

Case Report

A case of myopathy and markedly elevated creatine kinase levels with hypocalcemia, hypomagnesemia, and hyposelenemia due to short bowel syndrome after rectal cancer resection

Takayuki Katayama, M.D., Ph.D.¹⁾ *, Kae Takahashi, M.D.¹⁾, Osamu Yahara, M.D., Ph.D.¹⁾ and Toru Yamada, M.D., Ph.D.²⁾

Abstract: A 66-year-old Japanese man was referred to our hospital with myalgia and muscle weakness. He had a history of rectal cancer, which invaded into the urinary bladder and ileum and was treated with chemotherapy, radiotherapy, resection of the rectum, colostomy, and ileal conduit construction. He showed recurrent markedly elevated serum creatine kinase levels and concurrent hypocalcemia. Muscle magnetic resonance imaging demonstrated abnormal signals in the proximal limb muscles, and needle electromyography showed myopathic changes. Further examination revealed hypomagnesemia and hyposelenemia with underlying short bowel syndrome. Calcium, magnesium and selenium supplementation improved his symptoms and laboratory findings.

Key words: myopathy, hypocalcemia, hypomagnesemia, selenium, short bowel syndrome

Introduction

Hypocalcemia may cause paresthesia, tetany, and seizures as common manifestations¹⁾. In rare cases, it can cause muscle weakness and creatine kinase (CK) elevation, and such cases have been reported as ‘hypocalcemic myopathy’^{2)–7)}. It may also cause marked CK elevation, although hypocalcemic myopathy has to be differentiated from necrotizing myopathy, myositis, and rhabdomyolysis in such cases⁸⁾⁹⁾. Herein, we report a case of myopathy with marked CK elevation accompanied by hypocalcemia, hypomagnesemia, and hyposelenemia due to short bowel syndrome, which arose after rectal cancer resection.

Case report

A 66-year-old Japanese man was referred to our clinic because of myalgia and muscle weakness. He had been well until he was diagnosed with rectal cancer at the age of 61 (pT4b [invading the urinary bladder and ileum], N0M1 [liver],

Stage IV). He received pre-surgical chemotherapy (bevacizumab, levofolinate, fluorouracil, and oxaliplatin), but the regimen was changed (to capecitabine and oxaliplatin and then fluorouracil and irinotecan) because of adverse effects (an allergy to levofolinate and hematuria due to oxaliplatin). Radiotherapy (intensity modulated radiation therapy [IMRT], 45 Gy/5 weeks) to the pelvic cavity was also performed. Subsequently, he underwent resection of the rectum (Hartmann’s operation), colostomy, bypassing of the jejunum and transverse colon, and ileal conduit construction. The residual length of the small intestine was approximately 100 cm. An opium tincture (10%, 3 ml/day) was prescribed for post-surgical chronic diarrhea.

At the age of 62, he developed lumbago and lower limb pain, and pregabalin treatment was started. At the age of 65, his serum CK level increased (to approximately 500 U/l; normal: 59–248). Two months later, he was admitted to our hospital because of urolithiasis (uric acid stones), and laboratory tests noted marked increases in his CK (9,916 U/l), lactate dehydrogenase (714 U/l, normal: 124–222), and aspartate transaminase (153 U/l, normal: 13–30) levels (Fig. 1A). The

*Corresponding author: Department of Neurology, Asahikawa City Hospital [1-1-65 Kinsei-cho, Asahikawa 070-8610, Japan]

¹⁾ Department of Neurology, Asahikawa City Hospital

²⁾ Department of Surgery, Asahikawa City Hospital

(Received October 17, 2022; Accepted February 4, 2023; Published online in J-STAGE on April 25, 2023)

