. (b) T2-weighted MRI shows diffuse signal hyperintensities in the deep cerebral white matter. (The right side is shown on the left-hand side of each figure). (c) Conventional arterial portography revealed small portal-systemic collateral vessel of a left gastro-renal venous shunt (arrowhead).

coloration were scattered in the subcortical white matter (Fig. 2a). Deep white matter revealed diffuse greyish discoloration. The cerebral cortex, subcortical gray matter, brainstem and cerebellum appeared normal.

Microscopic findings

Histological examinations were performed using HE, KB and Bielschowsky stains and immunohistochemical methods. HE staining revealed slight dilatation of perivascular and perineuronal spaces in the deep layer of the cerebral cortex (Fig. 2b), multiple focal tissue rarefaction in the subcortical white matter, and diffuse tissue rarefaction in the deep white matter (Fig. 2c). Bilateral putamina, globus pallidi, caudate nuclei and thalami were well preserved. There were Alzheimer type II astrocytes (Fig. 2d), which showed large, pale nuclei with marginated chromatin and scanty cytoplasm, some in the cerebral cortices, globus pallidus, and thalamus, a few in the putamen, caudate nucleus, and claustrum. No Alzheimer type I glial cells or Opalski's cells were present. KB and Bielschowsky staining

revealed severe myelin pallor and axonal loss in the subcortical and deep white matter, including the U-fiber area (Fig. 2e,f). Subcortical white matter lesions were small and distributed in multiple regions, whereas deep white matter lesions were most severe and diffusely extended. Conversely, the internal capsule and pyramidal tract of the brainstem and cerebellar white matter were relatively spared. Immunostaining for GFAP (Dako, Glostrup, Denmark) showed no or only slight proliferation of reactive astrocytes in the cerebral cortex and white matter lesion (Fig. 2g). Proliferation of reactive astrocytes was slight compared with the severity of tissue degeneration. These pathological findings were observed at almost the same intensity throughout the frontal, temporal and occipital lobes. No fat-laden macrophages or metachromatic substance were evident. No arteriosclerosis or infiltration of inflammatory cells was evident in the cerebral white matter. Senile plaques and neurofibrillary tangles were not observed in the hippocampus. These pathological findings were consistent with hepatic encephalopathy and final diagnosis was PSE without portal hypertension and liver cirrhosis.

