Clinical and laboratory analysis of late-onset glutaric aciduria type I (GA-I) in Uighur: A report of two cases

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Abstract. The aim of the present study was to investigate the clinical, biochemical and genetic mutation characteristics of two cases of late-onset glutaric aciduria type I (GA-I) in Uighur. The clinical data and glutaryl-CoA dehydrogenase (GCDH) genetic test results of two cases of late-onset GA-I in Uighur were collected and analyzed, and reviewed with relevant literature. One patient with late-onset GA-I primarily exhibited clinical intermittent headache, while the other patient was asymptomatic. The urinary organic acid analysis detected a large number of glutaric acid and 3-hydroxy glutaric acid, 3-hydroxy-propionic acid. One patient exhibited white matter degeneration in cranial magnetic resonance imaging (MRI) and the other patient showed no abnormality. The two patients both exhibited c. 1204C>T, p.R402W, heterozygous mutation, and c. 532G> A, p.G178R, heterozygous mutation. Besides central nervous system infectious diseases, patients with clinical headache, cranial MRI-suggested bilateral temporal lobe arachnoid cyst and abnormal signals in the basal ganglia should be highly suspected as late-onset GA-I. Early diagnosis and correct treatment are key to improve its prognosis.

Introduction

Glutaric aciduria type I (GA-I) is a rare autosomal recessive disease with abnormalities in organic acid metabolism, and is caused by the functional defects of glutaryl-CoA dehydrogenase (GCDH), which results in metabolic disorders of lysine, hydroxylysine and tryptophan, leading to the excessive accumulation of bypass metabolites, such as glutaric acid, 3-hydroxy-glutaric acid and other toxic substances. This results in an increase in urine levels of glutaric acid and 3-hydroxy-glutaric acid (1). It has been reported that the incidence rate of GA-I is ~1:100,000 (2). Approximately 90% of patients develop GA-I in early childhood, and the remaining 10% of patients show mild symptoms or no symptoms (3). In recent years, GA-I in the Chinese population has gained increasing interest (4-7). However, a large number of children do not receive a timely diagnosis and proper treatment clinically. In particular, no research about GA-I in Uighur has been reported. Therefore, further research is required in order to determine the incidence of GA-I in Chinese children. The present study collected and analyzed the clinical, biochemical, neuroimaging and genetic mutation information of two patients with GA-I in one Uighur family, admitted to the Department of Pediatrics, The First Hospital of Xinjiang Medical University (Urumqi, China) in 2014. The study was conducted in accordance with the declaration of Helsinki, and received approval from the Ethics Committee of Xinjiang Medical University. Written informed consent was obtained from all participants.

Case reports

Case 1. A 12-year-old Uighur girl from Xinjiang, China, was admitted to the Department of Pediatrics, The First Affiliated Hospital of Xinjiang Medical University in October 2014 for an intermittent headache (0.5-2 h in duration) over a period of 2 months. The headache typically occurred once every 3-5 days, with no increasing or decreasing trend. The patient reported no other particular discomfort. Hospital examination revealed that blood glucose, creatine kinase, blood lactate and alanine transaminase levels were within normal ranges. Outpatient cranial magnetic resonance imaging (MRI) revealed white matter degeneration. As a result, a diagnosis of encephalitis or inherited metabolic disease was considered.

Regarding previous disease history, the patient exhibited normal growth and development, intelligence, vision and hearing, but exhibited poor physical strength and endurance since childhood, could not tolerate hunger, and had no particular bad habits. The patient was from a non-consanguineous marriage.

On physical examination, the patient had a clear mind, symmetrical body and no weight loss. Cheek skin exhibited a scattered red rash, and cranial nerve examination revealed no abnormalities. The muscle strength of the bi-upper and bi-lower limbs was grade 5 in the MRC scale (8); the muscle tonus of the four limbs was normal, with normal tendon reflexes in the upper and lower limbs. No bilateral pathological signs were...
detected, and the body's superficial sensation examinations were normal. The finger-to-nose test was normal, with no meningeal irritation.

