CASE REPORT

Metoclopramide Therapy and Movement Disorders in a Diabetic—Uremic Subject With Bilateral Basal Ganglia Lesions

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The etiologies of the syndrome of acute bilateral basal ganglia lesions in diabetic—uremic subjects have been postulated to involve metabolic and/or vascular factors related to diabetes mellitus, uremic toxins, metabolic acidosis, and hypoxemia. The role of dopamine receptor antagonists in the pathophysiology of this disorder has never been discussed before. We present a diabetic—uremic subject who developed bilateral basal ganglia lesions and involuntary movements after metoclopramide therapy. All workup test results were negative except that for impaired renal function. The involuntary movements disappeared after discontinuation of metoclopramide. She developed acute parkinsonism with gait disturbance after metoclopramide therapy several months after the first episode. Her gait gradually improved after discontinuation of metoclopramide. We suggests that metoclopramide therapy may further damage the vulnerable basal ganglia and lead to drug-induced parkinsonism and also the syndrome of acute bilateral basal ganglia lesions in this diabetic—uremic subject. Dopamine receptor antagonists should be avoided or used with caution in subjects with diabetes and uremia.

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1. Introduction

Although the syndrome of acute bilateral basal ganglia lesions in diabetic—uremic subjects was first reported in Taiwan,¹ reports of this syndrome also came from other Asian countries, Europe, and the United States.²–⁴ Although this syndrome is not a rare condition, the underlying mechanism is imperfectly defined. It has been suggested that increased levels of uremic molecules may cause metabolic injury on the basal ganglia that have been weakened by microangiopathic changes and energy utilization failures as the result of long-term diabetes mellitus.⁵,⁶ Only one case report mentioned the possible contribution of dopamine receptor antagonists in the pathophysiology of this specific disorder, and its significance was overlooked because of the presence of structural basal ganglia lesions on neuroimaging.¹

Herein, we describe a diabetic—uremic subject with this syndrome that manifested as involuntary movements after 10 days of metoclopramide therapy. She developed acute parkinsonism after 1 week of metoclopramide therapy several months after the first episode. The role of dopamine receptor antagonists in the pathophysiology of this specific disorder is discussed.

2. Case Report

This 56-year-old woman had poorly controlled hypertension for many years. She had been diagnosed with Type 2 diabetes mellitus in 1997 and was taking oral hypoglycemic agents to maintain her blood glucose between 120 and 260 mg/dL. Chronic renal failure (blood urea nitrogen [BUN]: 79.5 mg/dL; creatinine: 11.2 mg/dL; weekly urea clearance Kt/V: 1.67; weekly normalized creatinine clearance: 45.67 L) was diagnosed, and thereafter, she received continuous ambulatory peritoneal dialysis (CAPD) since April 1999. On November 21, 2003, she developed nausea and vomiting, and 20 mg oral metoclopramide per day was prescribed. On December 1, involuntary movements of the face, mouth, tongue, neck, and limbs occurred, and she visited the emergency room with generalized chorea and dystonia 2 days later. No exposure to antipsychotics or toxins was noted, and there was no family history of movement disorders. Her mental state was normal, whereas frequent facial grimacing, orolingual dyskinesias, and choreic movements of the limbs were noted. She was unable to stand or walk without support because of involuntary movements. Her blood pressure was 195/84 mmHg; blood glucose was 115 mg/dL; and other blood
laboratory evaluations, including calcium, phosphate, magnesium, aluminum, copper, ceruloplasmin, thyroid function test, and arterial blood gas, were within reference ranges, with the exception of BUN (52.0 mg/dL) and creatinine (11.9 mg/dL). Autoimmune serological tests, including rheumatoid factor and antinuclear antibody, and the test for human immunodeficiency virus and venereal disease research laboratory test for syphilis gave negative results. Computed tomography of the head showed hypodense lesions with mild mass effect over the basal ganglia bilaterally (Figure 1). Five milligrams of biperiden was given intramuscularly but in vain. Metoclopramide was discontinued, and CAPD was continued during hospitalization, and she was discharged with a normal gait and no involuntary movements 3 days later.