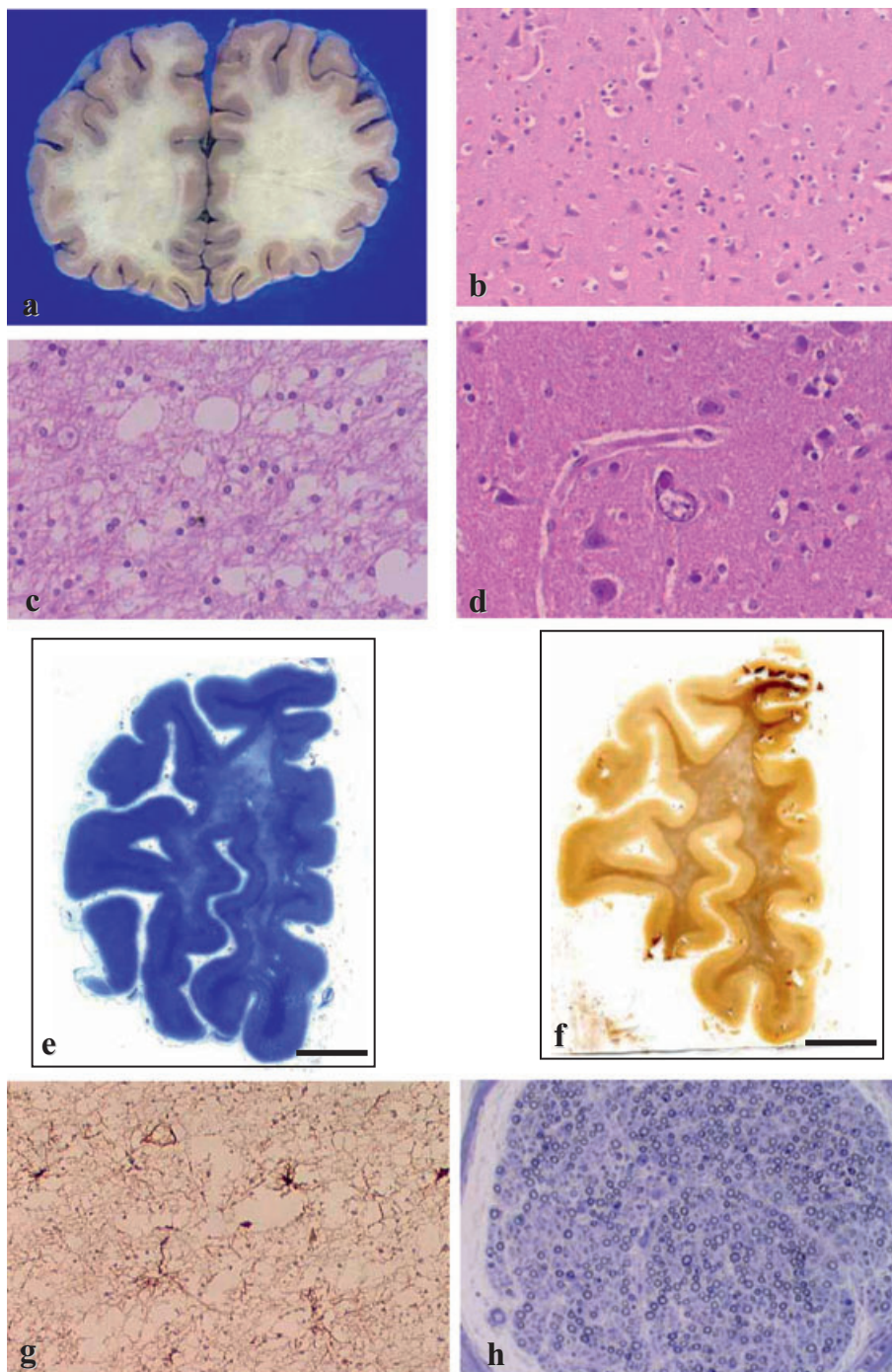


Fig. 2 (a) Multiple small lesions with greyish discoloration were scattered in the subcortical white matter. Diffuse greyish discoloration in the deep white matter. (b) Slight dilatation of perivascular and perineuronal space in the deep layer of the cerebral cortex (HE $\times 50$). (c) Severe tissue rarefaction in white matter (HE $\times 100$). (d) Alzheimer type II astrocytes in the cerebral cortex. (HE $\times 200$). (e) Severe tissue rarefaction with loss of myelin in the frontal lobe (KB, scale bars 1 cm). (f) Severe tissue rarefaction with loss of axons in the frontal lobe (modified Bielschowsky, scale bars 1 cm). (g) Slight proliferation of reactive astrocytes (immunostain for GFAP $\times 100$). (h) Biopsy specimens from sural nerve showing the loss of large myelinated fibers. (Toluidine blue, $\times 50$).

DISCUSSION

The clinical picture in the present case was characterized by recurrent episodes of confusion, flapping tremor, cognitive impairment and polyneuropathy. Laboratory data showed slight hyperammonaemia and MRI demonstrated diffuse white matter lesions. A lysosomal enzyme, amino acid and long-chain fatty acid analysis excluded the known leukodystrophies and inherent metabolic disorders.

Although conventional arterial portography identified left gastro-renal shunt, the patient showed no sign of portal hypertension or liver cirrhosis. Venous shunt was thought to be congenital, because of the lack of any prior history of abdominal disease, trauma or operation until admission. To conclude that the gastro-renal shunt contributed to neurological symptoms is difficult, because of the slight increase in serum ammonia level and small shunt vessels. The shunt vessels were large enough to develop the encephalopathy

and serum ammonia levels were high in previous reports of PSE.^{9–12}

However, pathological findings were consistent with PSE, with the exception of severe tissue rarefaction due to severe loss of myelin and axons in the cerebral deep white matter. Thus PSE was diagnosed on the basis of neurological symptoms and pathological findings. Patients with PSE without portal hypertension or liver cirrhosis are often misdiagnosed with dementia or other psychoneurological diseases and occasionally hospitalized in psychiatric departments.⁶ This report suggests that a slight increase in serum ammonia and very small shunt vessels might be sufficient to cause development of PSE.

Peripheral demyelinating neuropathy was one of the clinical features in our patient. Nerve conduction studies for patients with liver disease have shown that both demyelination and axonal degeneration could develop.¹³ Two factors postulated for hepatic neuropathy are portal-systemic shunt and hepatocellular damage,¹⁴ so portal-systemic shunt appears to have been involved as a cause of peripheral neuropathy in the present case.

Neuropathological findings in PSE commonly include pseudolaminar spongiform change associated with numerous Alzheimer type II astrocytes in the deep layers of cerebral cortices and loss of myelin and axons in the subcortical white matter. Alzheimer type II astrocytes are distributed to the cerebral cortex, basal ganglia and cerebellum.¹⁵ In the present case, neuropathological evaluation also demonstrated slight dilatation of perivascular and perineuronal spaces in the cerebral cortex with some Alzheimer type II astrocytes, which displayed a limited distribution to the cerebral cortex and basal ganglia. These findings may be attributed to a slight increase in serum ammonia levels due to small shunt vessels. In addition, degeneration of deep white matter with diffuse tissue rarefaction was a unique pathological finding, corresponding to hyperintensity on T2-weighted MRI. We suggest that the portal-systemic shunt participated in the development of cerebral white matter lesions, which expanded with disease progression. Although we were not able to find a similar case in the literature, some MRI studies reported on the cerebral deep white matter lesions in hepatic encephalopathy.^{16–18} They suggested that cerebral white matter lesions might be due to mild brain edema by the impairment of the blood–brain barrier. Several experimental studies have suggested that swelling of cerebral cortical astrocytes is observed following ammonia infusion in primates or exposure of primary astrocyte cultures to ammonia.^{19,20} We speculate that tissue rarefaction in the white matter may have been caused by chronic brain edema due to dysfunction of astrocytes in the present case. Further studies are needed to clarify correlations between brain edema and astrocyte dysfunction in PSE.

