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Diffusion-weighted MR imaging of Carmofur-induced leukoencephalopathy

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Abstract Carmofur (1-hexylcarbamyl-5-fluorouracil), a derivative of 5-fluorouracil (5-FU), has been widely used in Japan as a postoperative adjuvant chemotherapy agent for colorectal and breast cancer. Periventricular hyperintensity on T2-weighted MR images in carmofur-induced leukoencephalopathy confront the physician with a broad range of differential diagnoses. We describe two cases of carmofur-induced leukoencephalopathy in which diffusion-weighted MR imaging revealed periventricular hyperintensity. We compared their findings with those of age-related periventricular hyperintensity in five patients and found discrepancies in signal intensity of periventricular areas. Our results suggest that diffusion-weighted MR imaging may be useful to differentiate carmofur-induced leukoencephalopathy from age-related periventricular hyperintensity.

Keywords Leukoencephalopathy · Chemotherapy · MR imaging · Leukomalacia · Fluorouracil

Introduction

Carmoful is an oral anticancer drug that has potential activity in vitro. Because of its ease of long-term oral administration, this agent has been used as postoperative adjuvant chemotherapy in Japan to date.

The frequency of carmofur-induced neurotoxicity has been reported to be less than 5 % in patients treated with carmofur [1]. Among them, the frequency of carmofur-induced leukoencephalopathy, severe neurotoxic side effect, is well-known but considered rare. Approximately 50 cases of carmofur-induced leukoencephalopathy have been reported in the international literature since Ohkoshi et al. [2] reported the first case in 1983.

Common initial symptoms of carmofur neurotoxicity are dizziness, numbness, memory deficit, cognitive impairment, and unsteady gait. In cases of leukoencephalopathy as severe carmofur neurotoxicity, stupor, akinetic mutism, or even coma can occur. Even after the drug is discontinued, subacute deterioration in consciousness, dementia, and muscle rigidity can be seen. In most cases, however, gradual improvement is expected to occur [1, 3, 4].

There is no clear relationship between severity of carmofur neurotoxicity and the duration and the total dose of carmofur administered by the time of onset of neurological symptoms.

Several investigators have reported the neuroradiologic findings of carmofur-induced leukoencephalopathy [3, 4, 5, 6]. Common findings include symmetrical periventricular hypoattenuation on CT and diffuse hyperintensity in the white matter on T2-weighted MR images; however, diffusion-weighted MR imaging findings had never been reported, to our knowledge. Since diffusion-weighted MR images reflect microscopic diffusibility of protons, this technique may provide a clue

