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Diagnosis, treatment and outcome of glutaric aciduria type I in Zhejiang Province, China

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Summary

Background: Glutaric aciduria type I (GA I; MIM 231670) is a rare autosomal recessive disorder resulting from glutaryl-CoA dehydrogenase deficiency. This article reports our experience in the diagnosis, treatment and outcome of GA I patients in Zhejiang Province, China.

Material/Methods: A total of 129,415 newborns (accounting for approximately one-tenth of the annual births in Zhejiang Province) and 9640 high-risk infants were screened for inborn errors of metabolism in the Neonatal Screening Center of Zhejiang Province during a 3-year period. Tandem mass spectrometry and gas chromatography-mass spectrometry were used for diagnosis of the patients. Dietary modification, carnitine supplementation and aggressive treatment of intercurrent illnesses were adapted for GA I patients.

Results: Three infants were diagnosed with GA I by high-risk screening (detection rate: 1/3,213) and 2 were diagnosed by newborn screening (incidence: 1/64,708). Four patients (3 by high-risk screening and 1 by neonatal screening) undergoing MRI examination showed remarkable changes on T2-weighted image. Four patients accepted timely treatment, and in the patient diagnosed by neonatal screening, treatment was delayed until hypotonia appeared 3 months later. Neuropsychological assessment showed mental and motor retardation in 3 patients after treatment, including the patient diagnosed by neonatal screening.

Conclusions: Individualized timely treatment and close monitoring of GA I patients needs to be optimized in China. Appropriate communication with parents may help to achieve successful management of GA I patients.

key words: **glutaric aciduria type I • newborn screening • diet modification • outcome**

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Background

Glutaric aciduria type I (GA I; MIM 231670) is a rare autosomal recessive disorder resulting from glutaryl-CoA dehydrogenase (GCDH) deficiency. The lack of GCDH leads to accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid (less frequently), and glutaryl carnitine (C5DC). The accumulation of glutaric acid and 3-OH glutaric acid in the brain leads to neuronal damage with loss of striatal neurons during sepsis/fever [1]. Overall prevalence is approximately 1 in 100,000 newborns, and varies in different countries [2,3]. Most affected children are clinically characterized by macrocephaly appearing at or shortly after birth, and initial normal development followed by a severe dystonic dyskinetic movement disorder and striatal degeneration [4,5]. GA I now can be detected with tandem mass spectrometry (MS/MS), which has been introduced to routine neonatal screening programs and high-risk screening for inborn errors of metabolism (IEM) in many countries. Early screening and diagnosis should prevent death and decrease morbidity in children with GA 1.

The outcome is poor in patients who have been diagnosed after acute encephalopathic crises [2,5–8]. Early diagnosis in neurologically asymptomatic patients followed by timely treatment is the best predictor for good prognosis. The treatment of GA I is still based on the clinical experience and medical history. A regimen including dietary modification, carnitine supplementation, riboflavin and aggressive treatment of intercurrent illnesses seems to prevent severe neurological complications of GA I [4,6].

In China, only 5 cities or provinces (Beijing, Shanghai, Wuhan, Guangdong Province and Zhejiang Province) have implemented screening for IEM by MS/MS or gas chromatography-mass spectrometry (GC/MS). We describe the diagnosis, treatment and outcome of GA I patients admitted in our department during the past 3 years.

Material and Methods

From January 2008 to December 2010, 129,415 newborns (accounting for approximately one-tenth of the annual births in Zhejiang Province) and 9640 high-risk infants were screened for GA I in the Neonatal Screening Center of Zhejiang Province. High-risk screening was carried out in patients with mental retardation of unknown etiology, convulsion, motor delay, language delay, consciousness disturbance, metabolic acidosis, jaundice, hepatosplenomegaly, recurrent vomiting, hypoglycemia and hyperammonemia.

MS/MS analysis of blood spot acylcarnitine profiles using an API tandem mass spectrometer (Waters Quattro, USA) was performed for each screened infant. Diagnosis of GA I was based on urine GA and 3-OH-GA detection levels by GC-MS (Shimadz QP-MS, Japan) and brain magnetic resonance imaging (MRI) results. The cut-off value of serum C5DC level was 0.03–0.14 μmol/L, urine GA 0–4 mg/g creatinine and 3-OH-GA level 0 mg/g creatinine.

