Renal insufficiency mimicking glutaric acidemia type 1 on newborn screening

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Abstract

Background: Glutaryl carnitine (C5DC) in dried blood spots is used as a biomarker for glutaric aciduria type 1 (GA-1) screening. C5DC, however, is the only screening marker for this condition, and various pathological conditions may interfere with C5DC metabolism. Recently, C5DC elevation has been reported in cases of renal insufficiency.

Method: Five patients who were positive for GA-1 on newborn screening with tandem mass spectrometry between September 2012 and March 2015 at Kobe University Hospital were enrolled in this study.

Results: GA-1 was not confirmed on urinary organic acids analysis in any of the patients. C5DC decreased immediately in four patients, but one patient, who had high C5DC for at least 4 months, was diagnosed with bilateral renal hypoplasia.

Conclusion: In the case of persistently elevated C5DC, renal insufficiency should be considered as a differential diagnosis.

Key words glutaric acidemia I, glutaryl carnitine, neonatal screening, renal insufficiency.

Glutaric acidemia type 1 (GA-1) is a rare acidemia caused by an inherited deficiency of glutaryl-CoA dehydrogenase (GCDH) that could lead to severe motor disorder, cognitive impairment, and enlargement of the ventricle. Early diagnosis on newborn screening and the early

implementation of medical and dietary treatment could prevent significant morbidity, mortality, and mental maldevelopment.[1] Glutaryl carnitine (C5DC) is an acylcarnitine derived from glutaryl-CoA, and it serves as a diagnostic biomarker on tandem mass spectrometry-based newborn screening of GA-1 in several countries, including Japan.[2] GCDH defect gives rise to 3-hydroxyglutaric acid (3OHGA) and glutaric acid (GA) in the urine, and to C5DC in the dried blood spot or plasma of a newborn. Recently, elevation of C5DC has also been reported in a case of other inherited metabolic disease, such as medium-chain acyl-CoA dehydrogenase deficiency.[3] It has also been observed that infants with congenital or acquired renal diseases have a high level of C5DC.[4] At Kobe University Hospital, five cases of elevated C5DC mimicking GA-1 were identified on newborn screening. Four of the five patients had a non-specific transient elevation of C5DC. One patient with renal insufficiency, however, maintained a high level of C5DC for at least 4 months. Here, we describe the clinical characteristics of elevated C5DC on newborn screening.

Case report

From September 2012 to March 2015, five patients were positive for GA-1 with an elevation of C5DC on newborn screening, and were referred to the

metabolic outpatient clinic at Kobe University Hospital. Simultaneous elevation of other acylcarnitines was not noted. None of the patients had neurological signs that would indicate GA-1, such as macrocephaly, dystonia, or dyskinesia. In all cases, gas chromatography–mass spectrometry urinary organic acids analysis was performed after the first visit to hospital. None of the patients had excess GA or 3OHGA excretion in the urine. Moreover, GA-1 was not confirmed in all cases. On repeat examination, C5DC had decreased at 1 month after initial elevation in four patients, but high C5DC persisted for at least 4 months in the fifth patient (Table 1). That patient was the second twin delivered by cesarean section at 36 gestational weeks. His birthweight was 1,850 g, lower than that of his brother, who weighed 2,340 g.

In that fifth patient, C5DC in dried blood spot at the age of 1 month was 0.25 nmol/mL (cut-off, 0.25 nmol/mL). At the first visit, he showed failure to thrive. Careful, in-depth evaluation indicated elevated serum creatinine, low estimated glomerular filtration rate (eGFR; 24 mL/min/1.73 m^2 calculated using the original Schwartz method[5]), metabolic acidosis with normal anion gap, and renal tubular damage with increased *N*-acetyl-beta-D-glucosaminidase (NAG; 6.1 U/L; reference range, 0–5.7) and β2-microglobulin (β2MG; 26 561 μg/L; reference range, 0–289),

indicating renal insufficiency. Diagnostic abdominal ultrasonography ultimately showed bilateral renal hypoplasia. The longitudinal dimensions of the right and left kidney were 39.0 mm and 39.7 mm, respectively, and were smaller than the reference dimensions of the kidney of an infant aged 1–3 months (50.0 ± 5.5 mm; 5–95th percentile, 42–59 mm;[6] Fig. 1). At the age of 4 months, C5DC remained high (0.29 nmol/mL; cut-off, 0.25). Serum albumin, blood urea nitrogen, and hematocrit were 4.5 g/dL (reference range, 4.1–5.0), 25.2 mg/dL (reference range, 9.0–22.0), and 36.1% (reference range, 39.0–52.0%), respectively, thereby indicating dehydration due to renal insufficiency. This results in slightly higher C5DC. At the age of 6 months, 8806H formula (Na, 2.7 mEq/100 mL; K, 0.8 mEq/100 mL; and P, 24 mg/100 mL) was given for renal insufficiency. Renal dysfunction persisted until at least the age of 2 years and 6 months, at which time the patient had a low eGFR ranging from 39.4 to 45.1 mL/min/1.73 m^2.