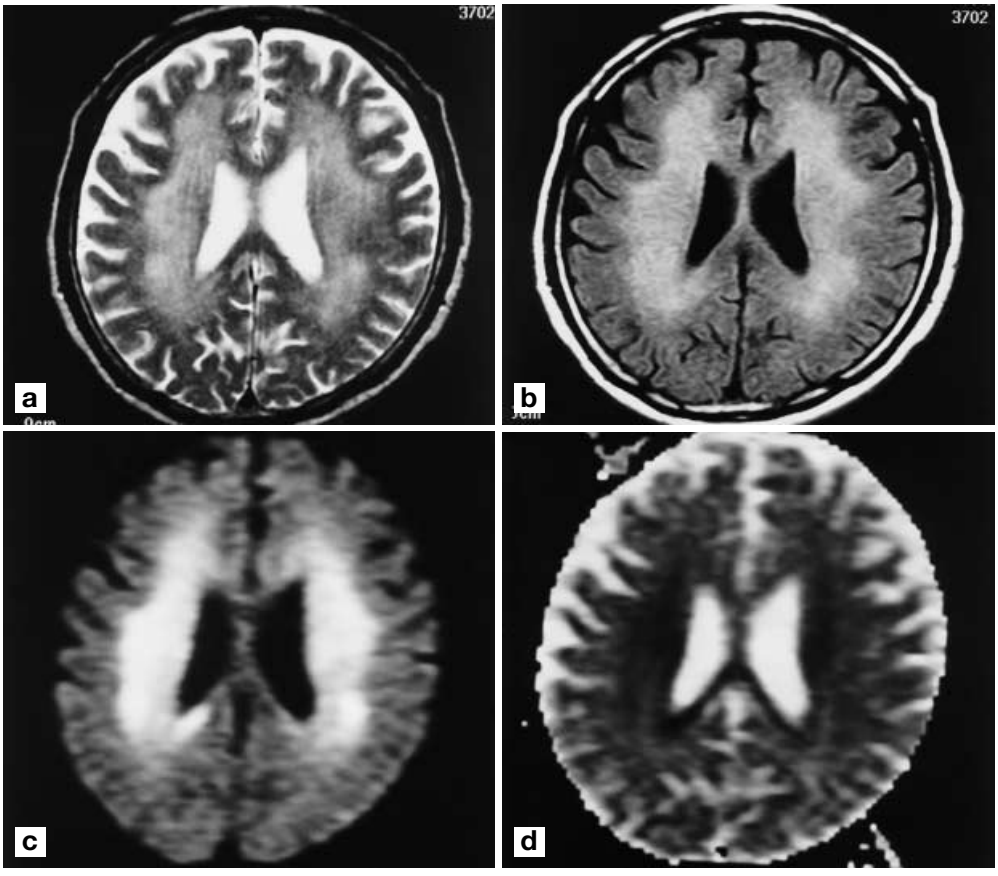

Fig. 1 a–d Case 1. A 59-year-old man with carmofur-induced leukoencephalopathy. **a** T2-weighted fast spin-echo (TR/TE = 4000 ms/100 ms, no. of excitations = 1, section thickness = 5 mm), and **b** fluid-attenuated inversion recovery (FLAIR; TR/TE = 6000 ms/120 ms, no. of excitations = 2, section thickness = 5 mm, TI = 2200 ms) image showing hyperintensity in the periventricular white matter. **c** Isotropic diffusion-weighted image, and **d** corresponding apparent diffusion coefficient (ADC) map showing periventricular hyperintensity and a corresponding decrease in ADC value

to assess the pathologic mechanisms of signal intensity alterations [7].

In this report we describe the diffusion-weighted MR imaging findings of carmoful-induced leukoencephalopathy and assess whether diffusion-weighted MR imaging makes it possible to differentiate carmoful-induced leukoencephalopathy from age-related periventricular hyperintensity.

Case reports

Case 1

A 59-year-old man who had undergone colectomy for sigmoid colon cancer was being treated with carmofur as postoperative adjuvant chemotherapy. One month after the start of carmofur at a daily dose of 900 mg, he complained of dysphasia and dizziness. On admission, brain MR imaging was performed at 1.5 T and showed periventricular hyperintensity on T2-weighted spin-echo and fluid-attenuated inversion recovery (FLAIR) images. There was no area of abnormal intensity on the pre- and postcontrast T1-weighted images. On the same occasion, diffusion-weighted images were obtained using a single-shot echo-planar sequence by applying a motion-probing gradient in the x, y, and z directions having b values of 1089, 1089, and 1208 s/mm^2 , respectively. Isotropic diffusion-weighted images were generated from data obtained, and they revealed an extensive area of hyperintensity in the periventricular white matter that was more prominent than on the T2-weighted spin-echo and FLAIR images (Fig. 1). Calculated apparent diffusion coefficient (ADC) maps showed an area of hypointensity corresponding to the abnormality on the diffusion-weighted images. The corpus callosum and posterior fossa components were normal in signal intensity on MR study. When the total dose reached 50.1 g, carmofur was discontinued. The patient received no other treatment that could produce leukoencephalopathy. The patient subsequently developed mild to moderate disturbance of consciousness. Follow-up MR imaging 3 months after the initial MR examination showed no interval change in the periventricular abnormality on T2-weighted and diffusion-weighted images. The ADC mapping was not performed. The patent died of multiple pulmonary metastases 6 months after admission.

Case 2

A 38-year-old woman underwent left mastectomy for invasive ductal carcinoma. The regimen of oral carmofur, 600 mg daily, was commenced as postoperative adjuvant chemotherapy. On day 13 after the start of chemotherapy, the patient began to complain of headache and nausea and was treated by supportive therapy. Two months later, she was brought to our hospital by the police after having been found wandering about confused and disoriented as to person and place. Immediately after admission to the psychiatric ward, she suddenly developed moderate disturbance of consciousness, followed by muscle rigidity. Brain CT scans obtained on ad-