Rinsho Shinkeigaku (Clin Neurol) 2023;63:286-290

doi: 10.5692/clinicalneurol.cn-001814

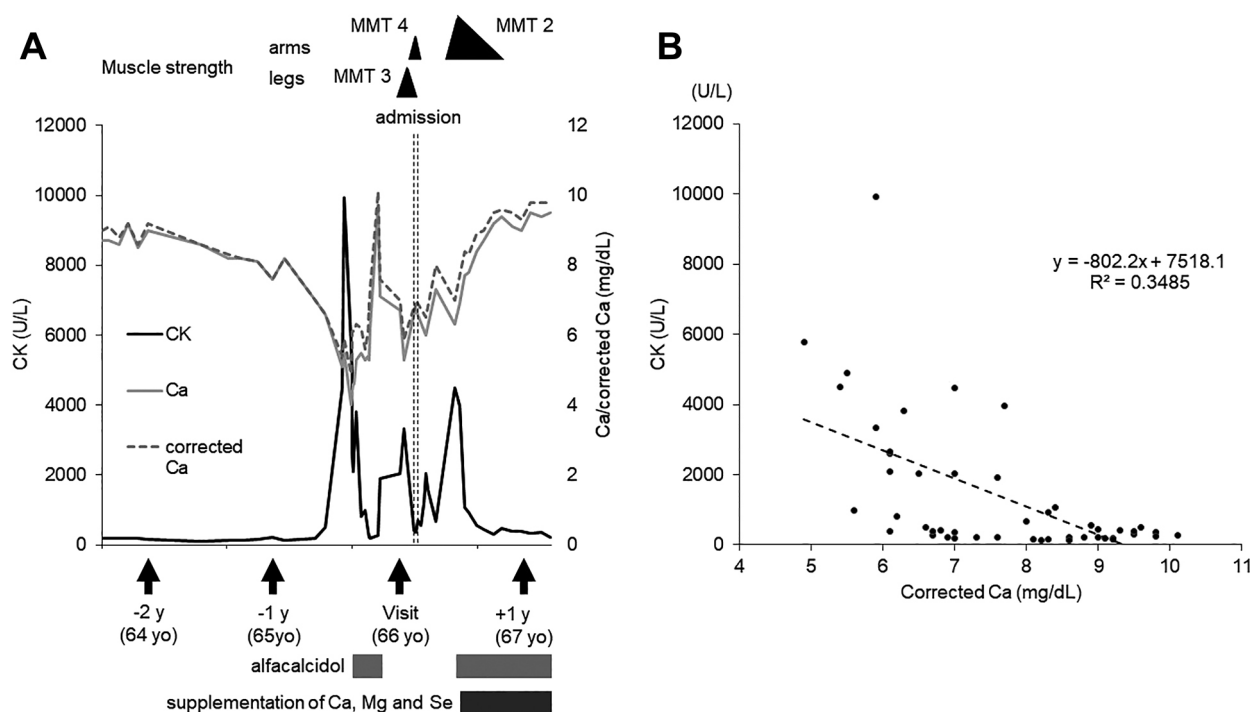


Fig. 1 Clinical course of the patient (A) and a scatterplot of his corrected serum calcium and creatine kinase (CK) (B) levels.

Corrected Ca (mg/dL) = measured serum Ca (mg/dL) + (4-albumin [g/dL]) (when the albumin level is less than 4.0 g/dL). CK, creatine kinase; MMT, manual muscle test

pregabalin was terminated because of a provisional diagnosis of drug-induced rhabdomyolysis, and thereafter, his CK level normalized. At the same time, hypocalcemia (4.0 mg/dL, corrected calcium 4.9 mg/dL, normal: 8.8–10.1 mg/dL) was noted, and it was treated with a drip infusion of electrolytes, including calcium chloride, and the oral administration of alfacalcidol (0.5 mg/day) for three months.

At the age of 66, he developed myalgia, limb weakness, and elevated CK levels (3,324 U/L), and he was referred to our hospital. He had no family history of neuromuscular disorders. He had not exercised excessively, suffered an infection, started receiving new drug treatment, or experienced any other exacerbating triggers before his CK levels increased. He had a history of smoking 10 cigarettes per day and occasionally drank alcohol. He was a craftsman with heavy physical labor.

