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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Mukul Vij is Senior Consultant Pathologist and Lab Director at Dr Rela Institute and Medical Center in Chennai, India (since 2018). Having received his MBBS degree from King George Medical College in 2004, Dr. Vij undertook postgraduate training at Sanjay Gandhi Postgraduate Institute of Medical Sciences, receiving his Master's degree in Pathology in 2008 and his PDCC certificate in Renal Pathology in 2009. After 2 years as senior resident, he became Assistant Professor in the Department of Pathology at Christian Medical College, Vellore (2011), moving on to Global Health City as Consultant Pathologist and then Head of the Pathology Department (2013). (L-Editor: Filipodia)

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Neonatal isovaleric acidemia in China: A case report and review of literature

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Abstract

BACKGROUND

Isovaleric acidemia (IVA) is a rare autosomal recessive inherited organic acidemia caused by a genetic deficiency of isovaleryl-CoA dehydrogenase (IVD). Its morbidity is low, but mortality is high. There is no effective cure for this disease. Early identification of IVA using clinical features can significantly slow disease progression and reduce mortality. Here we report a Chinese neonate with two mutations of IVD and share valuable information on this disease.

CASE SUMMARY

A 12-day-old male neonate with "poor response for 1 d and repeated convulsions accompanied by high muscle tension for 6 h" was hospitalized. The patient was the first child of nonconsanguineous ethnic Chinese parents. He was delivered by cesarean section due to breech position at 39 + 1 wk of gestation with a birth weight of 3.27 kg. Initially, he suffered from dyspnea and rhinobyon, and at 10 d after birth the patient suddenly developed poor feeding, low response, lethargy and seizures. Organic acid analysis of blood and urine by tandem mass spectrometry and gas chromatography mass spectrometry showed extremely high concentrations of isovaleryl glycine. The patient had an acute episode of IVA causing severe metabolic stress and eventually died.

CONCLUSION

A new case of an IVA patient carrying c.1193G>A (p.Arg398Gln) and c.1208A>G (p.Try403Cys) mutations is reported in China.

Key Words: Isovaleric acidemia; Isovaleryl-CoA dehydrogenase; Sweaty feet odor; Case report; Mental retardation; Literature review

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Core Tip: Isovaleric acidemia is a rare autosomal recessive inherited organic acidemia caused by a genetic deficiency of isovaleryl-CoA dehydrogenase (IVD), with a high mortality. We describe a 12-day-old male neonate diagnosed with IVD after tandem mass spectrometry and gas chromatography mass spectrometry analysis. Organic acid analysis of blood and urine showed extremely high concentrations of isovaleryl glycine. DNA sequencing of the IVD gene in the family revealed c.1193G>A mutation inherited from his mother and c.1208A>G mutation inherited from his father. Furthermore, the clinical characteristics and prognosis were discussed in combination with reported cases over the past 14 years.

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INTRODUCTION

Isovaleric acidemia (IVA) is a rare inherited organic acidemia caused by a genetic deficiency of isovaleryl-CoA dehydrogenase (IVD), an enzyme in the catabolic pathway of leucine, which catalyzes the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA^[1]. This deficiency leads to abnormally high concentrations of isovaleric acid and its derivatives in cells, blood and urine, which results in severe, life-threatening metabolic encephalopathy.

The clinical presentation of IVA appears to be highly variable ranging from severely affected to asymptomatic patients. Clinical features include poor feeding, vomiting, acidosis, ketosis, progressive alteration of consciousness, seizures and finally deep coma and death without appropriate therapy. The characteristic odor of “sweaty feet” caused by isovaleric acid is often noted during metabolic crisis^[2]. The clinical diagnosis of IVA can be confirmed by mutation of the IVD gene. The IVD gene is encoded by the nuclear gene, which is located on chromosome 15q14-15, consisting of 12 exons that span 15 kb of genomic DNA^[3]. To date, more than 70 heterogeneous mutations in the IVD gene have been reported in patients with IVA.

Here we report a case of IVA in a Chinese neonate who was compound heterozygous for a novel 4-bp duplication together with a missense mutation known to be common in Chinese populations, which has been reported previously. Furthermore, the clinical characteristics and prognosis are discussed in combination with reported cases over the past 14 years.