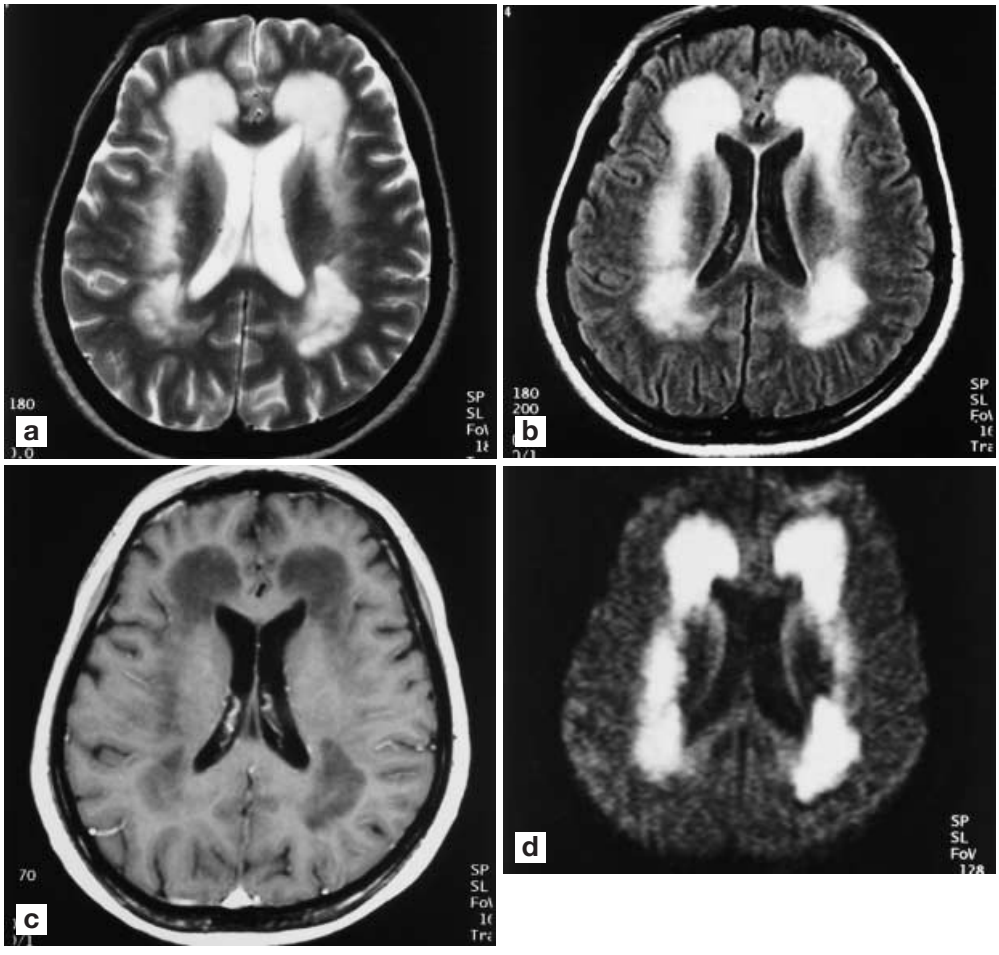

Fig. 2 a–d Case 2. A 38-year-old-woman with carmofur-induced leukoencephalopathy. **a** T2-weighted fast spin-echo (TR/TE = 4000 ms/90 ms, no. of excitations = 1, section thickness = 5 mm), **b** FLAIR (TR/TE = 6000 ms/119 ms, no. of excitations = 1, section thickness = 5 mm, TI = 2200 ms), and **c** contrast-enhanced T1-weighted spin-echo (TR/TE = 500 ms/14 ms, no. of excitations = 2, section thickness = 5 mm) images showing the periventricular area of prolonged T1 and T2 without contrast enhancement. **d** Diffusion-weighted image with a motion-probing gradient of 1192 s/mm^2 applied in the z direction showing conspicuous hyperintensity in the periventricular area