A physical examination revealed post-surgical scars on the abdomen and stomas for the gastrointestinal and urinary tract. A neurological examination revealed muscle weakness of the proximal extremities (bilateral gluteus maximus; manual muscle test [MMT] score 3) and difficulty of squatting. The strength of other muscles was normal. He did not show tetany, the Trousseau sign, or the Chvostek sign.

He was admitted to our hospital 6 weeks after his first visit, as his hospitalization was delayed due to the coronavirus pandemic. A neurological examination at the admission revealed

muscle weakness of the proximal upper extremities (bilateral deltoid, biceps brachii, brachioradialis and triceps brachii; MMT score 4). The MMT scores of iliopsoas, gluteus maximus, quadriceps femoris, hamstrings, tibialis anterior and triceps surae muscles were 5. His CK level improved spontaneously (422 U/L) and isozyme analysis of his CK revealed MM-predominance. His serum aldolase level was also high (11.8 U/L; normal: 2.1–6.1). Laboratory tests revealed hypocalcemia (6.6 mg/dL) without hypoalbuminemia. His serum phosphorus level was 2.2 mg/dL (normal: 2.5–4.5). His serum potassium concentration at the admission was low (2.6 mEq/L, normal: 3.6–4.8) but it was normalized quickly with oral supplementation of potassium L-aspartate (7.2 mEq/day). His serum sodium, chloride and copper concentrations were normal. His serum zinc concentration was mildly low (68 µg/dL, normal: 80–130) and it was treated with polaprezinc (150 mg/day). His renal and thyroid function were normal.

Muscle magnetic resonance imaging (using the short tau inversion recovery [STIR] method) showed hyperintense areas in the deltoid, infraspinatus, internal obturator, and piriformis muscles (Fig. 2A and B). Needle electromyography detected fibrillation potentials and positive sharp waves at rest, and polyphasic and low-amplitude potentials during voluntary contraction together with the early recruitment of neuromuscular units, which suggested acute myopathic changes (Fig. 3).