Treatment regimen

Standard treatment for GA I patients was initiated immediately after diagnosis. Oral L-Carnitine (100–200 mg/kg/d) and riboflavin (200–300 mg/d) were administered. Lys-restricted diet was recommended, with natural protein intake limited to 0.5–1.5 g/kg/d and special amino acid formula (lysine-free, low-tryptophan) at 2–3 g/kg/d.

When the patients were symptomatic or in emergent conditions such as infections, fever, vomiting, convulsion, or unconsciousness, aggressive treatment was adopted including fever and infection control, anti-convulsion therapy, cessation of protein for 24 hours, high carbohydrate supplementation and acid-base correction therapy.

Neuropsychological assessment

The Bayley-I was used to evaluate the mental and motor development of children aged 0 to 30 months. Raw scores from mental and motor scales were converted to standardized scores with a mean ±SD of 100±15, providing a Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). Standard scores on subtests of the Bayley-I were converted to a categorical variable with the following criteria: (a) significantly delayed performance, scores ⩽69 (>2 SD below 100); (b) mildly delayed performance, scores of 70 to 84 (between 1 and 2 and SD below 100); and (c) performance within normal limits, scores of ⩾85. At the time of the neuropsychological assessment, patients 1, 2, 3 and 4 were aged 28 months, 30 months, 27 months and 8 months, respectively. Patient 5 was too young to have the assessment.

Results

From 2008 to 2010, 3 patients were diagnosed with GA I by high-risk screening (detection rate: 1/3,213) and 2 were diagnosed by newborn screening (incidence: 1/64,708). The clinical details of the patients are reviewed and summarized below.

Case 1 is a girl born at 35 weeks of gestational age. Her head circumference was 48 cm (>97 centile) at 4 months of age, and she had very mild hypotonia of the lower limbs. Her serum C5DC level was 0.42 μmol/L (cut-off, 0.03–0.14 μmol/L), urine 3-OH-GA level 21.98 mg/g creatinine (cut-off value: 0 mg/g creatinine), and GA level 1933.98 mg/g creatinine. The patient was followed clinically, but she showed poor treatment adherence. Persistent macrocephaly since birth was found and hypotonia resolved during 2 years of observation. Cranial MRI at 28 months of age showed widened bilateral ventricles, temporal atrophy, abnormal high signals in the frontal lobe, abnormal high signals and cystic lesions in the bilateral parietal and occipital lobes on T2-weighted image (Figure 1A). Physical and mental development (Bayley-I: MDI=88, PDI=85) were all normal at the last observation at 28 months of age.

Case 2 is a girl born by caesarean section following normal gestation. She was referred to our hospital because of emergent seizure, vomiting and unconsciousness at 19 months of age. She had 6 admissions due to respiratory tract infections and non-febrile seizures before this admission. The first seizure episode occurred at approximately 11 months of age. Physical examination showed hypotonia and dyskinesia of the limbs. Biochemistry on admission revealed hypoglycemia, hypokalemia and ketoacidosis. Serum C5DC

