Recurrent rhabdomyolysis and glutaric aciduria type I: a case report and literature review

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Case report

Background: **Glutaric acidemia type I (GA-I) is a rare metabolic disorder caused by mutation of the glutaryl-CoA dehydrogenase (*GCDH*) gene. The occurrence of rhabdomyolysis with GA-I is extremely rare.**

Methods: **We reported a child with recurrent rhabdomyolysis and undiagnosed glutaric acidemia type I (GA-I). And a literature review was performed.**

Results: **A 4.5-year-old girl was admitted to our hospital due to recurrent rhabdomyolysis for 3 times within three years. At the third admission, she was diagnosed with GA-I by biochemical testing and mutation analysis. The girl was found to have a serine to leucine replacement mutation of the *GCDH* gene in exon 8 at position 764. Other three patients with rhabdomyolysis and GA-I were discovered by literature searching.**

Conclusion: **This report highlights that patients with GA-I may have an increased risk of rhabdomyolysis.**

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Key words: **GCDH mutation; glutaric acidemia type I; rhabdomyolysis**

Introduction

Glutaric acidemia type I (GA-I), a rare (1:100 000) metabolic disorder, is caused by the mutation of the glutaryl-CoA dehydrogenase (*GCDH*) gene.[1] This mutation results in GCDH deficiency and the accumulation of lysine, hydroxylysine, and tryptophan and their intermediate breakdown products including glutaric acid, glutaryl-CoA, 3-hydroxyglutaric acid, and glutaconic acid.[1] The accumulation of 3-hydroxyglutaric acid and glutaconic acid can lead to damage to the brain and other organs. Macrocephaly at birth and later movement disorders, typically occurring between 6 and 18 months of age, are key manifestations of GA-I.[1] High blood and/or urine glutarylcarnitine (C5DC) detected at newborn screening is suggestive of GA-I.[2] This report describes a patient with rhabdomyolysis and GA-I. This is a noteworthy case because the occurrence of rhabdomyolysis associated with GA-I is extremely rare.

Case report

A 2.5-year-old girl was admitted to the hospital for 2-day fatigue, paleness, high fever (>39ºC), and a convulsion. On physical examination, her muscle strength was measured grade 4 (Table 1) and urine was dark brown. Routine urine and blood tests revealed: 3+ urine protein and 2 red blood cells/high power field; hemoglobin (Hb), 121 g/L (reference: 110-130); alanine aminotransferase (ALT), 3050 U/L (reference: 7-35); lactate dehydrogenase (LDH), 3990 U/L (reference: 140-280); creatine kinase (CK), 108640 U/L (reference: 134-391); CK-MB, 1794 U/L (reference: 10-13); and blood myoglobin, 257.4 μg/L (reference: 0.1-70). As rhabdomyolysis was diagnosed, the girl received symptomatic treatment including fluid supplementation and urine alkalization for 3 days. Echocardiography and ecocardiography showed nothing abnormal, suggesting no myocardial damage. Her urine was clear, and muscle

Table 1. Muscle strength grading

Grade 0	No muscle contraction.
Grade 1	Trace contraction is noted in the muscle by palpating while the patient attempts to contract it.
Grade 2	Able to actively move the muscle when gravity is eliminated.
Grade 3	Move the muscle against gravity, but not against resistance from the examiner.
Grade 4	Move the muscle group against some resistance from the examiner.
Grade 5	Move the muscle group and overcome the resistance of the examiner. This is the normal muscle strength.

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strength returned to grade 5.

One year later, she was re-hospitalized for shortness of breath and fatigue for 3 days. Her muscle strength was grade 2/3, and urine color was normal. Urine testing showed negative urine protein and 2 red blood cells/high power field; Hb, 125 g/L; ALT, 1209 U/L; LDH, 6140 U/L; and CK, 43 440 U/L. Spinal fluid analysis revealed a leukocyte count of 2×10^6 cells/L (reference: 4-11×10^6); CK, 227 U/L (reference: 0-22); and total protein, 336.9 mg/L (reference: <450). Paneth's globulin was negative. Cranial magnetic resonance image revealed a bilateral arachnoid cyst. Muscle biopsy was performed to rule out a possible underlying defect in muscle metabolism,[3] and pathological examination revealed decreased muscle fiber density (Fig.). The girl received urine alkalization and cell membrane stabilization for two weeks, and her muscle strength returned to normal.