Cranial MRI showed bilateral temporal lobe arachnoid cyst, focal patchy T2 flair high signals in semi-oval area, corner and anteroposterior horns of the lateral ventricle, indicating white matter degeneration (Figs. 1 and 2). The figures were captured at two month intervals, and no significant change was identified.

Case 2. A 6-year-old Uighur girl from Xinjiang was the sister of case 1, and presented with no clinical symptoms. Physical examination and imaging tests showed no abnormalities.

**Laboratory tests and diagnosis.** Tandem mass spectrometry (MS/MS) and gas chromatography/mass spectrometry (GC/MS) were used to analyze blood acylcarnitine and urine organic acids in the patient with suspected GA-I. To detect blood acylcarnitine and amino acids by MS/MS, venous blood was sampled, dripped onto special filter paper, and sent for detection after drying. An MS/MS instrument (API 2,000; Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA) was used for the testing. For the detection of organic acids by GC/MS, urine samples were treated with urease, hydrochloric acid hydroxylammonium, sodium hydroxide and hydrochloric acid, and a GC/MS instrument (QP2010; Shimadzu Corporation, Kyoto, Japan) for detection.

The results of MS/MS and GC/MS detection are presented in Tables I-III. Urinary glutaric acid and 3-hydroxy-glutaric acid in the two patients were increased, and glutaric acid levels were increased by 2,510.08- and 1,172.28-fold compared with the normal reference value (0), in cases 1 and 2, respectively. Levels of 3-hydroxy glutaric acid were increased by 22.58- and 12.19-fold compared with the normal reference value (0) (Tables I and II) in cases 1 and 2, respectively. Blood acylcarnitine analysis showed that glutaryl carnitine in the cases 1 and 2 were both within the normal ranges, 170.8 and 31.0 nmol/hrPr; 152.4 and 27.6 mmol/l hr/MgPr, respectively (reference values, 134.1-325.1 nmol/l hr/MgPr and 19.0-68.2 nmol/l hr/MgPr, respectively). As a result, a diagnosis of leukodystrophy could be excluded (Table IV).

Genetic analysis of GCDH in the two patients and their parents was performed by gene DNA sequencing. Polymerase chain reaction amplified all exons and para-intronic regions of GCDH, and a DNA automatic analyzer was used to analyze the amplification products. Two mutations were detected in the patients: Loci c. 1204C >T, p.R402W, heterozygous mutation, originating from the father; and c. 532G >A, p.G178R, heterozygous mutation, originating from the mother. These two mutations had been previously reported, and were considered as the pathogenic mutations (9,10).

Electromyography showed no abnormalities in any muscles (bi-rectus femoris and bi-gastrocnemius). In conclusion, a diagnosis of late-onset GA-I was decided for both cases.

**Treatment and follow-up.** After the diagnosis of GA-I was confirmed by MS, no muscle biopsy was performed according to patients' wishes. The patients were administered a low-fat, low-protein and high-carbohydrate diet, and large doses of vitamin B2 (50 mg, tid) and L-carnitine (100 mg/kg/day) were supplemented for symptomatic treatment. The headache symptom in case 1 disappeared, and follow-up review showed that lactic acid, enzymes and liver functions were all within normal ranges. The follow-up was lasted for two months, and the patients expressed no clinical symptoms within that period.

**Discussion**

GA-I is a relatively rare disease among organic aciduria that was first reported in 1975 by Goodman (11), and >200 pathogenic mutations have been reported to date (12). The incidence rates of GA-I vary between different races, and it has been reported as ~1/60,000 individuals in China (13). To date, there are no reports of GA-I in Uighur children. GA-I typically induces acute encephalopathic crisis within 3 to 36 months of delivery, due to non-specific factors, such as infection, fever and vaccinations. These typically result in induced striatal neuron degeneration, and often result in severe neurological sequel, such as dystonia and extrapyramidal symptoms (14). An early diagnosis, together with a reasonable diet, energy supplements and active treatment towards complicating diseases (such as induced acute encephalopathy) could significantly improve the prognosis; however, nearly one-third of pediatric patients experiencing GA-I suffer from severe neurological sequela even after aggressive treatment (15).