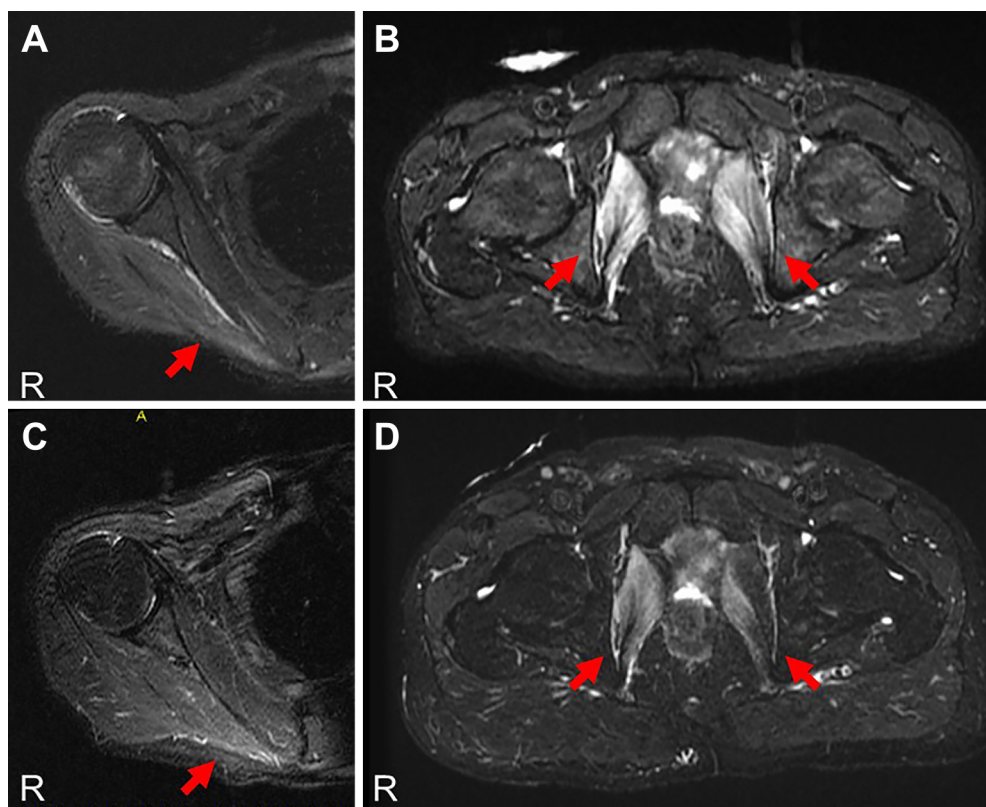


Fig. 2 Muscle magnetic resonance imaging (short tau inversion recovery [STIR] method).

(A) Upper limb girdle (repetition time [TR]: 6,400 ms, echo time [TE]: 59 ms, inversion time [TI]: 158 ms) and (B) lower limb girdle (TR: 9,150 ms, TE: 61 ms, TI: 159 ms) at the admission. (C and D) Follow-up images 1.5 years after the admission. Hyperintense areas were observed in the infraspinatus and internal obturator (arrows). Follow-up images showed partial improvement of the hyperintense areas.

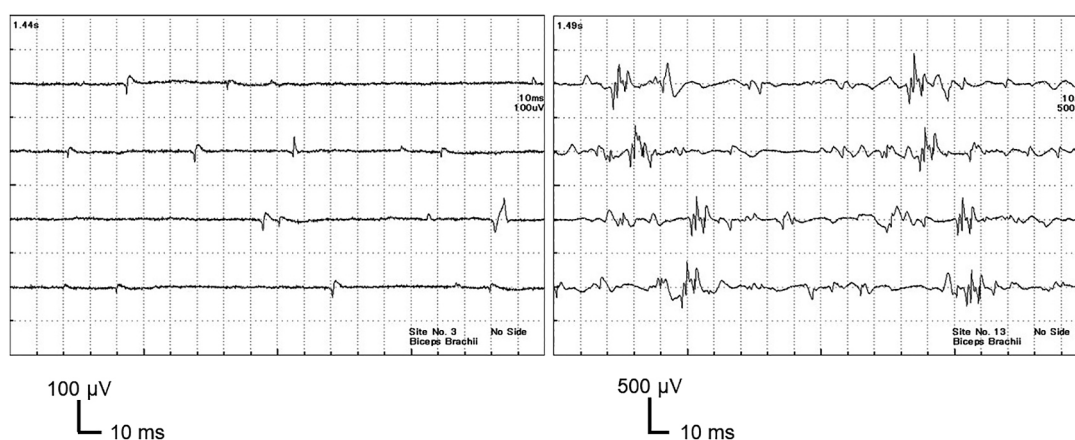


Fig. 3 Needle electromyography (left biceps brachii).

Fibrillation potentials and positive sharp waves at rest (left panel) and polyphasic and low-amplitude potentials during voluntary contraction (right panel) were seen.

Serological tests for rheumatoid factor, anti-nuclear antibody, anti-Sjögren's-syndrome-related antigen A (SS-A/Ro), anti-aminoacyl tRNA synthetase (ARS), anti-melanoma differentiation-associated gene 5 (MDA5), anti-Mi-2, anti-transcriptional

intermediary factor 1-gamma (TIF1-γ), anti-small recognition particle (SRP), anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), and anti-mitochondrial-M2 antibodies were all negative. His serum carnitine and plasma vitamin B1

were within normal ranges. His serum vitamin E was slightly decreased (0.67 md/dl, normal: 0.75–1.41). Ischemic forearm exercise test showed normal elevation of blood lactate (from 10.6 mg/dl to 57.1 mg/dl, normal at rest: 3.0–17.0 mg/dl) which ruled out glycogen storage disease.

