Mystery Case: Parkinsonism in a diabetic uremic patient

Yusuke Osaki, MD
Koji Fujita, MD
Takashi Abe, MD
Masafumi Harada, MD
Yuishin Izumi, MD
Ryuji Kaji, MD

Correspondence to
Dr. Fujita:
kof198@gmail.com

A 71-year-old man noticed a sudden feeling of weakness in the limbs after a routine hemodialysis session, and was admitted to the hospital. He had a history of hypertension and diabetes mellitus for approximately 20 years and diabetic nephropathy requiring hemodialysis for over 1 year. He was taking metformin, which was changed from sulfonylurea 2 months before. His consciousness level deteriorated 1 day after symptom onset, and laboratory examination revealed a blood glucose level of 42 mg/dL. His level of consciousness improved after glycemic treatment, but the weakness did not. MRI of the brain revealed abnormalities in the bilateral basal ganglia (figure e-1 on the *Neurology*[®] Web site at Neurology.org).

The patient was referred to our hospital 8 days after symptom onset. Neurologic examination revealed normal consciousness, symmetric rigid-akinetic parkinsonism (rigidity of the neck and limbs, akinesia, severe postural instability, Myerson sign, and absence of tremor), proximal muscle weakness, bilateral hyperreflexia, and bilateral Babinski signs. Blood tests were as follows: hemoglobin 9.8 g/dL, hematocrit 32.9%, mean corpuscular volume 83.1 fL, blood urea nitrogen 44 mg/dL, creatinine 9.2 mg/dL, sodium 134 mEq/L, potassium 4.0 mEq/L, calcium 8.8 mg/dL, inorganic phosphorus 4.7 mg/dL (reference range 2.5–4.5 mg/dL), magnesium 3.0 mg/dL (reference range 1.9–2.5 mg/dL), iron 26 µg/dL (reference range 60–210 µg/dL), glucose 158 mg/dL, and HbA1c 6.1%. Brain MRI (3.0T) acquired 10 days after symptom onset demonstrated edematous changes in the basal ganglia bilaterally, particularly in the putamen and globus pallidus (figure 1A). Abnormalities in the bilateral globus pallidus on diffusion-weighted imaging and apparent diffusion coefficient (ADC) map were less evident than they were on the initial MRI (figure 1, B and C). Of note, pseudocontinuous arterial spin labeling (pCASL), which is a perfusion imaging technique without contrast media use, revealed marked hyperperfusion in the bilateral basal ganglia (figure 1D), accompanied by dilated perforating branches, or lenticulostriate arteries (figure 1, E and F).

The differential diagnosis included cerebral venous thrombosis, methanol/cyanide poisoning, and hypoxic-ischemic encephalopathy; they were ruled out on the basis of the patient's history and laboratory findings. Extrapontine myelinolysis was considered. However, the estimated change in serum osmolality during the hemodialysis session was only 5 mOsm/L. Moreover, the abnormalities in the bilateral globus pallidus were not consistent with the features of extrapontine myelinolysis. He was suspected of having posterior reversible encephalopathy syndrome, which is often associated with hypertension. His blood pressure was 200/80 mm Hg 1 day after symptom onset. However, his clinical and radiologic features were more compatible with diabetic uremic syndrome, which is an important differential diagnosis in cases of long-term kidney failure, most often, but not always, observed in patients with diabetes mellitus and hemodialysis. The HbA1c was thought to be artificially low because of the anemia.

The patient's parkinsonian symptoms improved gradually; levodopa and steroid pulse therapy provided equivocal benefit. Follow-up MRI performed 23 days after symptom onset, when the symptoms had ameliorated, revealed decreased hyperintensity with some cystic changes in the bilateral globus pallidus on T2-weighted imaging and mild hypoperfusion on pCASL (figure 1, G–I). He was transferred for rehabilitation, but had frequent hypoglycemic attacks and died 1.5 months after symptom onset.

DISCUSSION The present case illustrates the clinical and radiologic features of diabetic uremic syndrome. We discuss this syndrome's epidemiology, neurologic features, and findings on diffusion imaging, perfusion imaging, and magnetic resonance angiography (MRA). First, although this syndrome was originally described in Asians, it has also been reported in Caucasians.^{1,2} The incidence of this syndrome remains unclear. However, a total of only 12 cases were diagnosed during a 5-year period in a large general hospital in Taiwan.¹

Supplemental data
at *Neurology.org*

From the Departments of Clinical Neuroscience (Y.O., K.F., Y.I., R.K.) and Radiology (T.A., M.H.), Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan.

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Figure 1 Follow-up brain MRI

(A–F) MRI performed 10 days after symptom onset. (A) T2-weighted imaging shows hyperintensity in the bilateral lentiform nuclei. (B) The hyperintensity is less evident on diffusion-weighted imaging. (C) The apparent diffusion coefficient is increased around the bilateral lentiform nuclei, but the abnormality is less clear in the globus pallidus bilaterally. (D) Pseudocontinuous arterial spin labeling reveals marked hyperperfusion in the bilateral basal ganglia. (E, F) Axial (E) and 3D (F) time-of-flight magnetic resonance angiography demonstrate dilated perforating branches of the middle cerebral arteries, or lenticulostriate arteries (arrows). (G–I) MRI performed 23 days after symptom onset. (G) T2-weighted imaging reveals hyperintense spots, suggesting cystic lesions, in the lentiform nucleus. (H) Diffusion-weighted imaging demonstrates subtle hyperintensity because of T2 shine-through in the lentiform nucleus. (I) Pseudocontinuous arterial spin labeling shows mildly decreased perfusion in the bilateral lentiform nuclei.