REFERENCES

1. Hazell AS, Butterworth RF. Hepatic encephalopathy: an update of pathophysiologic mechanisms. *Proc Soc Exp Biol Med* 1999; **222**: 99–112.
2. Sherlock S, Summerskill WH, White LP, Phear EA. Portal-systemic encephalopathy; neurological complications of liver disease. *Lancet* 1954; **267**: 454–457.
3. White LP, Phear EA, Summerskill WH, Sherlock S. Ammonium tolerance in liver disease: observations based on catheterization of the hepatic veins. *J Clin Invest* 1955; **34**: 158–168.
4. Inose T. Hepatocerebral degeneration, a special type. *J Neuropathol Exp Neurol* 1952; **11**: 401–408.
5. Watanabe A. Portal-systemic encephalopathy in non-cirrhotic patients: classification of clinical types, diagnosis and treatment. *J Gastroenterol Hepatol* 2000; **15**: 969–979.
6. Yokota T, Tsuchiya K, Umetani K, Furukawa T, Tsukagoshi H. Choreoathetoid movements associated with a spleno-renal shunt. *J Neurol* 1988; **235**: 487–488.
7. Inoue E, Hori S, Narumi Y *et al.* Portal-systemic encephalopathy: presence of basal ganglia lesions with high signal intensity on MR images. *Radiology* 1991; **179**: 551–555.
8. Victor M, Adams RD, Cole M. The acquired (non-Wilsonian) type of chronic hepatocerebral degeneration. *Medicine* 1965; **44**: 345–396.
9. Konno K, Ishida H, Uno A, Ohnami Y, Masamune O. Large extrahepatic portosystemic shunt without portal hypertension. *Abdom Imaging* 1997; **22**: 79–81.
10. KCS, Matsutani S, Maruyama H *et al.* Portal-systemic encephalopathy in two patients without liver cirrhosis and portal hypertension. *Hepatol Res* 2002; **23**: 122–129.
11. Nishimoto Y, Hoshino H, Sato S *et al.* Extrahepatic portosystemic venous shunt without portal hypertension. *Intern Med* 1997; **36**: 886–889.
12. Watanabe M, Fukusato T. Extrahepatic portal-systemic encephalopathy without portal hypertension. *Intern Med* 1998; **37**: 716–717.
13. Kharbanda PS, Prabhakar S, Chawla YK, Das CP, Syal P. Peripheral neuropathy in liver cirrhosis. *J Gastroenterol Hepatol* 2003; **18**: 922–926.
14. Chopra JS, Samanta AK, Murthy JM, Sawhney BB, Datta DV. Role of porta systemic shunt and hepatocellular damage in the genesis of hepatic neuropathy. *Clin Neurol Neurosurg* 1980; **82**: 37–44.
15. Butterworth RF, Giguère JF, Michaud J, Lavoie J, Layrargues GP. Ammonia: key factor in the pathogenesis of hepatic encephalopathy. *Neurochem Pathol* 1987; **6**: 1–12.

16. Matsusue E, Kinoshita T, Ohama E, Ogawa T. Cerebral cortical and white matter lesions in chronic hepatic encephalopathy: MR-pathologic correlations. *AJNR* 2005; **26**: 347–351.
17. Yuki N, Yoshioka A, Yamaya Y, Saiki M, Hirose G. A case of portal-systemic shunt encephalopathy due to congenital portal vein hypoplasia presenting with abnormal cerebral white matter lesions on the MRI. *Rinsho Shinkeigaku* 2002; **42**: 544–547.
18. Minguez B, Rovira A, Alonso J, Cordoba J. Decrease in the Volume of white matter lesions with improvement of hepatic encephalopathy. *AJNR* 2007; **28**: 1499–1500.
19. Pilbeam CM, Anderson RM, Bhathal PS. The brain in experimental portal-systemic encephalopathy. I. Morphological changes in three animal models. *J Pathol* 1983; **140**: 331–345.
20. Norenberg MD, Lapham LW, Nichols FA, May AG. An experimental model for the study of hepatic encephalopathy. *Arch Neurol* 1974; **31**: 106–109.