Clozapine-Associated Myopathic Dysfunction

To the Editor:

Clozapine is an atypical antipsychotic drug that is reserved for the treatment of refractory schizophrenia. This drug is unique because of its less propensity to develop neurological side effects. Although there are sporadic reports of creatine kinase (CK) elevations in clozapine-treated patients as part of atypical neuroleptic malignant syndrome,[1] muscle dysfunction related to clozapine treatment is a rare phenomenon.[2] The author has previously reported tardive dystonia in a schizophrenic patient receiving clozapine monotherapy for 1.5 years.[3] Here, we are reporting a case of clozapine-associated muscle weakness assessed using conventional clinical, electrophysiologic, and pathologic methods.

Mr was a 54-year-old man with schizophrenia who was on regular treatment with clozapine monotherapy for the past 4 years. He had no history of muscle disease, malignancy, collagen vascular disease, renal insufficiency, thyroid disease, HIV infection, recent trauma or surgery, recent intramuscular injections, cocaine or alcohol abuse, a family history of muscle disease, or use of medications with known myotoxic effects. His symptoms were well-controlled without any untoward effects on a doze of clozapine 200 mg per day in the past 1 year. Then, gradually the patient started feeling weakness of both legs with difficulty to stand up from squatting and sitting position and to keep legs firmly on the ground while walking. Orthopedic examination was normal. He was referred to a neurologist, and CK was tested and found to be significantly elevated (400 U/L). As per the advice of the neurologist, clozapine dose was reduced gradually over a period of 6 months up to 25 mg per day without having worsening of symptoms and was not given any other medicines. However, his monthly CK level was consistently elevated. Owing to worsening of weakness of legs, finally the neurologist advised to stop clozapine completely and performed the following investigations. A computed tomography scan of the brain and magnetic resonance imaging of both the brain and spine were normal. Full biochemistry profile, liver function test, serum ceruloplasmin, and thyroid functions were normal.

Muscle strength graded using the Medical Research Council scale was 4. Electrophysiologic testing, consisting of needle electromyography, and nerve conduction studies were performed. Sural and ulnar sensory conductions, tibial and ulnar motor conductions, including F-waves, and tibial H-reflexes were studied on both legs. Electromyography was suggestive of myopathic dysfunction. The patient also underwent a quadriceps muscle biopsy, and other causes of myopathy were excluded by the following blood tests: chemistries, thyroid function tests, erythrocyte sedimentation rate, and antinuclear antibody. In the index patient, the CK level was normalized within 6 months after discontinuing clozapine. The patient's weakness of legs improved within 3 months after stopping clozapine, and muscle strength became grade 5. Until his last follow-up in psychiatry outpatient department, there is no emergence of psychiatric symptoms. His last CK level was 145 U/L.

We report consistent CK elevations with weakness of both legs in a patient with schizophrenia who was treated with clozapine monotherapy for a long period in the outpatient setting. We excluded other causes of muscle disease. Here, the CK levels were greater than 5 times the upper limit of normal which is usually seen in myopathic conditions. CK levels returned to normal, and muscle strength became normal within few months of stopping the drug. This suggests that clozapine may have an effect on muscle through an idiosyncratic reaction.[4]

Less commonly, clozapine treatment in patients with chronic psychotic disorders was associated with a mild, proximal myopathy that only rarely resulted in functionally significant proximal leg weakness.[5] Myopathic dysfunction in this patient was supported by the presence of CK elevations, proximal limb weakness, and characteristic electrophysiologic abnormalities. Clinical improvement in patient's muscle strength and CK level after cessation of clozapine further supported an association between clozapine and the development of myopathy.

Sandoz has reported spontaneous CK elevations in 98 clozapine-treated patients, and only 18 of these patients had confounding medical illnesses significant for muscle disease suggesting rhabdomyolysis is a potential adverse effect of clozapine treatment.[5] The mechanism of muscle dysfunction associated with clozapine treatment is unknown. Clozapine may have myotoxic effects in susceptible individuals through interactions with cytochrome P450 proteins or calmodulin inhibition. Differences among individuals in the

function of 1 or more enzymes involved in muscle metabolism may explain the apparent idiosyncratic effect of clozapine on muscle function.[5]

In conclusion, clozapine seems to be rarely associated with CK elevations in patients with chronic psychotic disorders. Very rarely, CK elevations in this setting may be severe and may be associated with rhabdomyolysis in the absence of neuroleptic malignant syndrome. In clinical practice, if patients on clozapine complain of muscle weakness, it would be better to perform a thorough neurological evaluation to exclude myopathic conditions although it is of marginal functional significance.

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The authors have no conflicts of interest to declare.

Consent was received from the patient to publish the case report, and information has been de-identified to protect anonymity.

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