At the age of 4.5 years, the girl was admitted to the hospital again because of running nose and vomiting for 3 days and difficulty in breathing for half a day. She suffered from mild respiratory distress and her muscle strength was grade 2. Her urine was yellow in color, and the results of blood tests were as follows: ALT, 2020 U/L; CK, 175 640 U/L; CK-MB, 1150 U/L; Hb, 132 g/L; and myoglobin, 509 μg/L (reference: 0-70). Blood analysis using Tandem mass spectrometry revealed C5DC, 1.02 mmol/mol creatinine (reference: 0.02-0.14); C5DC/C8, 17 (reference: 0.19-7); and C5DC/C16, 1.96 (reference: 0.01-0.07). She was treated by urine alkalization and cell membrane stabilization, and after three weeks her muscle strength returned to grade 4/5. Finally, she was discharged from the hospital.

Gas chromatography-mass spectrometry analysis of urine organic acids revealed: glutaric acid, 126.99 μmol/mmol creatinine (reference: 1.9-4); and 3-hydroxyglutaric acid, 3.39 μmol/mmol creatinine (reference: 0), consistent with GA-I. *GCDH* gene analysis on the patient, her parents, and sisters revealed a missense mutation in exon 8 (C764>T), leading to TCG>TTG and Ser>Leu. The girl had a homozygous mutation, whereas her parents and two sisters had a heterozygous mutation. DNA analysis of blood samples from 50 healthy subjects confirmed that this was a mutation, not a polymorphism.

After the diagnosis of GA-I, the patient was treated with carnitine (50 mg/kg per day), a protein/amino acid supplement (60 g/day) and a predominantly vegetarian and protein diet. Biochemical testing at the age of 5.1 years revealed no abnormalities; at the age of 5 years and 3 months, C5DC was 1.08, and glutaric acid and 3-hydroxyglutaric acid were 19.21 μmol/mmol

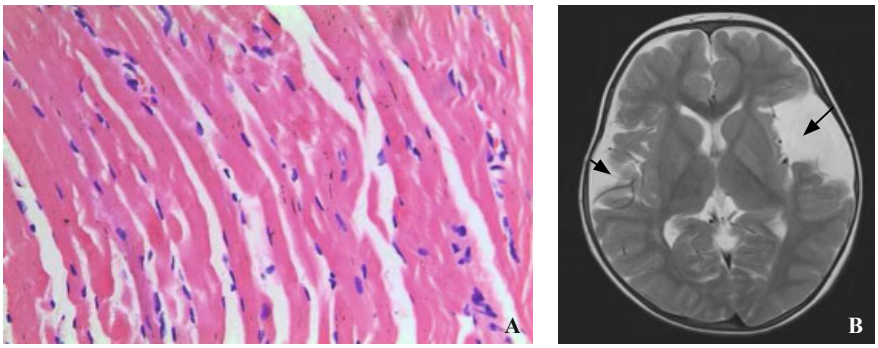

Fig. A: Quadriceps biopsy revealed decreased muscle fiber density (hematoxylin and eosin staining, original magnification × 400); **B**: Axial magnetic resonance image showing a bilateral arachnoid cyst in the middle cranial fossa (arrows) on T2 image.

Table 2. Summary of rhabdomyolysis in patients with glutaric aciduria type I (GA I)

Case	Age/sex	GA1		Rhabdomyolysis			
		History/age at confirmation	Treatments	Recurrent	Cause	Clinical manifestations	Outcome/follow-up
Wilson (1999)	4 y/M	Yes/NA	Carnitine and riboflavin supplement	Yes	Viral infection or unknown	Fever, shock, tachypnea, encephalopathy, myoglobinuria	Death
Chow (2003)	4.5 y/F	Yes/after birth	Protein restriction, carnitine and riboflavin supplement	No	Viral infection	Fever, shock, encephalopathy, myoglobinuria	Death
Jamuar (2012)	8 y/M	Yes/4 months	Low protein diet, carnitine and riboflavin supplement	Yes	Febrile illness	Fever, respiratory distress, dystonia, encephalopathy	Recurrent dystonia and rhabdomyolysis*
Present	5 y/F	No	No stadard treatment before diagnosis	Yes	Unknown	Fever, fatigue, respiratory distress, convulsion, myoglobinuria	Stable without symptoms

F: female; M: male; NA: not available. *: The patient experienced two episodes of mild rhabdomyolysis, and was severely disabled at 13 years of age.

creatinine and 5.22 μmol/mmol creatinine, respectively. The patient had normal growth and development without symptoms during a 3.5 year of follow-up.

