

# An Unpredicted Side Effect of Bisphosphonates in a Patient with Chronic Renal Failure Due to Multiple Myeloma: Reversible Parkinsonism

## Multipl Miyeloma Baęlı Gelişen Kronik Böbrek Yetmezlięi Olan Bir Hastada Bifosfonatların Beklenmeyen Yan Etkisi: Geri Dönüslü Parkinsonizm

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### ÖZET

Bu olgu sunumunda, multipl miyeloma baęlı kronik böbrek yetmezlięi zemininde kemoterapötik ajanın (zoledronik asit) derinleřtirdięi hipokalsemi ve bu metabolik bozukluęa baęlı olarak parkinsonizm epizotları geliřmiř olan özgün bir olgu sunulmaktadır. Multipl miyelom tanısı almıř ve altı aydır aylık bifosfonat tedavisi almakta olan 80 yařında kadın hasta, acil servisimize iki defa parkinsonizm epizodları ile bařvurdu. Replasman tedavisiyle düzelen parkinsonizm semptomlarına, her iki epizotta da düşük kalsiyum düzeyleri eřlik etmekteydi. Görüntülemelerde bazal gangliyonlarda herhangi bir patoloji izlenmedi. Her iki seferde de hastanın klinięinin kalsiyum replasmanı ile düzeltilmiř olması, epizodların asıl nedeninin hipokalsemi olduęunu düşündürmektedir. Bu, bazal gangliyonlarda oluřan yıkım sürecine baęlı bir hasardan ziyade, kemoterapötik ajanın metabolik yan etkilerine baęlı geri dönüslü fonksiyonel bir bozukluęu yansıtan özgün bir olgu olarak yorumlanmaktadır.

**Anahtar Kelimeler:** Parkinsonizm, sekonder, ilaçlar, hipokalsemi.

### ABSTRACT

## An Unpredicted Side Effect of Bisphosphonates in a Patient with Chronic Renal Failure Due to Multiple Myeloma: Reversible Parkinsonism

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In this report, we present a unique case in which the chemotherapeutic agent, i.e., zoledronic acid, deepened the hypocalcemia on the basis of chronic renal failure secondary to multiple myeloma and caused parkinsonism episodes. An 80-year-old female patient, who had been diagnosed as multiple myeloma and had been administered bisphosphonate therapy monthly for six months, was admitted to our emergency room with two parkinsonism episodes. Low serum calcium levels accompanied parkinsonism symptoms, which subsided with calcium replacement therapy in both episodes. Imaging did not reveal any pathology in the basal ganglia. The fact that the patient was cured both times with calcium replacement suggests that hypocalcemia was the actual cause. This can be interpreted as a unique case, reflecting the reversible functional impairment due to metabolic side effects of a chemotherapeutic agent rather than destructive changes in the basal ganglia.

**Key Words:** Parkinsonism disease, secondary, drugs, hypocalcemia.

## INTRODUCTION

Resting tremor, akinesia, cogwheel rigidity, and impairment of postural reflexes are characteristic features of parkinsonism. Cases of parkinsonism due to an identifiable cause are defined as secondary or symptomatic (1,2). Criteria for the diagnosis of parkinsonism secondary to drugs could be stated as (2):

1. Presence of two or more cardinal features of parkinsonism
2. Absence of parkinsonian symptoms before the exposure of the offending drug
3. Improvement in parkinsonian symptoms after the withdrawal of the offending drug
4. No better explanation for the parkinsonism

Secondary parkinsonism may be caused by various structural, toxic or metabolic etiologies. Basal ganglia are known to be vulnerable to several metabolic disorders as well as many toxins and drugs (2,3). Hypocalcemia due to different etiologies is one of these metabolic disorders that may act via corruption or breakdown of the basal ganglia network (4,5).

In this report, we present an acute transient parkinsonism case due to hypocalcemia secondary to zoledronic acid. This process is suggested to be exacerbated by the pre-existing chronic renal failure of multiple myeloma.