His muscle weakness and CK levels improved spontaneously, and he was discharged from our hospital. Three months later, however, he developed muscle weakness again (bilateral deltoid, MMT score 2), and his CK levels worsened (Fig. 1A).

Follow-up examinations revealed that his CK levels were significantly correlated with his serum calcium levels (Fig. 1B; Spearman's rank correlation test, $\rho = -0.6100$, $P < 0.0001$). Further tests for hypocalcemia revealed normal levels of 1,25(OH)₂ vitamin D₃ (26.6 pg/ml; normal: 20–60), calcitonin (0.56 pg/ml; normal: ≤ 9.52), and intact-parathyroid hormone (PTH; 23 pg/ml; normal: 10–65); however, low serum magnesium (0.4 mg/dl; normal: 1.8–2.6) and selenium (79 μ g/l; normal: 107–171) levels were observed. He exhibited low fractional excretion of calcium (0.193%; cut-off: 1%), and the magnesium concentration of his spot urine was also low (0.2 mg/dl; cut-off: 10 mg/dl). These findings excluded excessive renal excretion and led to a diagnosis of malabsorption due to short bowel syndrome. His electrocardiogram, chest X-ray, and echocardiogram did not show any abnormalities.

His hypocalcemia was treated with an intravenous injection of calcium gluconate (8.5 w/v%, 5 ml) and the oral administration of calcium aspartate (1,200 mg/day) and alfacalcidol (1 μ g/day). An intravenous drip infusion of magnesium sulfate (20–40 mEq, once every two weeks) and the oral administration of magnesium aluminate metasilicate (1,200 mg/day) were used to treat the patient's hypomagnesemia. Sodium selenite (100–300 μ g, once every two weeks) was also injected intravenously for hyposelenemia.

The patient's muscle strength was gradually normalized in five months, as did his serum CK (230 U/l), calcium (9.5 mg/dl), magnesium (1.6 mg/dl), and selenium (98 μ g/l) levels (Fig. 1A). Tocopherol (1 mg/day) was also prescribed later for low vitamin E but it did not influence the clinical symptoms.

Restudy of Needle electromyography 1.5 years after the admission detected small amounts of polyphasic and low-amplitude potentials during voluntary contraction, but the early recruitment of neuromuscular units and spontaneous activities disappeared. These findings suggested recovery from acute phase. Restudy of muscle magnetic resonance imaging also showed partial improvement of hyperintense areas in the infraspinatus and internal obturator muscles but not in the other muscles (Fig. 2C and D).

Discussion

In this case, the patient developed myopathy and marked hyperCKemia together with hypocalcemia, hypomagnesemia, and hyposelenemia and short bowel syndrome after undergoing resection for advanced rectal cancer and construction of an ileal conduit. The main cause of the CK elevation in this case seemed to be hypocalcemia because of the relationship between the patient's serum CK and calcium levels. On the other hand, the hypocalcemia was considered to have been caused by short bowel syndrome, as the length of the functional small intestine (less than 200 cm) met the definition for this syndrome in adults¹⁰. There has been no report of hypocalcemic myopathy caused by short bowel syndrome, and most cases of hypocalcemic myopathy are caused by hypoparathyroidism. It is unclear why the patient's serum calcium levels fluctuated spontaneously, but post-surgical chronic diarrhea or unstable oral calcium intake (triggered by urolithiasis, appetite loss and so on) are possible explanations. The time-lag between the decrease of serum calcium and the onset of muscle weakness could be explained by chronic loss of intra-corporeal or intracellular calcium. Pregabalin had been prescribed more than three years without CK elevation, and therefore it was unlikely as a cause of myopathy. This patient received radiotherapy but it was localized to the pelvic cavity. Therefore, it was not plausible as a cause of malabsorption. Furthermore, he did not experience local recurrence of the tumor or ileus, so his malabsorption was attributable to short bowel syndrome.

