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증 례

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Symptomatic Hypocalcemia Associated with *Dioscorea tokoro* Toxicity

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Dioscorea tokoro has long been used in Korean traditional medicine as a pain killer and anti-inflammatory agent. A 53-year-old male who consumed water that had been boiled with raw tubers of *D. tokoro* as tea presented with numbness and spasm of both hands and feet. Laboratory results showed hypocalcemia, hypoparathyroidism, and vitamin D insufficiency. During his hospital stay, colitis, acute kidney injury, and toxic encephalopathy developed. The patient received calcium gluconate intravenous infusion and oral calcium carbonate with alfacalcidol. His symptoms improved gradually, but hypocalcemia persisted despite the calcium supplementation. We suggest that ingestion of inappropriately prepared *D. tokoro* can cause symptomatic hypocalcemia in patients with unbalanced calcium homeostasis.

Key Words: *Dioscorea tokoro*, Hypocalcemia, Hypoparathyroidism

INTRODUCTION

Use of plants for health and medicine is widely followed in Korea according to the belief that plants are natural and safe and can promote health. Contrary to such popular belief, the use of herbal medicine can cause serious harm[1]. *Dioscorea* species, commonly known as yam, are widely used as a staple dietary component in Africa and Asia[2]. In Korea, it had been used for treatment of rheumatism, urinary tract infection, and sequela of stroke. Detoxification of yam is necessary before eating. Poisoning may result from the ingestion of partially detoxified tubers of *Dioscorea* that can lead to acute kidney injury (AKI) and toxic encephalopathy[3-5]. Herein, we report of a case of symptomatic hypocalcemia developed after drinking boiled water with raw tubers of *Dioscorea tokoro*.

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CASE REPORT

A 53-year-old male with a history of hypertension was presented to our emergency department (ED) complaining of general weakness and numbness and spasm of both hands and feet. Two days before admission, he had drunk a cup of boiled water with raw tubers of *D. tokoro*. Nausea and vomiting, edema and numbness of both hands and feet, and

general weakness developed 3-4 hours after ingestion and persisted. He had a history of cerebral infarction 2 years ago. He was not a chronic alcoholic and did not previously have a thyroid or parathyroid operation. The family history was negative for any of the autoimmune diseases associated with hypoparathyroidism.

On examination, his vital signs were blood pressure 100/70 mmHg, pulse 80/min, respiratory rate 18/min, and body temperature 36.5°C. Neurologic examination showed no specific abnormality except the complaint of numbness of both hands and feet. Laboratory findings revealed sodium of 138 mmol/L, potassium of 3.6 mmol/L, creatinine of 0.95 mg/dL (reference range (RR); 0.7-1.7 mg/dL), total calcium of 7.4 mg/dL (RR; 8.4-10.2 mg/dL), ionized calcium of 1.01 mmol/L (RR; 1.13-1.32 mmol/L), phosphorus of 3.6 mg/dL (RR; 2.5-4.5 mg/dL), and magnesium of 1.8 mg/dL (RR; 1.45-2.67 mg/dL). Thyroid stimulating hormone (TSH) and free T4 level was 0.378 ?IU/ml (RR; 0.55-4.78 μIU/ml) and 13.77 pmol/L (RR; 11.5-22.7 pmol/L), respectively. Electrocardiography (ECG) showed normal sinus rhythm with QT prolongation (corrected QT interval, QTc; 477 ms). Symptomatic hypocalcemia was suspected and calcium gluconate intravenous infusion was started. Parathyroid hormone (PTH) level on the hospital day (HD) 2 was 6.4 pg/mL (RR; 15.0-65.0 pg/ml). Calcium carbonate and alfacalcidol therapy were started on the HD 3. Calcium carbonate was increased to double dose on the HD 9 due to persistent hypocalcemia. Abdomen computed tomography (CT) and colonoscopy was performed on the HD 3 and 4, respectively, due to abdominal pain, hematochezia, and diarrhea demonstrated ischemic colitis. Acute kidney injury (AKI) developed on the HD3. Antibiotic therapy with hydration was initiated and gastrointestinal symptoms and renal function gradually improved. Brief generalized tonic-clonic seizure of about 1 minute and postictal confusion was shown on HD 4 and 10. Irritability, aggressive behavior, and restlessness were observed and treated with benzodiazepine and haloperidol between HD 4 and 6. Brain CT showed no acute abnormality or any calcification. Laboratory results, clinical course, and treatment during hospital stay are summarized in Table 1. Hypocalcemic symptoms and signs improved despite persistent hypocalcemia. He was discharged with mild dizziness and easy fatigability and received follow up. The calcium and PTH level was 7.8 mg/dL and 5.26 pg/ml, respectively, 1 month later. After then, he was lost to follow up.