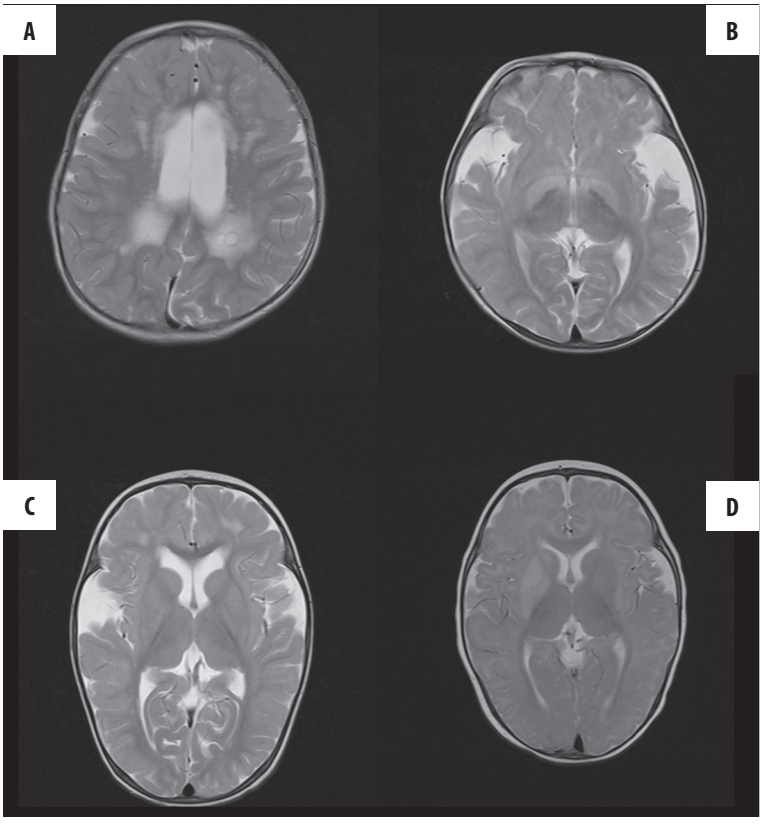

Figure 1. (**A**) Case 1, T2-weighted MRI at 4 months of age showed widened bilateral ventricles, temporal atrophy, abnormal high signals in the frontal lobe, abnormal high signals and cystic lesions in the bilateral parietal and occipital lobes. (**B**) Case 2, T2-weighted MRI at 30 months of age revealed obvious temporal lobe atrophy and abnormal high signals in the lentiform nucleus, widened sylvian fissures (characteristic bat wings appearance). (**C**) Case 3, T2-weighted MRI at 27 months of age. Multi patching signals in the white matter and frontotemporal atrophy and widened sylvian fissures (characteristic bat wings appearance). (**D**) Case 4, T2-weighted high signals in the right basal ganglia, frontotemporal atrophy and high signals in the left basal ganglia lentiform nucleus at 8 months of age.

was 1.15 μmol/L; urine 3-OH-GA and GA were 13.12 and 4329.32 mg/g creatinine, respectively. T2-weighted MRI showed obvious temporal lobe atrophy and abnormally high signals in the lentiform nucleus (Figure 1B). An aggressive treatment regimen was implemented to manage the emergency condition. Bayley-I testing at 30 months of age showed mildly delayed performance, with an MDI score of 82 and a PDI score of 78. The girl had normal physical development at the last observation at 32 months of age.

Case 3 is a boy aged 17 months on admission. He was admitted due to seizure, vomiting, hypotonia and dyskinesia of the limbs, and unconsciousness. He had a history of recurrent febrile seizures for about 6 months before the admission. His serum C5DC level was 0.78 μmol/L and urinary 3-OH-GA level 26.31 mg/g creatinine, and GA 2461 mg/g creatinine. He had severe hypoglycemia (blood glucose: 0.3 mmol/L), hypokalemia (K^+: 3.09 mmol/L) and metabolic acidosis (PH=7.272, $HCO3^-$=16.3mmol/L) on admission. MRI showed multiple patching signals in the white matter, frontotemporal atrophy and remarkably widened sylvian fissures (Figure 1C). Aggressive treatment with protein restriction was given. Standard treatment was recommended with carnitine supplementation and lys-restriction diet after emergency. He had significant mental delay, with an MDI score of 58 and a PDI score of 63 at 30 months of age.

Case 4 is a boy diagnosed after expanded newborn screening. His serum C5DC was 0.34 μmol/L at birth, and increased to 1.53 μmol/L at 1 month of age on recall visit. Urine 3-OH-GA level was 11.01 mg/g creatinine, GA 154.45 mg/g creatinine. He was then diagnosed with GA I; treatment was recommended but it was refused by the parents. They neglected our recommendation of early treatment for the boy, and the follow-up visits were discontinued; therefore, we maintained close contact with the parents by regular phone calls. The boy showed dyskinesia of the left limbs at 5 months of age, and his parents finally accepted our treatment recommendation. T2-weighted brain MRI showed high signals in the right basal ganglia, frontotemporal atrophy and high signals in the left basal ganglia lentiform nucleus at 8 months of age (Figure 1D). Neuropsychological assessment showed mental retardation of the patient at 8 months of age, with an MDI score of 62 and a PDI score of 73.

Case 5 is a boy born at term after an uneventful cesarean delivery. His head circumference was normal at birth. Newborn screening showed positive results, with serum C5DC level of 0.86 μmol/L. Confirmation testing showed serum C5DC level increased to 2.70 μmol/L, with increased 3-OH-GA and GA in the urine at 2 months of age. Blood biochemistry showed mild metabolic acidosis and abnormal liver function, with increased glutamate-pyruvate transaminase (ALT) of 154 U/L (reference range: 5–50 U/L); MRI examination was refused by the parents. Standard treatment was given at 2 months of age. The boy developed well and blood ALT decreased to normal levels after 1 month of therapy at 3 months of age.

