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【 CASE REPORT 】

Xanthinuria Type 1 with a Novel Mutation in Xanthine Dehydrogenase and a Normal Endothelial Function

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Abstract:

Whether or not extremely low levels of serum uric acid (SUA) in xanthinuria are associated with impairment of the endothelial function and exercise-induced acute kidney injury (EIAKI) is unclear. A 59-year-old woman without EIAKI or urolithiasis had undetectable levels of UA in serum and urine and elevated levels of hypoxanthine and xanthine in urine. A genetic analysis revealed homozygous mutations in the XDH gene [c.1585 C>T (p. Gln529*)]. Flow-mediated dilation was within the normal range. This is the first report of a case with extremely low levels of SUA, xanthinuria with novel mutations of xanthine dehydrogenase (XDH) and a normal endothelial function.

Key words: xanthinuria type1, XDH gene, endothelial function

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Introduction

Hypouricemia is arbitrarily defined as a serum uric acid (SUA) concentration <2–3 mg/dL (1). Transient hypouricemia is observed in 1.86% of hospitalized patients and is often caused by malignancy or medical treatment (2). In contrast, persistent hypouricemia is observed in 0.15% of outpatients (3) and is caused by genetic mutations that inhibit the production of UA or enhance its renal excretion (1). For example, mutations in xanthine dehydrogenase (XDH) cause hypouricemia and xanthinuria (4), while mutations in *SLC22A12* encoding urate transporter 1 (URAT 1) (5), and *SLC2A9* encoding glucose transporter 9 (GLUT 9) (6) enhance renal excretion and cause hypouricemia.

Xanthinuria is a rare autosomal recessive disorder caused by mutations in the XDH gene that impair their enzyme activity (4). It is characterized by hypouricemia accompanied by increases in the plasma and urinary levels of xanthine and hypoxanthine. Xanthinuria is classified into two types: type I is caused by a deficiency of XDH alone, and type II is caused by a deficiency of both XDH and aldehyde oxi-

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Table. **Plasma and Urinary Level of Uric Acid, Hypoxanthine, and Xanthine.**

	blood	normal	urine	normal
Hypoxanthine (μmol/L)	0.8	1.1-3.0	42.3	4.0-5.7
Xanthine (μmol/L)	2.8	0.7-1.2	146.5	3.5-4.6
Uric Acid (mg/dL)	<0.1		<0.1	

dase (7, 8). Newborns with type II xanthinuria associated with sulfide oxidase deficiency (i.e. molybdenum cofactor deficiency) develop severe neurologic symptoms and often die within the second week of life.

Patients with renal hypouricemic are generally asymptomatic. However, several complications have been reported, such as exercise-induced acute kidney injury (EIAKI) in 7-10% of cases and urolithiasis in 10% of cases (9). EIAKI is caused by vasoconstriction of the renal artery after exercise (10). Sugihara et al. reported that an extremely low level of UA (<0.8 mg/dL) impairs the endothelial function as evaluated by flow-mediated dilation (FMD) (11). However, no reports have described the relationship between xanthinuria and the endothelial function.

We recently experienced a patient with xanthinuria with a novel mutation of XDH who had a normal endothelial function.

Case Report

A 59-year-old woman consulted us for an extreme low level of SUA found by a medical checkup. Her systolic and diastolic blood pressures were 171 and 122 mmHg, respectively, indicating hypertension. A biochemical examination revealed undetectable levels of UA in both the plasma and urine. Her estimated glomerular filtration rate was 144.8 mL/min/1.73 m^2.

Serum and urinary levels of oxypurine and genetic and enzymatic analyses of XDH.

Concentrations of hypoxanthine and xanthine in plasma and urine were measured by high-pressure liquid chromatography (12). The plasma hypoxanthine level dropped to 0.8 mmol/L, which was below the normal range (1.1-3.0 mmol/L), whereas the plasma xanthine concentration increased to 2.8 mmol/L, which was above the normal range (0.7-1.2 mmol/L). The urinary hypoxanthine concentration was increased to 42.3 mmol/L, which was above the normal range (4.0-5.7 mmol/L), and the urinary xanthine concentration was also elevated to 146.5 mmol/L, which was above the normal range (3.5-4.6 mmol/L) (Table).