The present patient developed not only parkinsonism but also pyramidal signs, which was not described originally¹ but has been recognized recently.^{2,3} The pyramidal tract disorders may have been caused by the edematous lesions located in the basal ganglia, which involved the corticospinal tract in the posterior limb of the internal capsule. Other symptoms of the syndrome include disturbances in consciousness, dysarthria, dysphagia, and chorea.^{1–4} Neurologic symptoms improve in some patients, and lesions usually regress (as assessed by conventional MRI); however, the overall prognosis is poor in the majority of cases.¹

The diffusion abnormalities observed in the present case were consistent with those reported previously.^{4–6} ADC was mildly increased mainly in the putamen, and was markedly increased around the lentiform nucleus, indicating vasogenic edema, but it was decreased in the globus pallidus in the acute phase, indicating cytotoxic edema. In the latter part of the disease course, ADC was increased in the globus pallidus and cystic changes were observed. The mechanisms underlying the discrepancy in ADC changes observed between the putamen and the globus pallidus remain unclear.

The cerebral perfusion changes that occur in this syndrome are poorly understood. The present case showed an increase in basal ganglia perfusion in the acute stage, and a decrease in the later stage, using the pCASL method. These findings are in line with a previous case report that showed that basal ganglia perfusion was increased on SPECT 3 weeks after symptom onset and was decreased 2 weeks later.⁵ In contrast, another case report suggested that lenticular perfusion decreased on CT perfusion using contrast media 1 month after symptom onset, and normalized 3 weeks later.⁷ However, the interpretation of that case may not be accurate because the images show different regions (the globus pallidus in the initial CT and the putamen in the follow-up CT) as the same structure.⁷ Taken together, these findings lead us to propose that basal ganglia perfusion is increased in acute stages and is decreased in the later stages of this syndrome. Furthermore, the present case illustrates the usefulness of pCASL, which is readily available on many clinical MRI scanners, for perfusion assessment in patients with kidney failure, for whom contrast media (such as gadolinium) are contraindicated.

Finally, we observed dilated lenticulostriate arteries on time-of-flight MRA in the present case. A previous case also showed prominent lenticulostriate arteries on MRA, which corresponded to the extent of basal ganglia lesions.⁵ It was speculated that the abnormal dilation of lenticulostriate arteries led to focal hyperemia (shown in SPECT) and resulted in the basal ganglia lesion on conventional MRI.⁵ Interestingly, an animal study suggested that myogenic constriction of cerebral arteries is impaired in uremic hypertensive rats.⁸ In addition, a human study demonstrated that cerebral vasodilatory capacity is decreased in patients with anemia secondary to chronic renal failure,⁹ indicating that anemia deserves more attention, although hematologic findings have rarely been described in this syndrome.³ Considering the frequent occurrence of peridialytic blood pressure changes,¹⁰ it is tempting to speculate that blood pressure changes contribute to failed autoregulation of perforating arteries, resulting in edematous lentiform nucleus lesions in cases of long-term kidney failure, particularly in those with diabetes and anemia.

The present case highlights the clinical and radiologic characteristics of diabetic uremic syndrome, or more precisely, uremic lenticulostriate syndrome. This clinical entity deserves greater attention from neurologists, nephrologists, and radiologists.

AUTHOR CONTRIBUTIONS

Dr. Osaki: acquisition of data, analysis/interpretation of the data, drafting/revising the manuscript. Dr. Fujita: design/conceptualization of the study, acquisition of data, analysis/interpretation of the data, drafting/revising the manuscript. Dr. Abe: acquisition of data, analysis/interpretation of the data, drafting/revising the manuscript. Dr. Harada: acquisition of data, analysis/interpretation of the data, drafting/revising the manuscript. Dr. Izumi: analysis/interpretation of the data, drafting/revising the manuscript. Dr. Kaji: acquisition of data, analysis/interpretation of the data, drafting/revising the manuscript.

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DISCLOSURE

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group e-mail sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media.

Sixty-seven percent of respondents correctly identified the key MRI abnormalities of basal ganglia edema, with 33% also picking out the findings of dilated lenticulostriate arteries on MRA and hyperperfusion of the basal ganglia on pCASL. Sixty-seven percent also correctly recognized diabetic uremic syndrome as being the most likely diagnosis. The most complete answer was provided by Scott Yuan. Thirty-three percent of respondents also specifically recognized this patient's lentiform fork sign—the bilateral symmetrical basal ganglia hyperintensities surrounded by a more hyperintense rim delineating the lentiform nucleus—as being a hallmark of his uremic syndrome. A previous Teaching NeuroImages case demonstrated this finding in metformin-associated encephalopathy, which can cause a similar parkinsonian syndrome.¹

Aravind Ganesh, MD

Department of Clinical Neurosciences, University of Calgary, Canada

Nuffield Department of Clinical Neurosciences, University of Oxford, UK

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