Discussion

Newborn screening for GA I, although proven successful, has not been widely included in routine screening programs in China. To date, only Shanghai and Zhejiang in China have implemented newborn screening for GA I. Before the introduction of the MS/MS method, GA I was a rare disease,

difficult to diagnose and often misdiagnosed as other neurological diseases. The exact incidence of GA I in China is unclear, and the incidence is 1/64,708 in our studied population, which is similar to that reported by Linda et al. (range, 1:76,000 to 1:181,000; mean, 1:106,000) [2]. The reported incidence may be much higher when the screening coverage rate is increased. Many GA I patients still cannot be diagnosed and treated, especially in the less affluent cities in western China.

Symptoms of GA I are varied, but most cases have no clinical symptoms except macrocephaly or mild hypotonia at or after birth. The initial clinical manifestations of GA I in infancy are often relatively mild, presenting as hypotonia, feeding difficulties, and irritability [9]. One patient in this series had only macrocephaly at birth and it persisted until the last observation. Another 2 patients were asymptomatic at diagnosis by newborn screening and 1 of them, who did not receive timely treatment, showed unilateral dyskinesia 5 months later. Similar to results of other reports [5,10], all symptomatic patients in this series presented symptoms before 2 years of age. Symptoms may be exacerbated and crises appear to be likely in a majority of patients diagnosed after the onset of neurologic symptoms [11]. Seizures and coma appear in the patients, and GA I may be misdiagnosed as encephalitis, R syndrome, or other neurological crises [5]. In this series, 2 patients who developed several episodes of seizures before admission had long been misdiagnosed as having febrile seizures and epilepsy; both of them had metabolic and encephalopathic crises on admission.

All 4 patients who underwent MRI had remarkable changes on T2-weighted image, including extensive abnormal signals in the white matter and basal ganglia, ventriculomegaly and frontotemporal atrophy, and widened sylvian fissures ("bat wing" appearance). The asymptomatic patient presenting with only persistent macrocephaly (Case 1) showed brain injury by MRI, despite early treatment. However, this patient had normal physical and mental development and never experienced an encephalopathic crisis. The other patient, who only had lateral limbs dyskinesia without encephalopathic crisis, showed remarkable MRI changes. Hsieh et al. [12] also reported subtle basal ganglia lesions in a patient who did not experience any frank encephalopathic crisis. Long-term outcomes of these asymptomatic patients with obvious brain MRI changes are still under evaluation, and close monitoring of these patients is required. Two patients experiencing several encephalopathic crises had severe lesions in the white matter and frontal temporal lobe. MRI imaging is helpful for diagnosing and evaluating the outcome of the GA I patients.

Early treatment is of utmost importance for a good outcome in GA I patients, and approximately 90% of the untreated GA I patients have severe neurological disorders [5]. Since in China there are no treatment guidelines for GA I, we managed the patients based on our own clinical experience and the guidelines for treatment of GA I by Kölker et al. [2]. A dietary treatment (protein and lysine restriction) in combination with carnitine and riboflavin, and aggressive supportive care if with acute neurological crises, were adopted for the patients. The restricted protein diet recommendation is age-dependent, and is individualized so as to meet the normal growth and development needs of children. As reported by Kölker et al., [2] the frequency of acute encephalopathic crises is lower in pre-symptomatically diagnosed patients treated with Lys-restriction than with restricted protein diet; therefore, we recommended Lys-restricted combined with protein restriction for all the patients. Emergent treatment is considered essential to prevent encephalopathic crises during intercurrent illness [8,12,13]. Intercurrent illness management is the focus of GA I treatment [4], which may be accompanied with hypoglycemia, hypokalemia, ketosis, acidosis, and hyperammonemia, as well as other neurological complications. Our aggressive treatment includes high energy intake, and balancing body fluids and pH state by rehydration and buffering. The 2 patients with encephalopathic crises on admission never experienced crises again after aggressive treatment and standard treatment during a 2-year period of observation. Close contact with parents and educating parents to pay attention to and protect against encephalopathic crises are required.

The outcome is poor in patients who have been diagnosed after acute encephalopathic crises [6–8,14]. As reported [2,6,11], newborn screening and early institution of a therapeutic protocol have been beneficial to the patients. Two patients in our study experiencing acute encephalopathic crises had impairment in motor development and mild or significant mental retardation, but 1 patient (Case 1) without encephalopathic crises showed normal mental development after treatment. Delayed treatment will worsen the outcome of the patient, which was evidenced by 1 of our patients who showed significant mental retardation after delayed treatment for progressive dyskinesis. Early diagnosis reduces neurological complications, but severe complications may ensue in some patients even with early diagnosis and careful management [15]. An expanded newborn screening disease panel will increase the coverage and improve the neurological outcome of affected individuals [16].

