Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8746-21
Intern Med 61: 2061-2065, 2022
http://internmed.jp

【 CASE REPORT 】

Nephrotic Syndrome and Atypical Posterior Reversible Encephalopathy Syndrome in a Patient with Parkinson's Disease

Ryo Tokimura[1,2], Eiichi Ito[1], Yoshihiro Sugiura[1] and Yoshikazu Ugawa[3]

Abstract:
A 59-year-old man with advanced Parkinson's disease treated using levodopa-carbidopa intestinal gel (LCIG) presented with leg edema, hypoalbuminemia, and proteinuria at 1 year after the treatment. He subsequently developed a generalized tonic-clonic seizure, and brain magnetic resonance imaging indicated vasogenic edema in the white matter of the left frontal subcortex. He was diagnosed with nephrotic syndrome (NS) and atypical posterior reversible encephalopathy syndrome (PRES). LCIG cessation and corticosteroid treatment improved the NS. To our knowledge, this is the first case report of NS and atypical PRES in patients with Parkinson's disease. Patients being treated with LCIG should be closely monitored for NS.

Key words: Parkinson's disease, levodopa-carbidopa intestinal gel, nephrotic syndrome, posterior reversible encephalopathy syndrome, reversible posterior leukoencephalopathy syndrome, case report

(Intern Med 61: 2061-2065, 2022)
(DOI: 10.2169/internalmedicine.8746-21)

Introduction

Levodopa-carbidopa intestinal gel (LCIG) is an established device-aided treatment for patients with advanced Parkinson's disease (PD) presenting with motor fluctuations. Most adverse effects of LCIG have been associated with percutaneous endoscopic gastronomy, with the jejunal tube affecting the gastrointestinal tract, or device-related adverse effects (1).

Nephrotic syndrome (NS) consists of peripheral edema, heavy proteinuria, and hypoalbuminemia. Although most NS cases are primary or idiopathic, several medical backgrounds are predisposing factors to NS, including diabetes mellitus, systemic lupus erythematosus, and adverse effects from certain medications (2). There have been no previous reports of NS among LCIG-treated patients.

Posterior reversible encephalopathy syndrome (PRES), which is also called reversible posterior leukoencephalopathy syndrome, presents with acute neurological symptoms in the setting of acute hypertension, eclampsia, or immunosuppressant use (3). Typical magnetic resonance imaging (MRI) findings for PRES are transient hyperintensity lesions in T2-weighted and fluid-attenuated inversion recovery images of the parieto-occipital lobes, while unilateral or frontal lesions occur in atypical cases (4). PRES has been reported among pediatric patients with NS but rarely in adult patients.

We herein report a patient with advanced LCIG-treated PD who subsequently developed NS and atypical PRES.

Case Report

A 59-year-old man was admitted to our hospital in 2019 for follow-up of a medical condition. He had first noticed tremors in the right upper and lower extremities at 42 years old and been diagnosed with PD at 45 years old (Hoehn & Yahr stage I). Oral levodopa-carbidopa and dopamine agonists improved his symptoms. However, motor fluctuations started at 54 years old, and psychiatric symptoms (hallucinations and impulse control disorders) emerged at 57 years old. At 58 years old, LCIG treatment (1,400 mg/day) was started in association with rotigotine 6.75 mg/day and is-

[1]Department of Neurology, National Hospital Organization Fukushima National Hospital, Japan, [2]Department of Neurology, The University of Tokyo Hospital, Japan and [3]Department of Human Neurophysiology, Fukushima Medical University, Japan
Received: September 28, 2021; Accepted: November 3, 2021; Advance Publication by J-STAGE: December 18, 2021
Correspondence to Dr. Ryo Tokimura, RGM79pile@gmail.com