Patients with incubative disease would exhibit no acute encephalopathic crisis, but would experience gradually progressive nervous system damage (16). Currently, pathogenesis study of GA-I typically focusses on the selective accumulation mechanisms of GA, other metabolites in the brain, and the neurotoxic mechanisms of GA and other metabolites (17). The abnormal increasing of GA, 3-hydroxyglutaric acid and other metabolites in the brain might cause striatal neuronal degeneration, wide white matter degeneration and gliosis. The abnormal accumulation of metabolites would cause excitatory damage, energy metabolism damage and oxidative stress. In addition, other risk factors, such as glial activation, vascular injury, inflammatory factors and other causative factors, are involved in collaborative neurotoxic damage (18).

In the present study, case 1 exhibited neurological symptoms during treatment, with an onset age of 12 years. The patient lacked specific clinical symptoms, and lesions were only identified after completing a brain MRI. Following the MRI, the patient's family members were recommended for blood acylcarnitine and urine organic acid analysis. The results showed that the patient's sister (case 2) also had GA-I, but experienced no clinical symptoms or signs. Macrocephaly is a typical characteristic of GA-I (14), but this characteristic did not appear in either cases 1 or 2. Early onset GA-I commonly exhibits hypoevolutism or reverse development, muscle tonus disorder and seizure, and nearly
half of patients exhibit acute neurological degeneration when under stress (19). The symptoms of late-onset GA-I are relatively mild, with primary clinical manifestations of motion retrogression and paroxysmal headache, which typically develop premorbidly. Patients usually have a relatively good prognosis and fast recovery, and their intelligence and motion abilities can resume to normal, suggesting that the age of onset is associated with clinical prognosis (20). In the present study, case 1 exhibited headache with normal cognitive functions, and cranial MRI exhibited focal patchy T2 flair high signals in the semi-oval area, corner and anteroposterior horns of the lateral ventricle. The clinical symptoms disappeared after treatment, while cranial MRI exhibited no significant changes, consistent with previously reported literature (21,22).

Achieving a clinical diagnosis of GA-I is difficult, and urine organic acid analysis is the key technology in screening and diagnosing GA-I. However, diagnostic screening could rely on GC/MS technology to analyze the levels of urine glutaric acid and 3-hydroxy-glutaric acid and MS/MS technology could be used to analyze the level of acetylcarnitine in blood. In addition, GCDH activity detection or gene testing can be used to diagnose GA-I (23,24). In the present study, the two cases were confirmed because of the markedly increased concentrations of urine glutaric acid and 3-hydroxy-glutaric acid. The results from these two patients showed that glutaryl carnitine was increased, while free carnitine was reduced; therefore, it is recommended that the suspected GA-I patients should undergo urine organic acid analysis, the blood acylcarnitine ester spectrum should be monitored in order to confirm diagnosis.

GCDH is a key enzyme in the catabolic pathways of tryptophan, lysine and hydroxylysine, and can catalyze the oxidative decarboxylation of glutaryl coenzyme A, generate crotonyl coenzyme A and CO₂; the gene for this enzyme was located at 19p13.2, which is associated with >200 types of pathogenic mutations (12). Different mutations result in different degrees of enzyme deficiency, and the residual enzyme activity is associated with a patient’s biochemical phenotype (urinary GA content), but is not associated with clinical phenotype (12). The analysis of GCDH mutation could further confirm the disease, thus guiding the genetic counseling of patients’ family members and the prenatal diagnosis of the next child. There may exist differences of

Figure 1. November 13, 2014, focal patchy T2 flair high signals of the bilateral temporal tip arachnoid cyst, semi-oval area and anteroposterior horns of the lateral ventricles (case 1). (A) The white matter around the lateral ventricle shows markedly increased signal in the diffuse-weighted image. (B) The bilateral fissure cisterns are widened, especially on the left side in the T2 Flair image. (C) The ventricle expands in the sagittal T2 image, and exhibits mild dropsy. (D) the lateral ventricle expands in the coronal T2 image.
Table I. Gas chromatography/mass spectrometry results of urine in case 1.