DISCUSSION

We assumed initially that neurologic manifestations

Table 1. Laboratory results, clinical course, and treatment during hospital stay

	HD1	HD2	HD3	HD4	HD6	HD8	HD9	HD10	HD13	HD16
Calcium	7.4	6.6	7.2	7.1	6.5	7.0	6.5	6.0	7.1	7.2
Phosphorus	3.6	5.0	4.7	4.7	5.0	6.2	5.1	4.5	4.1	4.0
Ionized Ca	1.01	1.07		1.02					1.04	1.08
Albumin	4.3	3.8		3.5		3.4	3.5			
Creatinine	1.07	1.20	2.45	2.65	3.22	1.98	1.47			
Magnesium	1.8		2.1	1.8	2.2					
PTH		6.4			7.3					
25-OH VitD3					10.5				14.2	
Clinical course			Hematochezia	Seizure				Seizure		
Treatment			Calcium carbonate 500 mg+alfacalcidol 0.5 ug twice per day				Calcium carbonate 1,000 mg+alfacalciol 0.5 ug twice per day			

HD: hospital day

Reference range, Calcium (8.4-10.2 mg/dL); Phosphorus (2.5-4.5 mg/dL); Ionized Calcium (1.13-1.32 mmol/L); Albumin (3.5-5.3 g/dL); Creatinine (0.7-1.7 mg/dL); Magnesium (1.45-2.67 mg/dL); PTH (15.0-65.0 pg/ml)

25-OH Vitamin D3 (ng/ml): Vitamin D deficiency: <10.0/Vitamin D insufficiency: 10.0-30.0/Vitamin D sufficiency: 30.1-150.0/Vitamin D toxicity: >150.0

such as seizure and numbness of both hand and feet and QTc prolongation on ECG were consequence of acute hypocalcemia. When the previous laboratory studies were examined, the calcium level was 9.5 mg/dl 9 months ago. Also, careful history taken from our patient revealed no previous neurologic manifestations associated with hypocalcemia.

The causes of hypocalcemia are diverse and include vitamin D deficiency or resistance, hypoparathyroidism, magnesium disorder, infusion of phosphate or citrated blood transfusions, or critical illness[6]. We suggest that the causes of hypocalcemia in our patient were a combination of hypoparathyroidism (low PTH level), vitamin D insufficiency, and *D. tokoro* toxicity.

Our patient had normal magnesium levels and did not have history of neck surgery, take medications which suppress PTH secretion, family history of hypocalcemia, other endocrinopathy, or congenital defect with any suggesting a cause for hypoparathyroidism[7]. Considering that there were no precipitating causes of hypoparathyroidism, we speculate that hypoparathyroidism of our patient was latent type or a result of direct toxicity of *D. tokoro* less likely.

Vitamin D deficiency defined as 〈 20 ng/ml is common in urban older Koreans[8]. *D. tokoro* contains various steroidal saponins[9-11]. Diosgenin is the main steroidal saponin of *Dioscorea* species and structurally similar to cholesterol and other steroids. Since its discovery, diosgenin has been the single main precursor in the manufacture of synthetic steroids in the pharmaceutical industry[12]. Steroid may result in significant hypocalcemia in the presence of deranged calcium homeostasis such as vitamin D deficiency[13] or hypoparathyroidism[14] as shown in our patient. Steroids decrease intestinal absorption of calcium and, also increase calcium excretion by the kidney through decreased tubular reabsorption[15]. Negative calcium balance finally is achieved. A healthy person with normal parathyroid function can counterbalance this negative calcium balance via increased parathyroid hormone production[16]. However, symptomatic hypocalcemia may develop as in our patient due to concurrent hypoparathyroidism and vitamin D deficiency. In addition, steroidal glycosides of *Dioscorea* species have an antiosteoporotic effect[17] and inhibit bone resorption induced by parathyroid hormone[18].

In recent years, several cases of AKI developing after ingestion of *D. quinqueloba* have been reported. Although the exact pathogenesis of AKI induced by *D. quinqueloba* remains unknown, toxic effect of dioscorine and dioscine and dehydration associated with antecedent gastrointestinal complication such as vomiting and diarrhea were suggested as cause of AKI[3]. *Dioscorea* species are rich in dioscorine and dioscine which have convulsive, local anesthetic, and antidiuretic effects[19]. In one report, renal biopsy performed on an AKI patient brought on by *D. quinqueloba* intake showed interstitial nephritis[4]. The authors in the report suggest that an immune reaction caused by dioscorine and dioscine may have been the cause of AKI.