Discussion

By searching Medline, the Cochrane Library, EMBASE, and Google Scholar, we found three patients with rhabdomyolysis and GA-I (Table 2).[4-6] These patients aged from 4 to 8 years (except for our patient) suffered from GA-I, which was treated with carnitine and riboflavin, and protein was restricted. Recurrent rhabdomyolysis was thought to be caused by viral infection in two patients[4,5] and febrile illness in one.[6] Fever as a symptom of rhabdomyolysis occurred in all patients, and other common symptoms included encephalopathy, shock, myoglobinuria, and respiratory distress. Of the three patients, 2 died, and one became disabled.

Our patient had a serine to leucine replacement mutation of the *GCDH* gene in exon 8 at position 764. To our knowledge, this is a novel *GCDH* gene mutation. Findings of a study indicate that a single mutation (IVS10-2A>C) is the predominant one in patients with GA-I.[7] Overall, there are more than 200 GCDH gene mutations,[8,9] including R402W missense mutation.[1] Other GCDH mutations in Chinese with GA-I include A219T, R386G, IVS3+1G>A, G178R, and R355H;[10] c.245G>C (p.Arg82Pro);[11] and missense mutations (c.406G>T, C.416C>G, c.442G>A, c.640A>G, c.901G>A, c.979G>A, c.1207C>T), frameshift mutations (c.873delC, c.1172-1173insT, c.1282-1285ins71), and nonsense mutations (c.411C>G).[12] GCDH mutations include c.281G>A (p.Arg94Gln), c.401A>G (p.Asp134Gly), c.662T>C (p.Leu221Pro), c.881G>C (p.Arg294Pro), c.1173dupG (p.Asn392Glufs*5), c.1238A>G (p.Tyr413Cys) and c.1241A>C (p.Glu414Ala) in Indian patients;[13] 89 or 90delC, Y155C, IVS4+2T>C, G244S, Q352X, G354A, K361E, 1144-1145delGC, and S305L in Japanese;[14] and G390V and X439W in Italians and Portuguese.[15]

In our patient and those reported elsewhere, the most obvious potential precipitating factor for rhabdomyolysis is altered bioenergetics due to the metabolic disorder caused by GCDH deficiency. Indeed, genetic inborn errors of metabolism are known to cause rhabdomyolysis.[16] Investigation of GCDH in mice showed markedly decreased brain and skeletal muscle CK activity after administration of lysine.[17] Before each attack, our patient consumed a large amount of mutton which contains large anout of lysine.

Glutaryl-CoA dehydrogenase enzyme activity of fibroblasts or leukocytes is the "gold standard" for the diagnosis of rhabdomyolysis.[18] However, Kölker et al[18] reported that 2 disease-causing mutations and elevated 3-OH-GA and GA in urine were sufficient to diagnose the disease. Our patient had elevated 3-OH-GA and GA in urine (by gas chromatography-mass spectrometry) and a homozygous mutation (missense mutation in exon 8, C764>T); her parents and 2 sisters had a heterozygous mutation. These findings are sufficient to diagnose GA-1.

In summary, we described the fourth patient with rhabdomyolysis and GA-I. Compared with the reported patients, our patient had neither a history of GA-I or obvious manifestations of the condition nor any adverse neurological outcomes. We believe that the present case may help to identify risk factors and causes of rhabdomyolysis in patients with GA-I.

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Ethical approval: This study was approved by the Ethical Committee, Children's Hospital, Zhejiang University School of Medicine. This case report was prepared in accordance with the Health Insurance Portability and Accountability Act (HIPAA) regulations. The patient's parents/legal guardians provided informed consent for data collection and publication.

Competing interest: The authors have no conflict of interest related to the treatment of the patient or reporting.

Contributors: Qian GL guaranteed the integrity of the entire study, and prepared the manuscript. Hong F performed the literature research. Tong F contributed to the study concepts. Fu HD was responsible for the manuscript editing. Liu AM contributed to the manuscript review.

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