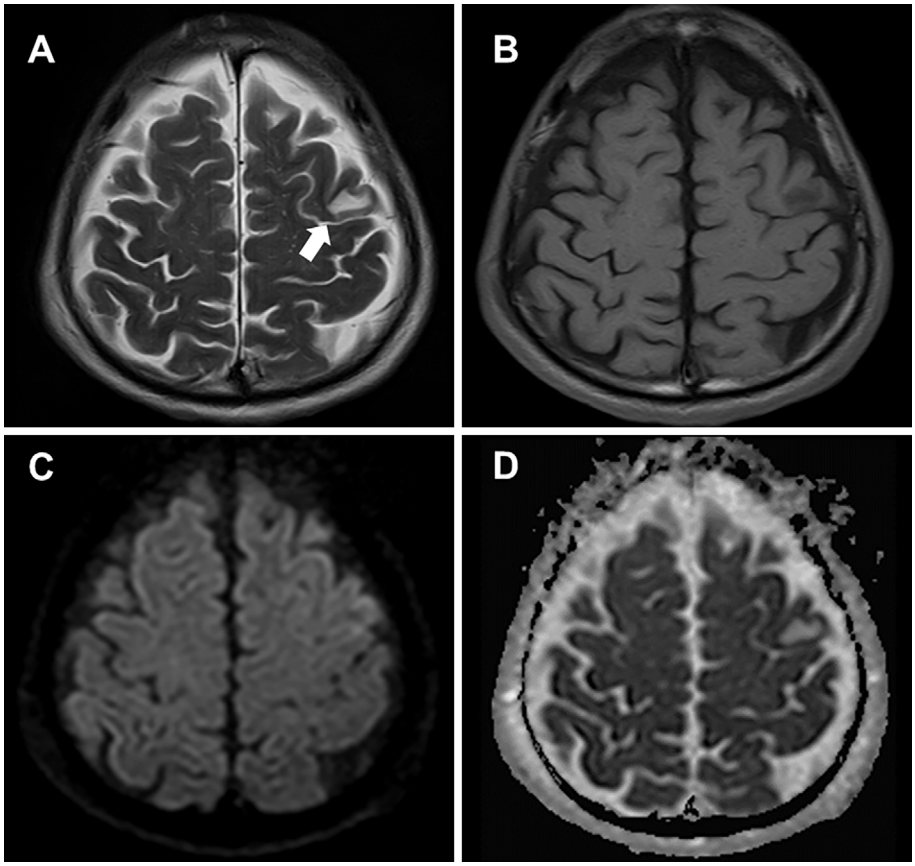

Figure 1. Brain MRI at admission. T2-weighted image (A) showing hyperintensity in the white matter of the left frontal subcortex (arrow). T1-weighted (B), diffusion-weighted (C), and apparent-diffusion-coefficient (D) images showing hypointensity and hyperintensity on the same lesion.

tradefylline 20 mg/day, which dramatically improved both his motor and nonmotor symptoms (Hoehn & Yahr stage III). His serum albumin level was normal (3.8 g/dL), and a urine dipstick test suggested no proteinuria. He had noticed swelling bilaterally in his legs one year after the initiation of LCIG, which gradually worsened over the following six months. He had neither a medical history of hypertension or diabetes mellitus nor a family history of Parkinson's disease, kidney disease or dialysis. He had never been treated with gold, penicillamine, nonsteroidal anti-inflammatory drugs, antihypertensive drugs, or immunosuppressants.

At 59 years old, the patient was admitted to the previous hospital due to sudden-onset generalized tonic-clonic seizure. On admission, his vital signs were normal except for slight hypertension (blood pressure of 142/84 mmHg). A physical examination revealed marked pitting edema in both legs. He had postictal drowsiness but was able to follow simple commands. He had akinesia, lead-pipe rigidity in all four extremities, and resting tremor of the tongue (Hoehn & Yahr stage IV). His total daily dose of LCIG at this time was 1,300 mg/day.

Laboratory data indicated severe hypoalbuminemia (1.5 g/dL) with heavy proteinuria (urine protein/creatinine (Cr) level of 13.20 g/gCr) and granular and waxy casts in the urine, findings consistent with the diagnostic criteria for NS. His proteinuria selectivity index was 0.3, and the serum D-dimer level was markedly elevated at 23,800 ng/mL. He had negative laboratory findings for the liver function, renal function, electrolytes, hemoglobin A1c, antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, M-protein, treponema pallidum antibody, human immunodeficiency virus, hepatitis B, hepatitis C, and tumor markers. Chest and abdominal computed tomography indicated thrombosis from the left renal vein to the inferior vena cava, pleural effusion, and ascites. Brain MRI indicated a lesion in the T2-weighted and fluid-attenuated inversion recovery images in the white matter of the left frontal subcortex, which was hyperintense in both diffusion-weighted and apparent-diffusion-coefficient images. These findings indicated vasogenic edema (Fig. 1). There was no evidence of venous sinus thrombosis or acute cerebral infarction. The above findings were suggestive of atypical PRES. A renal biopsy was not performed due to the risk of complications.

