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

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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

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-
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.
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

![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.](image-url)
**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, GTCS | - | 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).

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