Discussion

In the present five cases of elevated C5DC, four patients had transient elevation. Conversely, the fifth patient, with renal hypoplasia, maintained a high C5DC level. Elevated C5DC on newborn screening is considered to indicate GA-1,[2] but none of the present five patients with elevated C5DC

had GA-1. Given that C5DC is the only variable used for GA-1 screening, this unacceptably high rate of false positives and risk of less-than-100% sensitivity are concerning. It is also difficult to distinguish true GA-1 from other diseases, using only C5DC quantification, given that patients with GA-1 do not always have elevated C5DC.[7] Additionally, some patients may have either no, intermittently increased, or borderline elevated C5DC concentration.[8] Moreover, C5DC analyses may have considerable inter-assay variability:[2] in the present study, four of the five cases were confirmed as false positive on urine biochemistry. C5DC in the false-positive patients decreased in a short time, thereby indicating that repeat examination following initial elevation is necessary to avoid a risk of lower diagnostic sensitivity. The fifth patient had a persistently high C5DC level for at least 4 months. This case involved bilateral renal hypoplasia and impaired renal function. Three patients with transient elevation of C5DC did not have elevated creatinine (Table 1). Recently, it has been reported that neonates with renal failure had elevation of C5DC, mimicking GA-1 on newborn screening.[4] In the case of renal failure, concentration of C5DC in the dried blood spot correlated with the level of serum creatinine and GFR.[4,9] This suggests that a C5DC-positive patient may be considered

not only to have GA-1, but also to have renal insufficiency, in order to provide appropriate treatment.

The mechanism that led to elevation of blood C5DC in the case of renal insufficiency is unclear. Recently, sodium-dependent dicarboxylate cotransporter 3 (NaC3) and organic anion transporter (OAT) 1 and 4 have been identified as mediators of the translocation of GA and 3OHGA through the membrane.[10] In *Gcdh*-/- mice (a mouse model of GA-1), NaC3 and OAT1 expression was increased in the kidneys, indicating an adaptive response to increased plasma GA and 3OHGA. When metabolic crisis was induced in the Gcdh-/- mice, OAT1 was mislocalized in the tubule cells, and histomorphological changes in the kidneys, contributing to functional tubular injury, were induced.[10] This suggests that renal tubular cells play an important role in the translocation of metabolites GA and 3OHGA in the GA-1 mouse model. Therefore, renal insufficiency involving the tubular cells may alter the excretion level of metabolites and result in accumulation of GA, 3OHGA, and C5DC.

To ensure high diagnostic sensitivity in newborn screening for GA-1, a combination of C5DC with secondary variables, such as C5DC/(C8+C10), C5DC/C16, C5DC/C0, and C5DC/C8, has been proposed.[2,4] Given, however, that not only our local laboratory but also other local laboratories

in Japan measure single values of C0, C8, C10, and C16, established cut-offs for C5DC/acylcarnitine ratios are not available. Therefore, in Japan, the acylcarnitine profile alone is insufficient for distinguishing renal insufficiency from GA-1. Urine organic acid analysis is essential for confirming diagnosis, but this test requires additional time for completion and the obtaining of results. Serum creatinine, urine NAG, and β2MG assays are widely available and are less time-consuming for estimating renal insufficiency. The renal function test should be considered in cases of C5DC elevation without abnormal neurological signs for differential diagnosis.

Disclosure

The authors declare no conflict of interest.

Author contributions

M.M. and H.A. wrote the manuscript. H.A., M.Y., and T.K. collected and provided clinical data; R.B. and Y.H. analyzed the urine samples. M.N., K.T., M.N., H.N., and YT critically reviewed the manuscript. I.M., Y.H., and K.I. gave conceptual advice. All authors read and approved the final manuscript.

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Fig. 1 Patient 5: abdominal ultrasound showing bilateral hypoplastic kidneys measuring (a) 39.8 × 13.0 mm (right) and (b) 39.7 × 13.0 mm (left).

Table 1 Elevated C5DC on newborn mass-screening

Patient ID no.	Initial C5DC in dried blood spot (nmol/mL)	Cut-off (nmol/mL)	Duration of elevation (months)	Serum creatinine (mg/dL)	Diagnosis
1	0.35	0.28	1	0.28	False positive
2	0.40	0.30	1	0.17	False positive

3	0.39	0.30	1	Not examined	False positive
4	0.35	0.30	1	0.24	False positive
5	0.29	0.25	>4	0.81	Renal hypoplasia

C5DC, glutaryl carnitine.