Treatment was initiated using sodium restriction, diuretics, anticoagulant, and antiepileptic drugs. Corticosteroids were not administered initially because of their thrombosis exacerbation risk. He was alert, but two further generalized tonic-clonic seizures occurred on the third and fourth days after admission, while there were no subsequent additional seizures. He regained full consciousness over this time. Urine protein levels decreased slightly to 7.8 g/gCr at 2 months after admission, but the serum albumin value did not

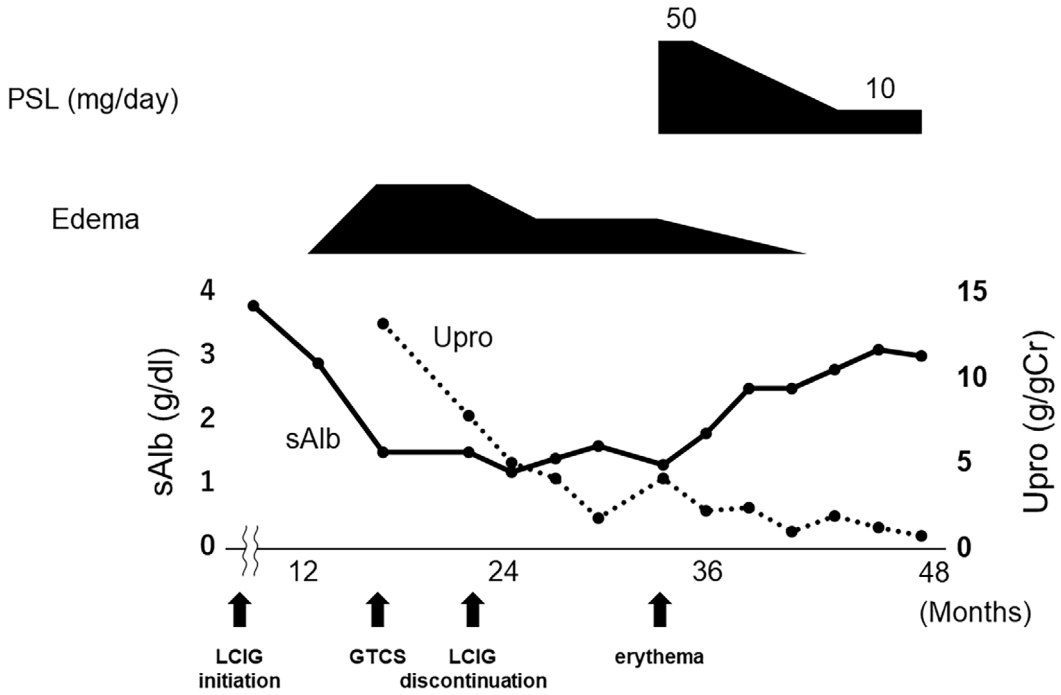

Figure 2. **Clinical course after levodopa-carbidopa administration. Levels of serum albumin (sAlb; solid line) and urinary protein (Upro; dotted line). LCIG: levodopa-carbidopa intestinal gel, GTCS: generalized tonic-clonic seizure, PSL: prednisolone**

change (1.5 g/dL). Follow-up MRI indicated that the vasogenic edema had gradually improved. LCIG treatment was finally ceased due to multiple tube removals and a decline in the activities of daily living at 23 months after its initiation (Hoehn & Yahr stage V).

He was transferred to our hospital for follow-up at two months after LCIG cessation. He had severe erythema in the face at six months after admission to our hospital, which was deemed an adverse effect of the antiepileptic drug. Oral prednisolone (50 mg/day) administered to deter this side effect subsequently improved both the erythema and bilateral leg edema. His serum albumin level increased to 3.1 g/dL, and proteinuria decreased to 0.76 g/gCr. Prednisolone was gradually tapered to 10 mg/day without relapse of his symptoms or laboratory findings. The serum creatinine levels did not increase during the follow-up period. Fig. 2 summarizes the clinical course and the serum albumin and urine protein levels.

Discussion

We reported our observations of NS and atypical PRES in a patient with PD in whom LCIG treatment had been initiated 17 years after the onset of the disease. LCIG cessation and corticosteroid treatment improved the NS and PRES.

The combination of PD and NS is rare. Huang et al. (5) concluded that NS increased the risk of PD. However, our survey of the literature revealed only three case reports of patients with both PD and NS (6-8). In the present report, the patient developed NS 17 years after the onset of PD and 1 year after the start of LCIG administration.

