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CASE REPORT

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Elevated muscle enzymes in a patient with severe hypocalcemia mimicking polymyositis

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Abstract We report a case of hypocalcemic myopathy confounded by polymyositis due to an elevated level of serum creatine kinase (CK). A 30-year-old man was referred to our hospital for the treatment of provisionally diagnosed polymyositis. His presentation with tetany, hyporeflexia, and general fatigue, in addition to muscle weakness on admission, prompted us to scrutinize a blood sample in search of secondary myopathy. Blood chemistry revealed an elevated level of serum CK, marked hypocalcemia, hyperphosphatemia, and a low serum level of intact parathyroid hormone. The Ellsworth Howard test confirmed the diagnosis of hypoparathyroidism. Supplementation with calcium and 1α-hydroxyvitamin D3 improved his muscle weakness rapidly, and his serum CK level returned to the normal range. Hypoparathyroidism should be included in differential diagnoses of elevated serum CK.

Key words Hypoparathyroidism · Myopathy · Vitamin D

Introduction

There are many other causes of the elevation of serum muscle enzymes in addition to the inflammation of myocytes. These include endocrinological abnormalities such as hypothyroidism, or electrolyte imbalance such as hypocalcemia and hypokalemia. Since the first report in 1972,[1] several cases of hypocalcemic myopathy with an elevated serum level of muscle enzymes have been reported.[2–5] Hypocalcemic myopathy is caused by conditions such as hypoparathyroidism, pseudohypoparathyroidism, and vitamin D deficiency. A decrease in plasma calcium concentration might disturb the membrane integrity of myocytes, resulting in a leakage of cytoplasmic enzymes such as creatine kinase (CK) and aldolase. The correction of hypocalcemia per se usually lowers serum level of CK to the normal range and muscle strength recovers. We present an unusual case of hypocalcemic myopathy associated with hypoparathyroidism, which was first considered to be inflammatory myositis, and was referred to us for treatment with corticosteroid.

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Case report

A 30-year-old man was admitted to our hospital on July 27, 1999, because of general fatigue and numbness of his extremities. In November, 1998, he had been found to have high serum levels of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and lactic dehydrogenase (LDH) during an annual medical check-up at his workplace. His own doctor had been monitoring his serum enzyme abnormalities since then. Because a high serum level of CK (3540 U/l) was found in addition to elevated levels of transaminases (GOT, 117 U/l; GPT, 63 U/l) and LDH (1047 U/l), he was provisionally diagnosed as having polymyositis, and referred to our hospital for treatment with corticosteroid. His family history and his own past history were unremarkable. He had developed normally in terms of physique and mental status. He had been working in the car manufacturing industry since he graduated from high school. He did not drink alcohol, but he had smoked a pack of cigarettes every day for 15 years.

On admission, he was 170 cm tall and weighed 57.7 kg. His body temperature was 37.2°C, and his pulse rate was 96/min and regular. His blood pressure was 134/84 mmHg. Serum antinuclear and anti-Jo-1 antibodies were absent (Table 1). His total serum CK was markedly elevated (6340 U/l), with an isoenzyme CK–MM of more than 98%. His serum levels of aldolase (11.2 IU/l/37°C) and LDH (1483 U/l) were also elevated. No muscle tenderness was

Table 1. Laboratory data on admission

WBC	7200/μl	ANF	–
RBC	517×10^4/μl	Anti-Jo-1 antibody	–
Platelets	28.1×10^4/μl	TSH	1.32 U/l
Ca	4.8 mg/dl	Free thyroxine	1.85 ng/dl
Pi	6.8 mg/dl	Cortisol	16.7 mg/dl
Mg	1.9 mg/dl	Creatinine clearance	96.9 ml/min
Fe	131 mg/dl	Urinary	
Cu	91 mg/dl	17-KS	6.4 mg/day
Ferritin	78.2 ng/dl	17-OHCS	11.8 mg/day
Ceruloplasmin	24 mg/dl	Ca	0.03 g/day
Albumin	4.9 g/dl	QTc in electrocardiogram	0.49 s
Total bilirubin	3.17 mg/dl	Nerve conduction velocity	Normal
Direct bilirubin	0.44 mg/dl	Electromyogram	Neurogenic in TA and GC
Coombs test	–	99mTc bone scintigram	Normal
GOT	54 U/l	Total bilirubin after 400 cal diet for 2 days	From 2.58 to 5.49 mg/dl
GPT	19 U/l	Ca^{2+}	0.64 mM/l (2.41–2.72)
LDH	1483 U/l	25 (OH) vitamin D3	18 ng/ml
CK	6340 U/l	1,25 $(OH)_2$ vitamin D3	44.4 pg/ml
CK isozyme		Intact PTH	4 pg/ml (10–65)
MM	98.1%	Ellsworth Howard test	
MB	1.2%	Urine phosphate	77.9 mg/2 h (>35)
BB	0%	Urine cyclic AMP	8.2 mM (>1)
		%TRP	97.3% (80–92)

GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; LDH, lactic dehydrogenase; CK, creatine kinase; ANF, antinuclear factor; TSH, thyroid stimulating hormone; 17-KS, 17-ketosteroid; 17-OHCS, 17-hydroxycorticosteroid; TA, m. tibialis anterior; QF, m. quadriceps femoris; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphate; GC, m. gastrocnemius

observed in his extremities, but asymmetrical muscle atrophy was detected in both lower legs. His muscle strength was mildly decreased in m. gastrocnemius and m. tibialis anterior of both legs; this was incompatible with polymyositis. An electromyographic investigation, which was performed on the right side of his body, revealed a neurogenic change in m. quadriceps femoris and m. tibialis anterior, both of which were atrophic, but the other muscles were grossly normal. A light microscopic examination of the muscle biopsied from the left m. biceps brachii and magnetic resonance imaging (MRI) of the thigh muscles showed no abnormalities. The examination of serum electrolytes revealed marked hypocalcemia (4.8 mg/dl), a low concentration of Ca^{2+} (0.64 mM/l), and hyperphosphatemia (6.8 mg/dl). The signs of Chvostek and Trousseau were prominent, and deep–tendon reflexes could hardly be elicited from the knee or the Achilles tendon. An electrocardiogram showed a prolonged QTc interval (0.49 s). These abnormalities prompted us to examine the calcium and phosphate metabolism: intact parathyroid hormone (PTH), 4 pg/ml (normal: 10–65 pg/ml); urinary excretion of calcium, 0.03 g/day; tubular reabsorption of phosphate, 97.3%. Infusion of 100 U parathyroid hormone (Teriparatide, Asahi Chemical Industry, Tokyo, Japan) increased urinary excretion of phosphate and urinary cyclic AMP to 77.9 mg/2 h and 69.9-fold, respectively, establishing the diagnosis of idiopathic primary hypoparathyroidism. The Wechsler adult intelligence scale test was within normal limits, but the patient was a little restless. Computed tomography (CT) of his head revealed mild symmetrical calcification in the basal ganglia (Fig. 1). His bone structures and physical constitution were normal. Albright osteodystrophy and lenticular cataract were not found. The development of the teeth was normal, and candidiasis was not detected on the skin or in the mouth. Serum total and indirect bilirubin were mildly elevated, which was considered to be constitutional. When he was challenged with a low caloric diet (400 kcal/day) for 2 days, his total bilirubin increased from 2.58 mg/dl to 5.49 mg/dl, supporting the diagnosis of Gilbert's syndrome.[6] The serum calcium and bilirubin levels of his father and brother were found to be normal, and no other family studies were performed. Because of the right-side-dominant

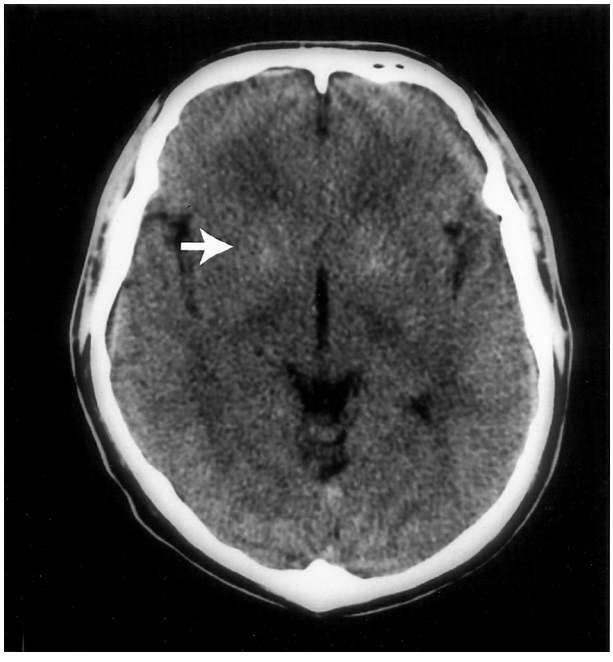

Fig. 1. Computed tomography of the patient's head shows mild symmetrical calcification in the basal ganglia (*arrow*)