Previous reports mentioned hypocalcemic myopathy involved proximal limb muscles^{2)–9)}, but the muscle-specificity or predisposition remains unclear. Muscle MRI would be useful to clarify more precise lesional distribution and characteristics of hypocalcemic myopathy.

Hypomagnesemia may cause weakness¹¹⁾¹²⁾ and secondary hypocalcemia due to increased renal and skeletal resistance to PTH, decreased 25(OH) vitamin D levels, and the suppression of PTH production¹¹⁾¹³⁾¹⁴⁾. To the best of our knowledge, there have not been any reports of hypomagnesemia-induced hyperCKemia.

Furthermore, selenium deficiency (also known as 'Keshan disease') may cause muscle weakness and cardiomyopathy, especially in cases involving inappropriate long-term parenteral nutrition¹⁴⁾¹⁵⁾. Hyposelenemia may also cause elevated CK levels, but it was probably only a minor factor in the hyperCKemia seen in this case because the patient's selenium levels recovered slowly, whereas his CK levels recovered faster.

This case suggests that hypocalcemia can cause myopathy and markedly elevated CK levels, which mimics polymyositis, necrotizing myopathy, and rhabdomyolysis. Conversely, rhabdomyolysis can cause secondary hypocalcemia because it increases calcium influx into myocytes due to Ca²⁺ ATPase

pump dysfunction¹⁶⁾. In this case, however, hypocalcemia seemed to be the primary cause because our retrospective analysis revealed that the hypocalcemia preceded the CK elevation.

There have been some cases of hyperCKemia due to hypocalcemia without muscle weakness, and these cases have been reported in cases involving a wide spectrum of hypocalcemic muscle dysfunction¹⁷⁻²¹⁾ although it remains somewhat controversial whether these cases should be named hypocalcemic “myopathy”.

Our extensive examinations excluded other metabolic disorders. Severe vitamin E deficiency also may cause myopathy^{22,23)}. Our case showed decrease of vitamin E consistent with malabsorption but it was mild, and therefore it seemed unlikely as a main cause of myopathy.

The main limitation of this study is that we did not perform a muscle biopsy because the patient's CK levels improved rapidly and spontaneously after admission. Previous studies described type 2 fiber atrophy due to hypocalcemic myopathy^{4,8)}, but others reported normal results³⁾ or non-specific changes⁶⁾.

Short bowel syndrome may cause multiple deficits of nutrients and various clinical manifestations depending on the deficits, and therefore clinicians should monitor the patients' signs and symptoms including neurologic symptoms carefully²⁴⁾.

In conclusion, this case showed that CK elevation may be caused by hypocalcemic myopathy with hypomagnesemia and hyposelenemia in patients with short bowel syndrome. This report will help clinicians to understand disorders associated with essential nutrients and their management.

Abstract of this work was presented at the 109th Hokkaido Regional Meeting of the Japanese Society of Neurology and recommended by the conference chairperson for the publication to *Rinsho Shinkeigaku*.

※The authors declare that there is no conflict of interest relevant to this article.