The effectiveness of the treatment is difficult to evaluate because of parents' poor compliance with treatment protocol in our study. Poor medical compliance exists not only in GA I but in most patients with rare diseases in China. The insufficient knowledge of the parents about rare diseases and their disbelief in modern medical practice might contribute to this lack of compliance. Mothers may insist on increasing feeding of ordinary powdered formula when worried about insufficient nutrition of their children. Therefore, appropriate communication and rare disease education for the parents is of paramount importance to ensure good compliance with the treatment. On the other hand, lack of health insurance coverage for children with rare diseases is an important factor affecting outcome. Treatment for rare diseases is often life-long and the cost might be a heavy burden to most families with low- or even middle-level incomes. In view of that, insurance coverage for treatment of rare diseases should be considered by the Chinese government so as to improve the outcome of patients with rare diseases.

Conclusions

Diagnosis and treatment of GA I are still in an early stage in China. Individualized timely treatment and monitoring of the patients need to be optimized. Appropriate communication and education of the parents may help to achieve successful management of GA I patients. The establishment

of and adherence to evidence-based treatment recommendations, as well as careful management provided by experienced metabolic disease experts, will improve the overall outcome of GA I patients.

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REFERENCES:

1. Funk CB, Prasad AN, Frosk P et al: Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. Brain, 2005; 128(Pt 4): 711–22
2. Kölker S, Christensen E, Leonard JV et al: Guideline for the diagnosis and management of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type I). J Inherit Metab Dis, 2007; 30: 5–22
3. Lindner M, Kolker S, Schulze A et al: Neonatal screening for glutaryl-CoA dehydrogenase deficiency. J Inherit Metab Dis, 2004; 27: 851–59
4. Funk CB, Prasad AN, Frosk P et al: Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. Brain, 2005; 128(Pt 4): 711–22
5. Boneh A, Beauchamp M, Humphrey M et al: Newborn screening for glutaric aciduria type I in Victoria: Treatment and outcome. Mol Genet Metab, 2008; 94: 287–91
6. Bjugstad KB, Goodman SI, Freed CR: Age at symptom onset predicts severity of motor impairment and clinical onset of glutaric aciduria type I. J Pediatr, 2000; 137: 681–86
7. Busquets C, Merinero B, Christensen E et al: Glutaryl-CoA dehydrogenase deficiency in Spain: evidence of two groups of patients, genetically and biochemically distinct. Pediatr Res, 2000; 48: 315–22
8. Hoffmann GF, Athanassopoulos S, Burlina AB et al: Clinical course, early diagnosis, treatment, and prevention of disease in glutaryl-CoA dehydrogenase deficiency. Neuropediatrics, 1996; 27: 115–23
9. Bishop FS, Liu JK, McCall TD, Brockmeyer DL: Glutaric aciduria type 1 presenting as bilateral subdural hematomas mimicking nonaccidental trauma. Case report and review of the literature. J Neurosurg, 2007; 106(Suppl.3): 222–26
10. Kölker S, Garbade SF, Greenberg CR et al: Natural history, outcome, and treatment efficacy in children and adults with glutaryl-CoA dehydrogenase deficiency. Pediatr Res, 2006; 59: 840–47
11. Kolker S, Garbade SF, Boy N et al: Decline of acute encephalopathic crises in children with glutaryl-CoA dehydrogenase deficiency identified by newborn screening in Germany. Pediatr Res, 2007; 62: 357–63
12. Hsieh CT, Hwu WL, Huang YT et al: Early detection of glutaric aciduria type I by newborn screening in Taiwan. J Formos Med Assoc, 2008; 107: 139–44
13. Monavari AA, Naughten ER: Prevention of cerebral palsy in glutaric aciduria type 1 by dietary management. Arch Dis Child, 2000; 82: 67–70
14. Kyllerman M, Skjeldal O, Christensen E et al: Long-term follow-up, neurological outcome and survival rate in 28 Nordic patients with glutaric aciduria type 1. Eur J Paediatr Neurol, 2004; 8: 121–29
15. Bijarnia S, Wiley V, Carpenter K et al: Glutaric aciduria type I: outcome following detection by newborn screening. J Inherit Metab Dis, 2008; 31: 503–7
16. Heringer J, Boy SP, Ensenauer R et al: Use of guidelines improves the neurological outcome in glutaric aciduria type I. Ann Neurol, 2010; 68: 743–52