In addition to hypocalcemia, neurologic manifestations in our patient including seizure, confusion, irritability, aggressive behavior, and restlessness can be explained by *Dioscorea* species toxicity. Kang and Heo reported a case of AKI with toxic encephalopathy following ingestion of juice made from raw tuber of *D. quinqueloba*[5]. After ingestion, nausea and vomiting developed, followed by seizure and decreased mental status. Decreased renal function and dioscorine and dioscine can be related to toxic encephalopathy.

CONCLUSION

our case shows that ingestion of insufficiently detoxified *Dioscorea* species can be harmful with effects including gastrointestinal complications, AKI with toxic encephalopathy, and hypocalcemia in a patient with deranged calcium homeostasis. People should be informed of the appropriate detoxification that includes placing certain tubers in running water for a few days, soaking in salt water, and boiling for several hours[2]. It should be noted that certain herbs used in traditional medicine can cause serious health effects if taken inappropriately and that doctors and family physicians should educate their clients on the proper use of certain herbs and plant medicines.

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CONFLICTS OF INTEREST

The authors have no competing interests relevant to the present study.

REFERENCES

1. De Smet PA. Herbal remedies. N Engl J Med 2002; 347:2046-56.
2. Steenkamp V, Stewart MJ. Nephrotoxicity associated with exposure to plant toxins, with particular reference to Africa. Ther Drug Monit 2005;27:270-77.
3. Kim CS, Kim SM, Choi JS et al. Dioscorea quinqueloba induces acute kidney injury. Clin Toxicol (Phila) 2012;50: 80.
4. Kim HY, Kim SS, Bae SH et al. Acute interstitial nephritis induced by Dioscorea quinqueloba. BMC Nephrol 2014;15: 143.
5. Kang KS, Heo ST. A case of life-threatening acute kidney injury with toxic encephalopathy caused by Dioscorea quinqueloba. Yonsei Med J 2015;56:304-06.
6. Fong J, Khan A. Hypocalcemia: updates in diagnosis and management for primary care. Can Fam Physician 2012;58: 158-62.
7. De Sanctis V, Soliman A, Fiscina B. Hypoparathyroidism: from diagnosis to treatment. Curr Opin Endocrinol Diabetes Obes 2012;19:435-42.
8. Song HR, Kweon SS, Choi JS et al. High prevalence of vitamin D deficiency in adults aged 50 years and older in Gwangju, Korea: the Dong-gu Study. J Korean Med Sci 2014;29:149-52.
9. Akahori A, Okuno I, Okanishi T et al. Studies on the steroidal components of domestic plants. LV. The steroidal sapogenins of the female flowers and the seeds of Dioscorea tokoro Makino. Chem Pharm Bull (Tokyo) 1968;16:1994-96.
10. Tomita Y, Uomori A, Minato H. Steroidal sapogenins and sterols in tissue cultures of Dioscorea tokoro Phytochemistry. 1970;9:111-14.
11. Sautour M, Mitaine-Offer A-C, Lacaille-Dubois M-A. The Dioscorea genus: a review of bioactive steroid saponins. Journal of natural medicines 2007;61:91-101.
12. Djerassi C, Rosenkranz G, Pataki J et al. Steroids, XXVII. Synthesis of allopregnane-3beta, 11beta, 17alpha-, 20beta, 21-pentol from cortisone and diosgenin. J Biol Chem 1952; 194:115-18.
13. Kinoshita Y, Masuoka K, Miyakoshi S et al. Vitamin D insufficiency underlies unexpected hypocalcemia following high dose glucocorticoid therapy. Bone 2008;42:226-28.
14. Oikonomou D, Laina A, Xydaki A et al. Steroid-induced hypocalcaemia with tetany in a patient with hypoparathyroidism. BMJ Case Rep 2014;2014.
15. Canalis E, Mazziotti G, Giustina A et al. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 2007;18:1319-28.
16. Fucik RF, Kukreja SC, Hargis GK et al. Effect of glucocorticoids on function of the parathyroid glands in man. J Clin Endocrinol Metab 1975;40:152-55.
17. Yin J, Han N, Liu Z et al. The in vitro antiosteoporotic activity of some glycosides in Dioscorea spongiosa. Biol Pharm Bull 2010;33:316-20.
18. Yin J, Kouda K, Tezuka Y et al. Steroidal glycosides from the rhizomes of Dioscorea spongiosa. J Nat Prod 2003;66: 646-50.
19. Broadbent JL, Schnieden H. A comparison of some pharmacological properties of dioscorine and dioscine. Br J Pharmacol Chemother 1958;13:213-15.