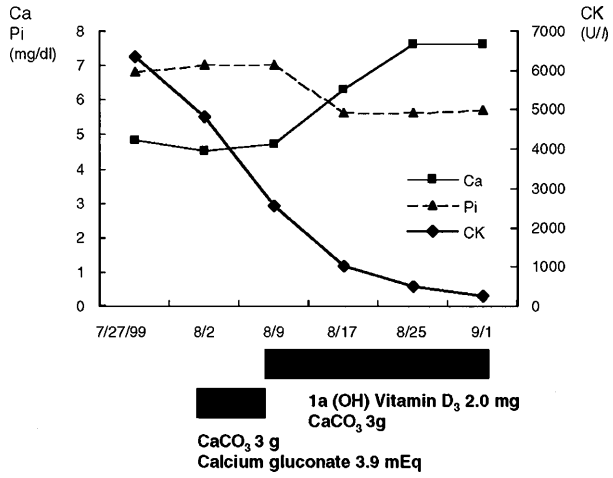

Fig. 2. Clinical course of the patient. Treatment with 1α hydroxyvitamine D_3 and calcium carbonate decreased the serum level of CK and normalized his calcium and phosphate metabolism. *CK*, creatine kinase

(asymmetrical) muscle atrophy of the bilateral m. gastrocnemius and m. tibialis anterior, as well as a neurogenic change in the electromyogram of these distal muscles, an organic lumbosacral lesion was suspected. MRI showed a large cystic lesion extending from the vertebral level of T11 down to L4, and the cord was displaced ventrally and compressed by the lesion. The coexistence of an arachnoid cyst was strongly suspected.

The patient was treated with 3 g calcium carbonate and 2 μg 1α-hydroxyvitamin D_3 per day. As shown in Fig. 2, serum levels of calcium, phosphate, and CK were normalized rapidly, and muscle weakness improved accordingly. To treat the arachnoid cyst in his lumbar spine, a shunt was placed between the arachnoid cyst and the peritoneum.

Discussion

The provisional diagnosis in this case before referral to our clinic was idiopathic inflammatory polymyositis. A subsequent careful examination during hospitalization revealed a marked hypocalcemia, which caused an elevation of CK. Hypocalcemic myopathy sometimes resembles idiopathic inflammatory polymyositis, and therefore electrolyte abnormalities should be ruled out in cases with CK-elevation in serum.

Conditions causing hypocalcemia are, in order of frequency, chronic renal failure, malabsorption syndromes, and hereditary and idiopathic hypoparathyroidism. Vitamin D deficiency, pseudohypoparathyroidism, hypomagnesemia, and autosomal dominant hypocalcemia with hypercalciuria (ADHH) are the known causes of hypocalcemia, although their exact frequencies are not known. Glu128Ala mutation in the Ca^{2+}-sensing receptor is the cause of ADHH, which is inherited in an autosomal dominant trait.[7,8] Because the patient's calcium excretion in urine decreased, and both his father and his brother exhibited normal serum calcium levels, ADHH was ruled out. His physique, intelligence, and T-cell count did not fit hereditary hypoparathyroidism, including DiGeorge syndrome. Therefore, we diagnosed his condition as idiopathic primary hypoparathyroidism. Although hypoparathyroidism has been known to be a cause of muscle weakness and CK elevation for 30 years,[1] little attenuation has been paid to it as a differential diagnosis of polymyositis. The frequency of increased levels of serum CK in Japanese patients with idiopathic primary hypoparathyroidism was reported to be 4.5%.[9] Hypocalcemia per se is considered to cause an elevation of serum CK.[1] Elevated levels of serum CK, along with hypocalcemia, were also observed in patients with pseudohypoparathyroidism,[10,11] and in a patient[12] and animals[13] with vitamin D deficiency. Several cases have been reported since 1972 concerning hypocalcemic myopathy or increased levels of serum CK in patients with idiopathic primary hypoparathyroidism.[2–5] Hypocalcemic myopathy is characterized by proximal dominant muscle weakness of the extremities, hyporeflexia, high levels of serum CK, and constant fatigue, although Kruse et al.[2] reported a case with proximal and distal muscle weakness. Muscle biopsy findings are either normal[2,14] or nonspecific, with focal atrophy of type II fibers[15] or myogenic change, e.g., myophagia, striking variations in the caliber of muscle fibers, and sarcolemmal nuclei showing central rows.[16] Streffer and Wiliamson[17] demonstrated the leakage of cellular enzymes in calcium-free media, which might be due to increased membrane permeability caused by decreased calcium concentration outside the cells. Yamaguchi et al.[3] demonstrated that hypocalcemia decreased the immunoreactivity of myoglobin in atrophic muscle fibers only and increased serum myoglobin, suggesting that hypocalcemia may directly cause myoglobin leakage from skeletal muscles. The question of why only some patients with hypoparathyroidism manifest hypocalcemic myopathy remains to be elucidated. It is postulated that some patients are more susceptible to hypocalcemia than others in terms of cell membrane integrity. In such patients, even a small change in serum calcium levels may disturb cell membrane integrity, resulting in a greater leakage of CK into the circulation.[18] This case manifested hyporeactive deep-tendon reflexes, but muscle weakness was not recognized except for the muscles affected by the arachnoid cyst. According to Ishikawa et al.,[19] the lower the serum calcium level became, the more frequently the muscle weakness and hypoactive deep-tendon reflexes occurred. Therefore, this case might have manifested muscle weakness if the patient's serum calcium level had been lower than it actually was. This case happened to be complicated by constitutional hyperbilirubinemia and the arachnoid cyst.