On April 22, 2004, she was admitted because of *Klebsiella pneumoniae* peritonitis, and a 1-week course of intravenous cephalosporin and 15 mg oral metoclopramide per day was prescribed. However, she developed mask face, swallowing difficulty, generalized rigidity, impaired postural balance, and shuffling gait during hospitalization. Impaired renal function (BUN: 48.0 mg/dL; creatinine: 10.8 mg/dL) and mild anemia (hemoglobin: 9.7 gm/dL) were noted, whereas blood glucose was 157 mg/dL and arterial blood gas was normal. Magnetic resonance imaging of the brain demonstrated old lesions of the basal ganglia bilaterally (Figure 2). Metoclopramide was stopped, and her gait gradually improved.

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**Figure 1** Head computed tomography in December 2003 showing hypodense lesions with mild mass effect over the basal ganglia bilaterally.

**Figure 2** Brain magnetic resonance imaging in April 2004. (A) T1-weighted imaging showing hypointensity and (B) T2-weighted imaging showing hyperintensity over the basal ganglia bilaterally. (C) Diffusion-weighted imaging showing hypointensity and (D) apparent diffusion coefficient trace map showing hyperintensity over the basal ganglia bilaterally, indicating an old insult with necrosis.
In this article, we present a diabetic–uremic subject who developed involuntary movements associated with bilateral basal ganglia lesions and parkinsonism after short courses of metoclopramide therapy. It was postulated that diabetes mellitus may make the basal ganglia vulnerable, and coexistent uremic toxins and metabolic acidosis may further exacerbate the damage of already impaired neurons and neurotransmission, all leading to the pathogenesis of the syndrome of acute bilateral basal ganglia lesions in diabetic–uremic subjects.\(^5\) In previous reports, worsening of renal failure, hypoxia, hyperglycemia, or metabolic acidosis were postulated as the probable causes of this syndrome, and a reduction in uremic toxins by dialysis or correction of metabolic acidosis, hyperglycemia, or hypoxemia was well correlated with improvement of the extrapyramidal syndrome.\(^15,7\)

However, neither acute deterioration of renal function nor severe metabolic acidosis, hypoxemia, or hyperglycemia occurred before the development of the syndrome in this subject, and treatment with metoclopramide was clearly temporally related to the onset of involuntary movements, which strongly suggests a causal relationship. In addition, no other etiologies found could explain the development of the involuntary movements in this specific situation.

Metoclopramide, a dopamine D\(_2\) receptor antagonist used for treatment of nausea and vomiting, may cause or exacerbate extrapyramidal movement disorders. It is unique that two different kinds of extrapyramidal symptoms—acute chorea–dystonia in the first episode and acute parkinsonism in the second episode—after metoclopramide therapy occurred in the same subject. In addition, compared with the longer duration (>2 months) and higher dose (30–40 mg/d) with metoclopramide therapy before the onset of symptoms of parkinsonism of reported subjects,\(^6\) a shorter duration and lower dose of metoclopramide therapy were used in our subject. Hyperglycemia may result in diminished dopaminergic transmission and increased sensitivity of postsynaptic dopamine receptors,\(^9\) and there is also evidence of the suppression of the central dopamine turnover in uremia in animal studies.\(^10\) An F-18 fluorodeoxyglucose positron emission tomography study in subjects with this syndrome also showed markedly decreased glucose metabolism in the basal ganglia,\(^4\) probably related to long-term diabetes mellitus and elevated levels of uremic toxins. Thus, dopamine receptor antagonists may further impair striatal dopamine transmission and produce dopamine receptor hypersensitivity in the already-compromised basal ganglia of diabetic–uremic subjects. In addition, a significant proportion of the total body clearance of metoclopramide depends on adequate renal function, the half-life is markedly prolonged in chronic renal failure,\(^11\) and the clearance of metoclopramide by CAPD is negligible because of its high molecular weight and large volume of distribution.\(^12\)

We speculated that metoclopramide therapy may further damage the vulnerable basal ganglia and lead to drug-induced parkinsonism and also the syndrome of acute bilateral basal ganglia lesions in this diabetic–uremic subject.

In conclusion, the syndrome of acute bilateral basal ganglia lesions and parkinsonism occur after metoclopramide therapy in this diabetic–uremic subject. Dopamine receptor antagonists should be avoided or used with caution in subjects with diabetes and uremia. A peripheral dopaminergic blocking agent, such as domperidone, which has an extremely low incidence of extrapyramidal syndrome or parkinsonism, may be safe in subjects with diabetes and uremia.\(^13\)

References