| No. | Test item                              | Results | Normal average | Normal min. | Normal max. | Results (average) | Results (max) |
|-----|----------------------------------------|---------|----------------|-------------|-------------|------------------|---------------|
| 1   | Lactic acid-2                          | 0.8     | 0              | 4.7         | 27.01       | 4.60             |               |
| 2   | 2-hydroxy-isobutyric acid-2            | 5.73    | 0              | 0           | 0           | -                | -             |
| 4   | Glycolic acid-2 293.59                 | 0.7     | 0              | 2.2         | 133.70      | 42.54            |               |
| 8   | 3-hydroxy-propionic acid-2             | 27.76   | 0.2            | 0           | 1.1         | 138.80           | 25.24         |
| 12  | 3-hydroxy-isobutyric acid-2            | 24.71   | 2.5            | 0           | 9           | 9.88             | 2.75          |
| 16  | 3-hydroxy-isovaleric acid-2            | 18.21   | 0.8            | 0           | 2.3         | 22.76            | 7.92          |
| 31  | Glycerol-3-keto-isocaproic acid-OX-2   | 11.62   | 0.3            | 0           | 0.8         | 38.73            | 14.53         |
| 48  | Isobutyryl-glycine-1                   | 16.46   | 0              | 0           | 0.4         | 2510.08          | -41.15        |
| 51  | Glutaric acid-24,769.16                 | 0       | 0              | 4           | 22.14       | 1922.29          |               |
| 55  | Propionyl glycine-2                    | 83.55   | 0              | 0           | 0           | -                | -             |
| 60  | Glutaconic acid-25.74                  | 0       | 0              | 0           | 0           | -                | -             |
| 81  | 2-hydroxy-glutaric acid-3              | 50.93   | 2.3            | 0.6         | 5.9         | -                | 8.63          |
| 82  | 3-hydroxy glutaric acid                | 22.58   | 0              | 0           | 0           | -                | -             |
| 86  | 3-hydroxy-phenylacetic acid-2          | 17.53   | 0.4            | 0           | 0.9         | 43.83            | 19.48         |
| 123 | Palmitic acid-1 98.61                  | 6       | 0              | 13.8        | 16.44       | 7.15             |               |
| 130 | 3,6-epoxy-dodecanedioic acid -2        | 9.84    | 1.6            | 0           | 5.2         | 6.15             | 1.89          |

*Abnormal.

Figure 2. January 20, 2015, focal patchy T2 flair high signals of the bilateral temporal tip arachnoid cyst, semi-oval area and anteroposterior horns of the lateral ventricles. (A) The white matter around the lateral ventricle shows markedly increased signal in the diffuse-weighted image. (B) The bilateral fissure cisterns are widened, especially on the left side in the T2 Flair image. (C) The lateral ventricle expands in the sagittal T1 image, and the corpora quadrigemina has expanded slightly. (D) The white matter at the forefoot of lateral ventricle shows a low signal in the ADC image, and the lateral fissure cistern widens.
GCDH hotspot mutations among GA-I patients in different races and regions. In Caucasians, c. 1204C >T was the most common hotspot mutation (9), while c. 914C >T was common in Japanese patients (10). However, there lacks a large-sample study in Asians. The present study diagnosed two patients with GA-I on a genetic level in Uighur, mainland of China, for the first time. Both patients expressed the c. 1204C >T missense mutation, and the detection of the GCDH gene mutation in their parents revealed that both parents were carriers of the disease-causing gene, which further suggests that this disease shows features of a typical autosomal recessive inheritance disorder. The two patients in this study had

Table II. Gas chromatography/mass spectrometry results of urine in case 2.