References

1. Wolf SM, Lusk W. Hypocalcemic myopathy. Bull Los Angeles Neurol Soc 1972;37:167–77.

2. Kruse K, Scheunemann W, Baier W, Schaub J. Hypocalcemic myopathy in idiopathic hypoparathyroidism. Eur J Pediatr 1982;138: 280–2.
3. Yamaguchi H, Okamoto K, Shooji M, Morimatsu M, Hirai S. Muscle histology of hypocalcaemic myopathy in hypoparathyroidism [letter]. J Neurol Neurosurg Psychiatry 1987;50:817–8.
4. Hower J, Struck H, Tackmann W, Stolecke H. CPK activity in hypoparathyroidism. N Engl J Med 1972;287:1098.
5. Battistella PA, Pozzan GB, Rigon F, Zancan L, Zacchello F. Autoimmune hypoparathyroidism and hyper-CK-emia [letter]. Brain Dev 1991;13:61.
6. Owens D, Sherlock S. Diagnosis of Gilbert's syndrome: role of reduced caloric intake test. Br Med J 1973;3:559–63.
7. Pollak MR, Brown EM, Estep HL, McLaine PN, Kifor O, Park J, et al. Autosomal dominant hypocalcaemia caused by a $Ca^{(2+)}$-sensing receptor gene mutation. Nat Genet 1994;8:303–7.
8. Pearce SH, Williamson C, Kifor O, Bai M, Coulthard MG, Davies M, et al. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor [see comments]. N Engl J Med 1996;335:1115–22.
9. Kohno H, Shimizu Y, Deura M, Saito N, Saegusa M, Kameka H. A case of idiopathic hypoparathyroidism presenting with a high level of AL-P, LDH, and CPK in the blood and calcifications of basal ganglia (in Japanese). Saishin Igaku 1981;36:350–6.
10. Piechowiak H, Grobner W, Kremer H, Pongratz D, Schaub J. Pseudohypoparathyroidism and hypocalcemic "myopathy". A case report. Klin Wochenschr 1981;59:1195–9.
11. Cape CA. Phosphorylase a deficiency in pseudohypoparathyroidism. Neurology 1969;19:167–72.
12. Ishikawa T, Kawai K, Kanayama M, Wada Y. Increased serum creatine kinase due to hypocalcemia in vitamin D deficiency. Pediatr Neurol 1987;3:37–9.
13. Ishikawa T, Kanayama M, Oba T, Horie T. Hypocalcemic-induced increase in creatine kinase in rats. Pediatr Neurol 1998;18:326–30.
14. Shane E, McClane KA, Olarte MR, Bilezikian JP. Hypoparathyroidism and elevated muscle enzymes. Neurology 1980;30:192–5.
15. Evans RA, Carter JN, Shenston B, Smith A, Hills E, Walls R, et al. Candidiasis–endocrinopathy syndrome with progressive myopathy. Q J Med 1989;70:139–44.
16. Hower J, Struck H, Tackmann W, Bohlmann HG. Myopathy and elevated serum enzymes in a case of hypoparathyroidism. Z Kinderheilkd 1974;116:193–6.
17. Streffer C, Williamson DH. The effect of calcium ions on the leakage of protein and enzymes from rat-liver slices. Biochem J 1965;95:552–60.
18. Akmal M. Rhabdomyolysis in a patient with hypocalcemia due to hypoparathyroidism. Am J Nephrol 1993;13:61–3.
19. Ishikawa T, Inagaki H, Kanayama M, Manzai T. Hypocalcemic hyper-CK-emia in hypoparathyroidism. Brain Dev 1990;12:249–52.