LCIG treatment was approved for advanced PD patients in Europe and Japan in 2004 and 2017, respectively. Most of the adverse effects are associated with percutaneous endoscopic gastronomy using a jejunal tube, gastrointestinal tract problems (granuloma, leakage, or local infection), and device-related adverse effects (tube removal and device occlusion). Dopamine-therapy-induced adverse effects (hallucinations, orthostatic hypotension, polyneuropathy, impulsive control disorder, and psychosis) have also been reported after LCIG treatment (1). However, no reports have described NS as an adverse effect of LCIG.

The correlation between NS and LCIG is currently unclear. One of the aforementioned reports suggested an association between oral levodopa-carbidopa use and NS (7). However, in the present case, levodopa-carbidopa was unlikely to have been the sole cause of NS due to the patient's history of treatment with oral levodopa-carbidopa almost 14 years before the NS onset. The absence of hypoalbuminemia and proteinuria before LCIG initiation and the lack of other possible causes for secondary NS supports the idea that LCIG induced NS in this patient. However, the cessation of LCIG may not have been responsible for the symptom improvement, as the proteinuria improved before the LCIG cessation, and the LCIG cessation did not speed up the improvement. Thus, the present patient may have coincidentally had PD and NS independently. Definitive conclusions regarding the association between LCIG and NS require the further accumulation of similar case reports.

PRES has also not been reported in patients with PD and

Table. **Reported Cases of Nephrotic Syndrome (NS) and Posterior Reversible Encephalopathy Syndrome (PRES).**

Reference	Age (years)/ sex	Symptoms	Medication	BP at admission (mmHg)	MRI	Cause of NS	Renal biopsy	Cause of PRES	Treatment
Present case	59/M	GTCS	LCIG	153/85	F	?	-	?	AED
9	51/F	Headache, blurred vision, GTCS	Corticosteroid, CSA	220/120	P, O	MCNS	+	HT, CSA	CSA discontinuation, AED
10	61/F	Headache, nausea, vomiting	-	180/110	P, O	MGN	+	HT	Antihypertensive
	39/F	Nausea, vomiting, blurred vision, GTCS	-	190/100	P	MPGN	+	HT	AED, antihypertensive
11	21/M	Headache, blurred vision, GTCS	Corticosteroid	124/58	F, T, P, O	MCNS	+	Corticosteroid?	AED, corticosteroid discontinuation
12	27/M	Headache, nausea, vomiting, GTCS	CSA	210/120	P, O	FSGS	N/A	CSA	CSA discontinuation
13	23/M	Headache, blurred vision, GTCS	Corticosteroid, antihypertensive	160/110	Multifocal	FSGS	+	HT	Antihypertensive
14	25/F	Headache, nausea, vomiting, GTCS	-	230/N/A	P, O	FSGS	N/A	HT	Antihypertensive
15	31/F	GTCS	-	201/119	P, O	MGN	+	HT	Antihypertensive
16	56/F	Headache, nausea, vomiting	Pazopanib	165/95	F, P, O	Pazopanib	N/A	Pazopanib?	Antihypertensive, pazopanib discontinuation
17	42/F	Headache, nausea, vomiting, GTCS	Antihypertensive	141/85	P, O	IgAN	-	Infection?	AED, antibiotics

GTCS: generalized tonic-clonic seizure, LCIG: levodopa-carbidopa intestinal gel, CSA: cyclosporine, BP: blood pressure, MRI: magnetic resonance imaging, F: frontal lobe, T: temporal lobe, P: parietal lobe, O: occipital lobe, MGN: membranous glomerulonephropathy, MCNS: minimal-change nephrotic syndrome, MPGN: membranoproliferative glomerulonephritis, FSGS: focal segmental glomerulosclerosis, IgAN: immunoglobin A nephropathy, HT: hypertension, AED: antiepileptic drugs, N/A: not available, F: female, M: male

NS. PRES is a disorder involving reversible subcortical vasogenic brain edema in patients with acute neurological symptoms (e.g., seizures, encephalopathy, headaches, and visual disturbances), and the typical medical backgrounds include blood pressure fluctuations, use of cytotoxic drugs, renal failure, autoimmune disorders, and pre-eclampsia or eclampsia (3). Typical MRI findings for PRES are transient hyperintense lesions in T2-weighted and fluid-attenuated inversion recovery images of the parieto-occipital lobes, while atypical cases present with unilateral or frontal lesions, such as in the present case (4). PRES has been reported in pediatric nephrotic patients but rarely in adults with this condition. There are a small number of adult cases showing an association between NS and PRES, as listed in Table (9-17). It is particularly interesting to consider that NS and PRES may have similar pathogenesis due to endothelial dysfunction. An increase in vascular permeability induced by severe hypoalbuminemia may manifest PRES in patients with NS. Based on these observations, we speculate that PRES was caused by NS in the present patient.