mission showed extensive periventricular low attenuation sparing the basal ganglia and thalamus. Brain MR imaging at 1.5 T performed on the sixth hospital day revealed areas of hyperintensity on T2-weighted spin-echo and FLAIR images and areas of hypointensity relative to the cortex on T1-weighted images, which corresponded to the areas of low attenuation on the brain CT scans. Echo-planar diffusion-weighted imaging was performed by applying a motion-probing gradient in the z direction with a b value of 1192 s/mm^2. The diffusion-weighted images revealed periventricular areas of marked hyperintensity that corresponded to the areas of hyperintensity seen on T2-weighted spin-echo and FLAIR images (Fig. 2). There is no signal abnormality in the corpus callosum and posterior fossa components. Gadolinium-enhanced T1-weighted imaging showed no evidence of metastasis. Since the MR findings suggested carmofur-induced leukoencephalopathy, the carmofur was discontinued. The total dose of carmofur administered was 51 g. Oxygen hyperbaric pressure therapy was started to treat the progressive consciousness disturbance of and muscle rigidity. Three months after admission, she was able to speak a couple of words spontaneously. Follow-up MR examinations were repeated during the period of 3 years in that the patient repeated hospitalization for the purpose of rehabilitation. An MR examination performed 20 months after the initial MR study showed slightly decreased periventricular hyperintensity on T2-weighted and diffusion-weighted images. An MR examination performed 14 months later demonstrated continuously decreased area of periventricular abnormal signal intensity on T2-weighted and diffusion-weighted MR images and significant cerebral atrophy. The patient was referred to another institution to continue on a rehabilitation program for persistent muscle rigidity and impaired consciousness.

Comparison group

Isotropic diffusion-weighted MR imaging, as described in case 1, was performed in addition to the routine MR protocol in five patients with extensive periventricular areas of hyperintensity on T2-weighted spin-echo MR images. The patient group consisted of three men and two women (mean age 74 years; age range age 66–83 years), who had headache, gait disturbance, or dementia, and were referred for brain MR examinations. None of them had a remarkable medical history except for antihypertensive therapy. Isotropic diffusion-weighted images of the patients showed no areas of abnormal intensity corresponding to the periventricular or subcortical areas of hyperintensity on the T2-weighted spin-echo images. With one of the comparison group, ADC map was obtained. No decreased ADC value was seen in the periventricular region (Fig. 3). In these five patients, a presumed radiological diagnosis of age-related periventricular hyperintensity was made on the basis of the MR imaging findings and clinical history.