A genetic analysis was approved by the ethics committee of the hospital, and written informed consent was obtained from the patient. *XDH* mutations were surveyed by bidirectional automated DNA sequencing of PCR-amplified genetic DNA. Homozygous mutations of c.1585 C>T (p. Gln529*) (Figure) were detected. These mutations are predicted to cause truncation of the XDH protein, which eliminates the molybdenum binding site. The plasma xanthine oxidoreductase (XOR) activity was undetectable.

The endothelial function as evaluated by FMD

Since hypouricemic patients with SUA <0.8 mg/dL have an impaired endothelial function (11), we measured the FMD in the patient and found that her value was 7.1%, which was within the normal range (over 6%).

Discussion

We identified novel homozygous mutations in XDH as the cause of xanthinuria type 1. XDH is a large molecule comprising 1,333 amino acids and composed of 3 functional domains (13). The middle domain contains a 2Fe/2S nonheme iron-binding site (Fe/S domain). The adjacent site contains a flavin-binding domain (FAD domain), and the COOH-terminal contains a molybdenum cofactor binding site (Moco domain) (14). XDH catalyzes oxidation of hypoxanthine to xanthine and then xanthine to uric acid in the final stages of purine metabolism (15). Xanthinuria resulting from a deficiency in XDH is characterized by hypouricemia, decreased urinary uric acid excretion, and increased levels of xanthine and hypoxanthine in serum and urine, respectively. Classical xanthinuria has been classified into two subtypes: type 1 lacks xanthine dehydrogenase activity alone, and type 2 lacks both XDH and aldehyde oxidase activity (7, 8).

The present case showed hypouricemia and a reduction in urinary uric acid excretion, accompanied by increased levels of xanthine and hypoxanthine in serum and urine, which is comparable to xanthinuria type 1. A genetic analysis of DNA prepared from white blood cells revealed homozygous mutations of c.1585 C>T in the XDH gene, which is predicted to cause truncation of the XDH protein (p. Gln529*). The truncated protein lacks the entire molybdopterin domain and is nonfunctional. These findings prompted us to conclude that the present case was xanthinuria type 1. The plasma XOR activity was undetectable in accordance with the barely detectable level of UA. Hypoxanthine in the serum was detectable but was below the normal level. Hypoxanthine is reported to be reabsorbed from the urine through UA transporters (16). The impaired renal reabsorption may have resulted in increased hypoxanthine clearance and a subsequent decrease in the serum concentration. Further studies will be necessary to verify this notion.

Xanthinuria is associated with urolithiasis that is composed of xanthine (16). The clinical course of isolated hereditary xanthinuria is usually mild. Nephrolithiasis is the most common manifestation, but arthralgia and muscle cramps (associated with xanthine deposition in muscle) have also been reported in adults (17). However, no report has described xanthinuria as being associated with complications induced by extremely low level of SUA, such as EIAKI. In contrast, renal hypouricemia is reported to be accompanied by EIAKI (9), which can be caused by spasm of the renal