References

- 1) Ropper AH, Samuels MA, Klein JP, et al. Chapter 39. The acquired metabolic disorders of the nervous system. In: Adams and Victor's Principles of Neurology. 11th ed. New York: McGraw-Hill; 2019. p. 1156-1183.
- 2) Wolf SM, Lusk W, Weisberg L. Hypocalcemic myopathy. *Bull Los Angeles Neurol Soc* 1972;37:167-177.
- 3) Kruse K, Scheunemann W, Baier W, et al. Hypocalcemic myopathy in idiopathic hypoparathyroidism. *Eur J Pediatr* 1982; 138:280-282.
- 4) Yamaguchi H, Okamoto K, Shooji M, et al. Muscle histology of hypocalcaemic myopathy in hypoparathyroidism. *J Neurol Neurosurg Psychiatry* 1987;50:817-818.
- 5) Van Offel JF, De Gendt CM, De Clerck LS, et al. High bone mass and hypocalcaemic myopathy in a patient with idiopathic hypoparathyroidism. *Clin Rheumatol* 2000;19:64-66.
- 6) Nora DB, Fricke D, Becker J, et al. Hypocalcemic myopathy without tetany due to idiopathic hypoparathyroidism: case report. *Arq Neuropsiquiatr* 2004;62:154-157.
- 7) Policepatil SM, Caplan RH, Dolan M. Hypocalcemic myopathy secondary to hypoparathyroidism. *WMJ* 2012;111:173-175.
- 8) Hirata D, Nagashima T, Saito S, et al. Elevated muscle enzymes in a patient with severe hypocalcemia mimicking polymyositis. *Mod Rheumatol* 2002;12:186-189.
- 9) Syriou V, Kolitsa A, Pantazi L, et al. Hypoparathyroidism in a patient presenting with severe myopathy and skin rash. Case report and review of the literature. *Hormones (Athens)* 2005;4:161-164.
- 10) Pironi L. Definitions of intestinal failure and the short bowel syndrome. *Best Pract Res Clin Gastroenterol* 2016;30:173-185.
- 11) Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. *Nutrients* 2015;7:8199-8226.
- 12) Barbagallo M, Veronese N, Dominguez LJ. Magnesium in aging, health and diseases. *Nutrients* 2021;13:463.
- 13) Abbott L, Nadler J, Rude RK. Magnesium deficiency in alcoholism: possible contribution to osteoporosis and cardiovascular disease in alcoholics. *Alcohol Clin Exp Res* 1994;18: 1076-1082.
- 14) Osaki Y, Nishino I, Murakami N, et al. Mitochondrial abnormalities in selenium-deficient myopathy. *Muscle Nerve* 1998;21:637-639.
- 15) Al-Mubarak AA, van der Meer P, Bomer N. Selenium, Selenoproteins, and heart failure: current knowledge and future perspective. *Curr Heart Fail Rep* 2021;18:122-131.
- 16) Khan FY. Rhabdomyolysis: a review of the literature. *Neth J Med* 2009;67:272-283.
- 17) Walters RO. Idiopathic hypoparathyroidism with extrapyramidal and myopathic features. *Arch Dis Child* 1979;54:236-238.
- 18) Piechowiak H, Gröbner W, Kremer H, et al. Pseudo-hypoparathyroidism and hypocalcemic “myopathy”. A case report. *Klin Wochenschr* 1981;59:1195-1199.
- 19) Ishikawa T, Inagaki H, Kanayama M, et al. Hypocalcemic hyper-CK-emia in hypoparathyroidism. *Brain Dev* 1990;12: 249-252.
- 20) Akmal M. Rhabdomyolysis in a patient with hypocalcemia due to hypoparathyroidism. *Am J Nephrol* 1993;13:61-63.
- 21) Barber J, Butler RC, Davie MW, et al. Hypoparathyroidism presenting as myopathy with raised creatine kinase. *Rheumatology (Oxford)* 2001;40:1417-1418.
- 22) Osoegawa M, Ohyagi Y, Inoue I, et al. A patient with vitamin E deficient, myopathy presenting with amyotrophy. *Rinsho Shinkeigaku* 2001;41:428-431.
- 23) Kleopa KA, Kyriacou K, Zamba-Papanicolaou E, et al. Reversible inflammatory and vacuolar myopathy with vitamin E deficiency in celiac disease. *Muscle Nerve* 2005;31:260-265.
- 24) Rubin DC. Chapter 325. Disorders of absorption. In: Harrison's Principles of Internal Medicine. 21st ed. New York: McGraw-Hill; 2022. p. 2458-2469.