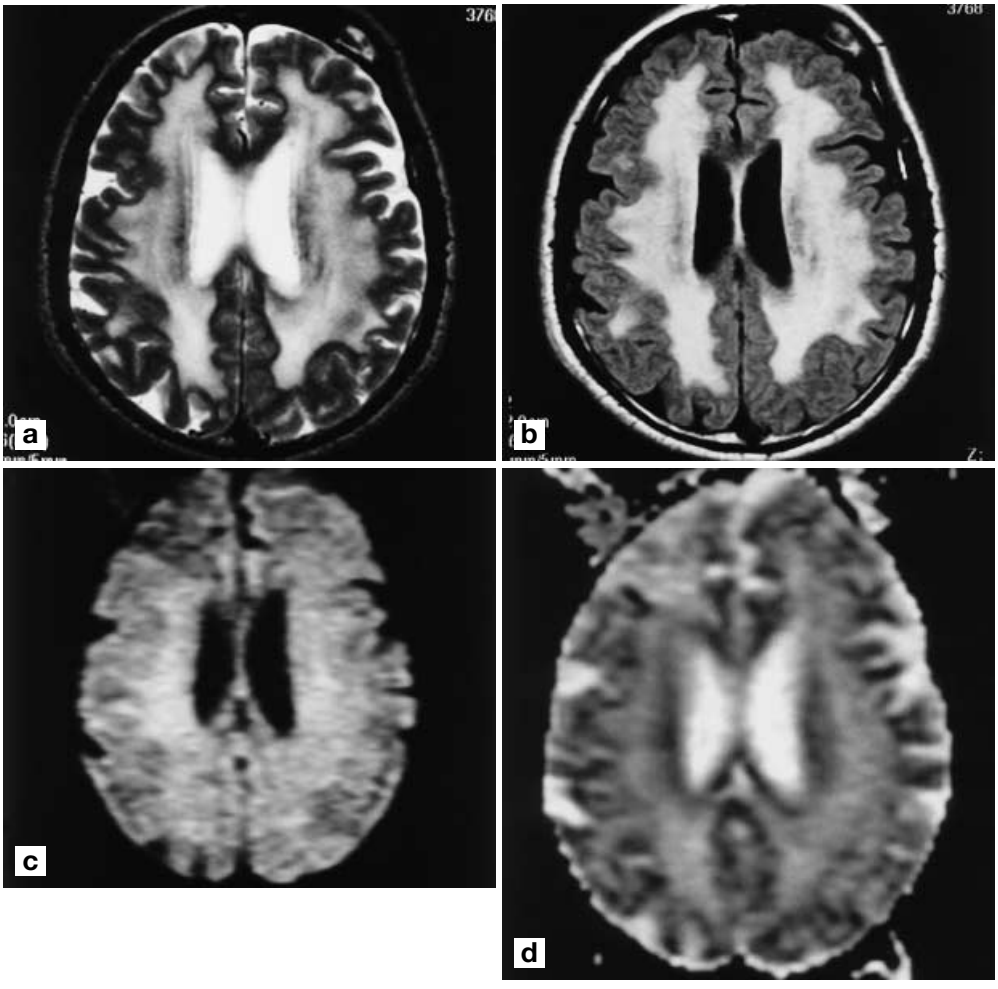

Fig. 3 a–d Comparison case. A 66-year-old man with age-related periventricular hyperintensity. **a** T2-weighted fast spin-echo (TR/TE = 4000 ms/100 ms, no. of excitations = 1, section thickness = 5 mm), and **b** FLAIR (TR/TE = 7000 ms/120 ms, no. of excitations = 2, section thickness = 5 mm, TI = 2200 ms) images showing extensive periventricular hyperintensity. **c** Isotropic diffusion-weighted image showing the absence of any prominent signal change in the periventricular white matter. **d** Corresponding ADC map showing no diffusion decrease in the periventricular region

Discussion

We obtained echo-planar diffusion-weighted MR images in two cases, in one of which ADC mapping was performed in addition to isotropic diffusion-weighted imaging. Diffusion-weighted images demonstrated an area of marked hyperintensity in the periventricular white matter in both cases. A corresponding decrease in ADC was observed in one case, but in the other case, however, we were unable to calculate the ADC values because two different diffusion gradient values were not used in diffusion-weighted imaging.

Our findings of hyperintensity on diffusion-weighted images with a corresponding decreased ADC value probably indicate cytotoxic edema in the involved region, as seen in acute ischemia, not interstitial fluid accumulation, such as seen in vasogenic edema.

Okeda et al. [8, 9] investigated carmofur-induced encephalopathy neuropathologically in dogs and cats, and found intramyelinic edema, including vacuole formation. Vacuoles measured 20–50 μm in diameter and were produced by splitting of the intraperiod line of myelin and necrosis without myelin destruction. The myelin vacuolation they observed presumably restricts fluid motion within myelin. Their findings strongly support our speculation that the diffusion-weighted imaging features of carmofur-induced leukoencephalopathy represent intracellular edema resulting from neurotoxicity, although their findings were experimentally obtained by using animals and may not be directly extrapolated to humans.

In case 2 we were able to perform long-term follow-up with MR examinations that demonstrated gradual interval reduction of periventricular hyperintensity in size on T2-weighted and diffusion-weighted MR mages and diffuse cerebral atrophy approximately 3 years later from the onset of neurological symptoms. The patient's symptoms, however, had not been significantly improved. We think that decreased size of the abnormal signal intensity may be due mainly to loss of the bran tissue volume rather than improvement of leukoencephalopathy.

Age-related periventricular hyperintensity is a term used to describe the neuroradiologic features of the white matter, including hypoattenuation on CT, hyperintensity on T2-weighted MR images, and the absence of contrast enhancement or a mass effect, which are etiologically unrelated to infection, inflammation, or demyelination [10]. These MR imaging findings are similar to those of carmofur-induced leukoencephalopathy. In our cases, the findings obtained by the routine MR imaging protocol were of limited value for differentiating carmofur-induced neurotoxicity from age-related periventricular hyperintensity. Although the clinical manifestations of age-related periventricular hyperintensity are generally minor compared with the radiologic observations, extensive and severe forms of age-related periventricular hyperintensity can manifest cognitive and motor dysfunction. For this reason, diffusion-weighted MR imaging can be expected to play an important role in making the correct diagnosis.

We found the differences between the diffusion-weighted MR imaging findings in carmofur-induced leukoencephalopathy and age-related periventricular hyperintensity. The MR images in the former revealed significant hyperintensity on diffusion-weighted images in the periventricular white matter, whereas the diffusion-weighted images in the latter showed a lack of any abnormal findings that corresponded to the hyperintensity on T2-weighted images.