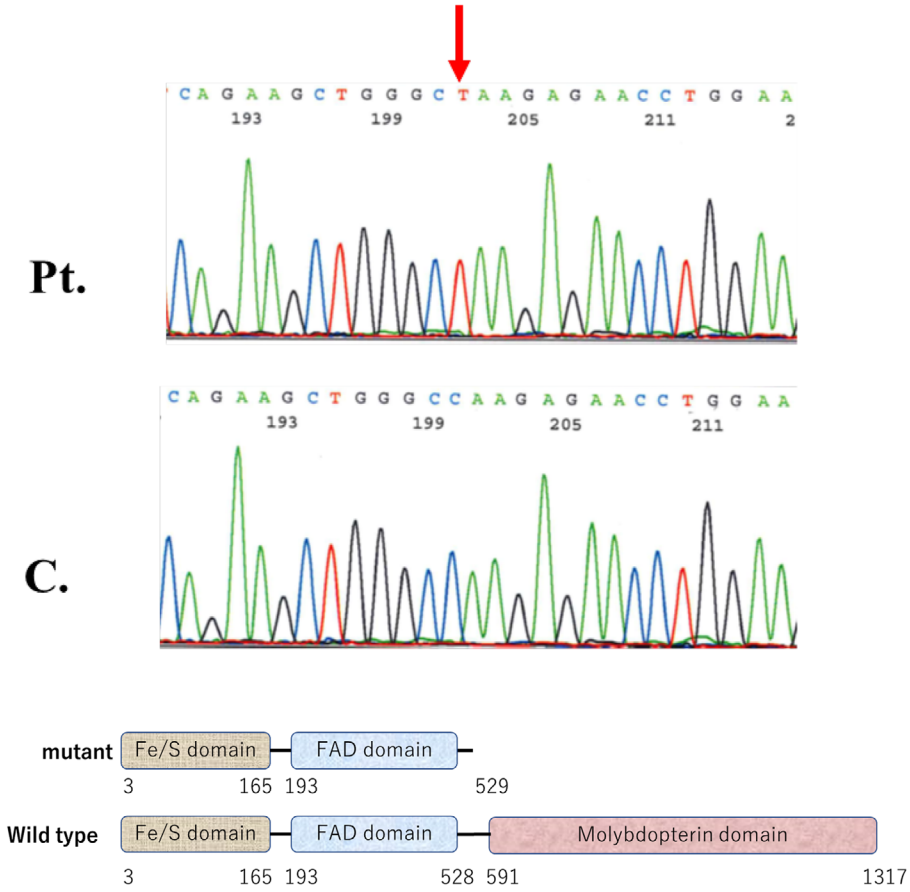

Figure. **Mutation of XDH gene and its structure.**

artery. UA acts as a scavenger *in vitro*, and renal hypouricemia is frequently associated with an impaired endothelial function (11). In the extracellular space, UA is one of the most potent antioxidants. It can scavenge superoxide, hydroxyl radicals, and singlet oxygen and can chelate transition metals. It is thought to be responsible for neutralizing more than 50% of free radicals in human blood (17). In addition, UA at physiological levels prevents hydrogen peroxide-induced inactivation of superoxide dismutase, an antioxidant enzyme capable of removing superoxide anion radicals (18). The endothelial function is defined as vasodilation induced by nitric acid from endothelial cells. Since shear stress stimulates production of NO through the phosphorylation of endothelial nitric oxide synthase (eNOS) (19, 20), the endothelial function is clinically determined by the FMD. Given the role of SUA as an antioxidant, an extreme reduction can also impair the endothelial function (11). Xanthine oxidase (XO) converted from XDH is one of the main sources of free radicals. While XO generates free radicals and reduces the level of nitric oxide (21), uric acid inactivates the free radicals derived from XO and preserves the level of NO and endothelial function (22, 23). Sugihara et al. reported that renal hypouricemia is frequently associated with an impaired endothelial function evaluated by FMD (11). Sugihara et al. found that renal hypouricemic patients harboring a homozygous mutation of the URAT1 gene (SUA=0.7 mg/dL), compound heterozygous mutation of the URAT1 gene (0.65 mg/dL), or heterozygous mutation of the URAT1 gene (SUA=2.0 mg/dL) showed an FMD of 2.7%, 4.7%, and 9.3%, respectively, and the FMD in renal hypouricemia with an SUA of <0.8 mg/dL was significantly lower than the values in patients whose SUA was ≥0.8 mg/dL. Therefore, at extremely low levels of SUA (<0.8 mg/dL), UA is presumably insufficient to inactivate free radicals generated by XO.

This is the first report suggesting that under extremely low levels of SUA, XO may be one of the main sources of free radicals, causing an impaired endothelial function, since the value of FMD in the present case was within the normal range. To confirm this hypothesis, the accumulation of further findings concerning the endothelial function in xanthinuria cases is necessary.

The authors state that they have no Conflict of Interest (COI).

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