This case report had some limitations. First, we were unable to identify the cause of NS due to the lack of a renal biopsy. Second, since the radiological findings were atypical of PRES, we cannot conclusively exclude other possibilities that might explain the MRI findings.

In conclusion, we described a patient with LCIG-treated PD presenting with NS and PRES. Patients being treated with LCIG should be closely monitored for NS.

The patient provided his written informed consent prior to publication of this report. Procedures were conducted in accordance with the Declaration of Helsinki.

The authors state that they have no Conflict of Interest (COI).

References

1. Blaise AS, Baille G, Carrière N, et al. Safety and effectiveness of levodopa-carbidopa intestinal gel for advanced Parkinson's disease: a large single-center study. Rev Neurol (Paris) **176**: 268-276, 2020.
2. Kodner C. Diagnosis and management of nephrotic syndrome in

adults. Am Fam Physician **93**: 479-485, 2016.

3. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol **14**: 914-925, 2015.

4. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol **189**: 904-912, 2007.

5. Huang ZH, Chen HC, Chou YC, et al. Does nephrotic syndrome without chronic kidney disease increase the risk of Parkinson's disease and secondary parkinsonism? A nationwide population-based study in Taiwan. BMJ Open **8**: e020821, 2018.

6. Heras M, Sáiz A, Fernández-Reyes MJ, et al. Spontaneous remission of nephrotic syndrome in a patient with diabetic nephropathy and Parkinson's disease. Nefrologia **31**: 368-369, 2011.

7. Chaitanya VB, Sangeetha B, Rao VN, Ram R, Vengamma B, Kumar VS. Membranous nephropathy associated with the use of levodopa-carbidopa combination. Indian J Nephrol **25**: 127-128, 2015.

8. Higashino M, Endo K, Rinno S, et al. A case of amantadine in a patient with nephrotic syndrome and an acute kidney injury. Tousekikaishi (J Jpn Soc Dial Ther) **53**: 271-277, 2020 (in Japanese).

9. Utsumi K, Amemiya S, Iizuka M, Iino Y, Katayama Y. Acute posterior leukoencephalopathy in a patient with nephrotic syndrome. Clin Exp Nephrol **7**: 63-66, 2003.

10. Aksoy DY, Arici M, Kiykim AA, et al. Posterior leukoencephalopathy and nephrotic syndrome: just a coincidence? Am J Med Sci **327**: 156-159, 2004.

11. Looi JL, Christiansen JP. Reversible posterior leukoencephalopathy associated with minimal change nephrotic syndrome. N Z Med J **119**: U2257, 2006.

12. de Oliveira RA, Fechine LM, Neto FC, Nicodemus JM, Silva GB Jr, Silva LS. Posterior reversible encephalopathy syndrome (PRES) induced by cyclosporine use in a patient with collapsing focal glomeruloesclerosis. Int Urol Nephrol **40**: 1095-1098, 2008.

13. Nabi Z, Al Korbi L, Ghailani M, Nadri Q, Abdelsalam M, Al Baqumi M. Reversible posterior leukoencephalopathy syndrome in a patient of FSGS with heavy proteinuria. Ren Fail **32**: 892-894, 2010.

14. Chowdhary M, Kabbani AA, Tobey D, Hope TD. Posterior reversible encephalopathy syndrome in a woman with focal segmental glomerulosclerosis. Neuropsychiatr Dis Treat **11**: 1111-1114, 2015.

15. Chang MY, Tsai BM, Hung SY, et al. Posterior reversible encephalopathy syndrome in an adult with nephrotic syndrome. Nephrology (Carlton) **19**: 514-515, 2014.

16. Miaris N, Maltezou M, Papaxoinis G, Visvikis A, Samantas E. Posterior reversible encephalopathy syndrome with concurrent nephrotic syndrome in a patient treated with pazopanib for metastatic renal cell carcinoma: case report and review of the literature. Clin Genitourin Cancer **15**: e99-e103, 2017.

17. Li KY, Chien CF, Tsai CL, et al. Infection-provoked reversible posterior leukoencephalopathy syndrome in an adult with nephrotic syndrome: a case report. BMC Neurol **20**: 349, 2020.