## CASE

An 80-year-old female patient was admitted to our emergency room with nausea, vomiting, acute onset tremor, and inability to walk or turn in bed. She had been diagnosed as multiple myeloma six months before and was administered dexamethasone and bisphosphonate therapy monthly. She suffered from the above-mentioned complaints for three days, following the initiation of the sixth zoledronic acid administration. Her relatives described generalized shakiness and slowness of movements and incapacity to perform her daily activities, even to eat or speak. In addition to multiple myeloma, her medical

history revealed comorbidities of hypertension, atrial fibrillation, previous right middle cerebral artery posterior branch occlusion, and chronic renal failure (due to multiple myeloma).

The neurological examination revealed hypophonia, disturbance in speech, rabbit sign, bilateral symmetrical pill-rolling resting tremor with a frequency of 4-5 Hz, moderate to severe bradykinesia, and rigidity. She walked with small steps and needed bilateral support. Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) score was 31/56. Serum calcium level was 4.3 mg/dL [reference ranges (RR): 8.4-10.5 mg/dL], blood urea nitrogen (BUN) was 61 mg/dL (RR: 6-23 mg/dL) and creatinine was 3.96 mg/dL (RR: 0.5-1.1 mg/dL) on initial laboratory studies. Other biochemical data were normal. The cranial imaging did not reveal any pathogenic process in the basal ganglia. Calcium replacement therapy was administered. The symptoms subsided the following day when the calcium level reached 6.2 mg/dL. The serum calcium level was 9.3 mg/dL when the patient was discharged (UPDRS-ME: 5/56).

Three weeks later, the patient was re-admitted with the same complaints. Serum calcium level was 4.0 mg/dL. Calcium replacement therapy was administered and improvement was observed as soon as the calcium level reached 6.0 mg/dL.

Episodes of hypocalcemia were considered to be related with the zoledronic acid and it was withdrawn from the regimen. The serum calcium level was stabilized and no further episodes were observed during the follow-up.

## DISCUSSION

In this paper, a case of acute transient parkinsonism secondary to iatrogenic hypocalcemia is presented. Although the former cases of secondary parkinsonism induced by hypocalcemia accompanied morphological changes on magnetic resonance imaging, our case implies reversible functional disturbances of the basal ganglia related with drug-induced acute hypocalcemia without any detectable abnormality in cranial imaging (4,5).

Our patient suffered from multiple myeloma, which is a B-cell malignancy causing destruction of the bones via osteoclastic activation (6). Bisphosphonates are included in the chemotherapeutic regimen of this disease and act via specific inhibition of the osteoclastic activity in various diseases such as metabolic bone diseases, postmenopausal osteoporosis, osteogenesis imperfecta, breast cancer, or metastasis of solid tumors to bones (7,8). Zoledronic acid is a new generation drug among the bisphosphonates.

Hypocalcemia was also mentioned for zoledronic acid (9). Serum calcium concentration decreases by following the inhibition of osteoclast-mediated bone absorption after the administration of zoledronic acid. In physiological conditions, activation of the compensatory hyperparathyroidism inhibits the deepening of hypocalcemia via enhancement of renal calcium uptake, production of 1, 25-hydroxyvitamin D and osteoclastic bone absorption in healthy subjects (9). However, hypocalcemia may deepen due to the failure of these compensatory mechanisms in chronic renal failure, i.e., the comorbidity from which our patient also suffered.

The underlying biochemical mechanisms of the hypocalcemia acting on the basal ganglia have not yet been clarified. However, flunarizine, i.e., a calcium-channel blocker, was observed to suppress the immune reactivity of tyrosine hydroxylase transiently, without causing any cell loss at nigrostriatal neurons. Regardless of the dosage, immunoreactivity of tyrosine hydroxylase was reduced one day after the administration of the offending drug and recovered later (10). A functional impairment should be speculated for zoledronic acid, which acts by reducing the calcium levels in blood and hence, down-regulates some of the specific receptors and/or biochemical pathways, similar to flunarizine.

To our knowledge, this is a unique case, since our patient revealed normal cranial imaging. This observation indicates a reversible functional impairment rather than a damaging process leading to morphological changes in the basal ganglia.

In conclusion, acute reversible parkinsonism should be considered in treatment regimens that cause hypocalcemia, such as bisphosphonates. Because of its reversible course with appropriate intervention, metabolic disorders should be considered in the differential diagnosis of acute movement disorders.

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