

Metformin-induced paroxysmal dystonia

Filiz Koc, MD, Deniz Yerdelen, MD.

Type 2 diabetes mellitus is generally encountered in people older than 40 years. In patients with type 2 diabetes mellitus, the pancreas initially secretes an adequate amount of insulin, but this insulin cannot be utilized by cells. As the disease progresses, however, insulin secretion from the pancreas becomes insufficient. The first clinical symptoms are an urgent need to urinate and thirst. In elderly patients, weakness, fatigue, and muscle pain may be seen.¹ Standard treatment includes oral antidiabetic drugs like sulfoarea, biguanides, and α -glucosidase.² In type 2 diabetes mellitus, especially in obese patients, the biguanide group of drugs, particularly metformin, is the first choice. Adverse effects include anorexia, nausea, vomiting, and diarrhea. Rarely, lactic acidosis may be seen. However, paroxysmal dystonia has not been associated with metformin treatment. Here, we present the clinical and laboratory features of a patient with paroxysmal dystonia associated with metformin treatment.

A 64-year-old woman was admitted to the clinic with complaints of weakness and fatigue. She had a 10-year history of hypertension and was taking an angiotensin-converting enzyme inhibitor, the combination losartan potassium (50 mg) and hydrochlorothiazide (12.5 mg) (one tablet/day) and acetylsalicylic acid (300 mg/day). Her family history was significant for a second-degree relative who had type 2 diabetes mellitus, which had developed when the relative was older than 50 years. Results of a physical examination showed her height to be 1.57 m, and her weight to be 95 kg. Her arterial blood pressure was 140/75 mm Hg, and her pulse was 68 beats per minute. Results of other physical and neurologic examinations were normal. The results of standard biochemical analyses showed the following: fasting glucose, 151 mg/dL, hemoglobin A_{1c}, 7.6% (normal range [NR], 4.8%-6%); insulin level, 3.70 mU/L (NR, 3-28 mU/L), C peptide, 1.89 ng/mL (NR, 0.78-1.89 ng/mL), and beta-2 microglobulin, 1.83 mg/L (NR, 0.66-2.74 mg/L). Metformin (850 mg/gün) was started. On the second day of the treatment, the patient's fasting glucose level decreased to 138 mg/dL and in the following days ranged from 121-126 mg/dL values. On the fifth day, paroxysmal dystonia developed in her toes, most prominently in the right big toe. These involuntary movements disappeared during sleep. Results of analyses of blood gases, urine, total blood count, and biochemical parameters were normal. Cerebral MRI revealed only 2 lacunes in the periventricular white matter. Due to the involuntary movements, the patient's metformin

was discontinued and after 36 hours, the dystonia disappeared. The patient was treated by modifying her diet for 8 months, no antidiabetic medications were given. During follow-up, her fasting glucose levels were between 120-130 mg/dL. To demonstrate the association of movements with metformin, the drug was started again. Detailed biochemical analyses before and after the drug therapy were performed, and normal values, except fasting glucose, were obtained. On the fourth day of metformin treatment, the same involuntary movements were again observed, and they disappeared after discontinuing the drug.

Dystonia is a group of movement disorders that vary in their symptoms, causes, progression, and treatments. This group of neurologic conditions is generally characterized by involuntary muscle contractions that force the body into abnormal, sometimes painful, movements and postures. The most characteristic finding associated with dystonia is twisting, repetitive movements that affect the neck, torso, limbs, eyes, face, vocal chords, and/or a combination of these muscle groups. Dystonia may be focal (affecting an isolated body part), segmental (affecting adjacent body areas), or generalized (affecting many major muscle groups simultaneously). There are many different causes for dystonia. Genetic as well as nongenetic factors contribute to all forms of dystonia.

Drug-induced dystonia has been described in many reports. Prolonged use of antipsychotic drugs, both typical and atypical antipsychotic drugs, with or without sudden withdrawal, as well as taking them at high dosages (for at least 3 months) may result in a variety of movement disorders such as tardive dystonia. Metoclopramide is a dopamine antagonist that is widely used in gastroesophageal disease and chemotherapy-induced emesis, and has been reported as a cause of dystonia. Other antiemetic drugs such as prochlorperazine and ondansetron also have been found to be associated with dystonic reactions.^{3,4} Metformin, a drug in the biguanide group, decreases carbohydrate absorption from the intestines. It has an anorectic effect and potentiates the effect of insulin in the tissue. Metformin does not increase insulin production in the body, so weight gain is seen less commonly. Due to this feature, it is a good choice in obese patients. Adverse effects seen during metformin use are rare and occur in approximately 40% of patients, especially if high doses are taken. Gastrointestinal system findings like abdominal discomfort, metallic taste in the mouth, nausea, vomiting, and changes in intestinal habits may occur. Vitamin B12 and folic acid absorption are prevented. Metformin does not increase insulin, so hypoglycemia does not occur if it is used solely. Hypoglycemia develops

due to anorexia and weight loss.² Another adverse effect is an increase in the blood lactate level. In patients with renal dysfunction, metformin may induce dangerous blood acidity. This special acidosis is lactic acidosis. Metformin also should be avoided in patients with infection, severe dehydration, cardiac deficiency, acute myocardial infarct, chronic liver disease, alcoholism, pregnancy, and lactation in which lactic acidosis is a risk.⁵

In this report, we described metformin as a cause of dystonia. Although the association was proven by discontinuing the drug and showing subsequent symptom resolution and then restoring the signs when the drug was taken again, the underlying mechanism for this association is not known. We sought to show that reversible involuntary movements could be induced by metformin, especially in elderly patients. We want to emphasize that before performing expensive investigations, physicians should consider the oral antidiabetic drugs being taken by patients, discontinue the drug, and continue treatment with another oral antidiabetic agents.

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From the Department of Neurology (Koc), Cukurova University Faculty of Medicine, Department of Neurology, (Yerdelen), Baskent University Faculty of Medicine, Adana, Turkey. Address correspondence and reprint requests to: Dr. Filiz Koc, Güzelyalı mah, 64 sok, Güler Apt. Kat 3/ daire 3, Seyhan, Adana, Turkey. Tel. +90 (322) 3386060. E-mail: koc.filiz@gmail.com

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