| No. | Test item | Results  | Normal average | Normal min. | Normal max. | Results (average) | Results (max.) |
|-----|-----------|----------|----------------|-------------|-------------|-------------------|---------------|
| 2   | 2-hydroxy-isobutyric acid-2 | 3.21*     | 0              | 0           | 0           | -                 | -             |
| 4   | Glycolic acid-2 | 12.23*    | 0.7            | 0           | 2.2         | 17.47             | 5.56          |
| 8   | 3-hydroxy-propionic acid-2 | 6.96*     | 0.2            | 0           | 1.1         | 34.80             | 6.33          |
| 32  | Phosphoric acid-3 | 93.47*    | 6.6            | 0           | 43          | 14.16             | 2.17          |
| 48  | Isobutyryl-glycine-1 | 9.84*     | 0              | 0           | 0           | -                 | -             |
| 51  | Glutaric acid-2 | 2,227.34* | 1.9            | 0           | 4           | 1,172.28          | 556.84        |
| 55  | Propionyl glycine-2 | 42.86*    | 0              | 0           | 0.4         | -                 | -             |
| 76  | 5-hydroxy-methyl-2-pyromucic acid-1 | 10.73*     | 0              | 0           | 0.4         | -                 | -             |
| 81  | 2-hydroxy-glutaric acid-3 | 22.09*    | 2.3            | 0.6         | 5.9         | 9.6               | 3.74          |
| 82  | 3-hydroxy glutaric acid | 12.19*    | 0              | 0           | 0           | -                 | -             |
| 86  | 3-hydroxyphenylacetic acid-2 | 4.14*     | 0.4            | 0           | 0.9         | 10.35             | 4.60          |
| 90  | 2-oxoglutaric acid-OX-2 (2) | 38.19*    | 3.5            | 0.3         | 21.3        | 10.91             | 1.79          |
| 123 | Palmitic acid-1 | 77.17*    | 6              | 0           | 13.8        | 12.86             | 5.59          |
| 130 | 3,6-epoxy-dodecanedioic acid-2 | 11.21*    | 1.6            | 0           | 5.2         | 7.01              | 2.16          |

*Abnormal.

Table III. Plasma acylcarnitine profile measured using tandem mass spectrometry in cases 1 and 2.

| Detection                           | Case 1 (µmol.l⁻¹) | Case 2 (µmol.l⁻¹) | Reference range (µmol.l⁻¹) |
|-------------------------------------|-------------------|-------------------|---------------------------|
| Free carnitine (C0)                 | 7.887*            | 6.011*            | 10-60                     |
| Isovaleryl carnitine (C5)           | 0.051*            | 0.058*            | 0.04-0.3                  |
| HMG-carnitine (C5DC)                | 0.81              | 1.177*            | 0-0.2                     |
| Octadecene acyl carnitine (C18DC)   | 0.191*            | 0.209*            | 0.3-1.8                   |
| C5DC/C3                            | 1.235*            | 2.367*            | 0-0.2                     |
| C5DC/C8                            | 36.175*           | 26.515*           | 0.1-2.5                   |
| C5DC/C16                           | 2.109*            | 4.042*            | 0.01-0.15                 |
| C16-OH/C3                          | 0.042*            | 0.067*            | 0-0.04                    |

*Abnormal.

Table IV. Plasma arylsulfatase A and galactocerebroside esterase profile measured using tandem mass spectrometry in two patients.

| Detection                                  | Case 1                  | Case 2                  | Reference range                  |
|--------------------------------------------|-------------------------|-------------------------|----------------------------------|
| Arylsulfatase A                            | 170.8 nmol/17 h/mgPr    | 152.4 nmol/17 h/mgPr    | 134.1-325.1 nmol/17 h/mgPr       |
| Galactocerebroside esterase                 | 31.0 nmol/17 h/mgPr     | 27.6 nmol/17 h/mgPr     | 19.0-68.2 nmol/17 h/mgPr         |

The two enzymes were within normal limits, so leukodystrophy was excluded.
diagnosis of glutaric aciduria, although early treatment may not completely avoid damage to the nervous system, it could reduce neurological complications and save a lot of medical expenses (13).

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