The histologic findings in age-related periventricular hyperintensity consist of a variable degree of axonal loss, demyelination, astrocytosis, diffuse neutrophil vacuolation, and hyalinotic arteriolar thickening [10]. We speculate that an increased volume of interstitial space due to reduction of axon and myelin in age-related periventricular hyperintensity markedly increases the mobility of the fluid in the extracellular space in the white matter, and we think that explains the absence of any abnormal intensity in the affected white matter on diffusion-weighted MR images in age-related periventricular hyperintensity. It is emphasized, however, that the potential limitations in this report include the small sample size and the lack of histologic confirmation of the MR imaging findings.

Differential diagnosis of periventricular white matter hyperintensity on diffusion-weighted MR images includes cisplatin neurotoxicity [11], global cerebral anoxia on late subacute period [12], and other cytotoxic processes. Suggestive diagnosis of carmoful-induced leukoencephalopathy, however, is readily obtained after knowing the patient's clinical history.

In conclusion, diffusion-weighted MR imaging provides significant information on the pathogenesis of carmofur-induced neurotoxicity that is likely to result from cytotoxic edema. The discrepancy in the signal intensity changes on diffusion-weighted MR images may be a clue to differentiation between carmofur-induced leukoencephalopathy and the severe form of age-related periventricular hyperintensity. Our experience also suggests that diffusion-weighted MR imaging may facilitate the prompt diagnosis of carmofur-induced leukoencephalopathy, which may lead to possible reverse of clinical symptoms.

References

1. Japan Pharmaceutical Information Center (2001) Drugs in Japan, 24th edn
2. Ohkoshi N, Kanazawa I, Nakanishi T, Tohata K, Koizumi J (1983) Central nervous system damage due to an antitumor agent, carmofur. A case report (abstract). Rinsho Shinkeigaku 23: 92
3. Aoki N (1986) Reversible leukoencephalopathy caused by 5-fluorouracil derivatives, presenting as akinetic mutism. Surg Neurol 25: 279–282
4. Kuzuhara S, Ohkoshi N, Kanemaru K, Hashimoto H, Nakanishi T, Toyokura Y (1987) Subacute leukoencephalopathy induced by carmofur, a 5-fluorouracil derivative. J Neurol 234: 365–370
5. Saitoh H, Shinohara Y, Fujita H, Aoki Y, Takagi S (1989) A case of carmofur-induced leukoencephalopathy. MR images and CT findings. Tokai J Exp Clin Med 14: 357–360
6. Matsumoto S, Nishizawa S, Murakami M, Noma S, Sano A, Kuroda Y (1995) Carmofur-induced leukoencephalopathy: MRI. Neuroradiology 37: 649–652
7. Schwartz RB, Mulkern RV, Gudbjartsson H, Jolesz F (1998) Diffusion-weighted MR imaging in hypertensive encephalopathy: clues to pathogenesis. Am J Neuroradiol 19: 859–862
8. Okeda R, Karakama T, Kimura S, Toizumi S, Mitsushima T, Yokoyama Y (1984) Neuropathologic study on chronic neurotoxicity of 5-fluorouracil and its masked compounds in dogs. Acta Neuropathol (Berl) 63: 334–343
9. Okeda R, Shibutani M, Matsuo T, Kuroiwa T, Shimokawa R, Tajima T (1990) Experimental neurotoxicity of 5-fluorouracil and its derivatives is due to poisoning by the monofluorinated organic metabolites, monofluoroacetic acid and a-fluoro-ß-alanine. Acta Neuropathol (Berl) 81: 66–73
10. Golomb J, Kluger A, Gianutsos J, Ferris SH, Leon MJ de, George AE (1995) Nonspecific leukoencephalopathy associated with aging. Neuroimaging Clin North Am 5: 33–44
11. Ito Y, Arahata Y, Goto Y, Hirayama M, Nagamutsu M, Yasuda T, Yanagi T, Sobue G (1998) Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. Am J Neuroradiol 19: 415–417
12. Arbelaez A, Castillo M, Mukherji SK (1999) Diffusion-weighted MR imaging of global cerebral anoxia. Am J Neuroradiol 20: 999–1007