CASE PRESENTATION

Chief complaints

A 12-day-old male neonate with “poor respond for 1 d and repeated convulsions accompanied by high muscle tension for 6 h” was hospitalized.

History of present illness

On the second day after birth, he was admitted to a local hospital due to dyspnea and rhinobyon and received anti-infection and other symptomatic treatment. The patient suddenly developed poor feeding (mixed feeding of 50-60 mL/time decreased to 20 mL/time at intervals of 3 h), low response, lethargy and seizures at 10 d after birth and was transferred to our hospital.

History of past illness

The patient had no history of past illness.

Personal and family history

The patient was the first child of nonconsanguineous ethnic Chinese parents. He was delivered by cesarean section due to breech position at 39 + 1 wk of gestation with a birth weight of 3.27 kg and an Apgar score of 9-10-10. His father was 27 years old. His

mother was 23 years old. Both were healthy, and his mother underwent an abortion two years ago in early pregnancy.

Physical examination

The patient's weight was 2580 g, with a significant loss of 690 g since birth, poor response, no frowning and crying after more than 10 times of foot stimulation, characteristic disagreeable "sweaty feet" odor, yellow skin, flat and soft anterior fontanelle, no neck resistance and hypermyotonia of extremities. Both upper limbs were in a state of flexion, his hands were clenched, lower limbs were stiff, grasp reflex was weakened, and rooting reflex, sucking reflex and Moro reflex were not elicited.

Laboratory examinations

Biochemical laboratory examinations indicated pancytopenia (hemoglobin 107 g/L, white blood cells 1.72×10^9 /L, platelets 11×10^9 /L), increased calcitonin levels (3.180 ng/mL), metabolic acidosis (pH 7.320, bicarbonate 16.50 mmol/L, base excess -9.60 mmol/L), persistent hypocalcemia (1.06-1.24 mmol/L), hyperammonemia (110-543 μ mol/L) and positive ketonuria and urinary protein. Cerebrospinal fluid was yellow and limpid, the Pandy test was positive, white blood cells were 3×10^6 /L, glucose was 6.55 mmol/L, and protein was 1.80 g/L. Tandem mass spectrometry (MS/MS) and urine gas chromatography mass spectrometry (GC/MS) found isovaleryl glycine.

Genetic testing of the IVD gene (NM_002225) was performed using genomic DNA isolated from peripheral leukocytes. The patient had compound heterozygous mutations: c.1193G>A (p.Arg398Gln) and c.1208A>G (p.Try403Cys). The p.Arg398Gln variant was inherited from his mother, whereas p.Try403Cys was inherited from his father (Figure 1). Both variants were missense mutations in accordance with an autosomal recessive inherited disease, which has been previously reported^[4,5].

Imaging examinations

Cerebral ultrasound showed that the cerebral parenchyma and white matter of the periventricular were damaged with intraventricular hemorrhage (grade I-II), and encephaledema.

FINAL DIAGNOSIS

He was diagnosed with IVA 7 d later.

TREATMENT

The patient was treated with anti-infection, granulocyte stimulating factor, human immunoglobulin to enhance immunity, correcting electrolyte disorders and fasting and parenteral nutrition to supply calories. He also received several transfusions of blood products.

OUTCOME AND FOLLOW-UP

The patient developed a persistent poor response and internal environment disturbance. His parents gave up treatment after 4 d, and he was discharged from hospital. He subsequently died.

DISCUSSION

IVA is an autosomal recessive disorder caused by a defect in IVD, a mitochondrial matrix enzyme that catalyzes the oxidation of isovaleryl-CoA to 3-methylcrotonyl-CoA in the leucine degradation pathway^[1]. It was first reported by Tanaka *et al*^[6] and diagnosed by GC/MS and urine organic acid analysis technology in 1966. Neonatal screening studies of IVA have been conducted in many countries and regions, and the incidence of IVA in Germany is 1 in 62500^[7] and in the United States is 1 in 250000^[8]. The incidence in China is about 1 in 190000 diagnosed by neonatal MS/MS^[9]. We performed a literature review by searching the Wanfang database, CNKI and the VIP

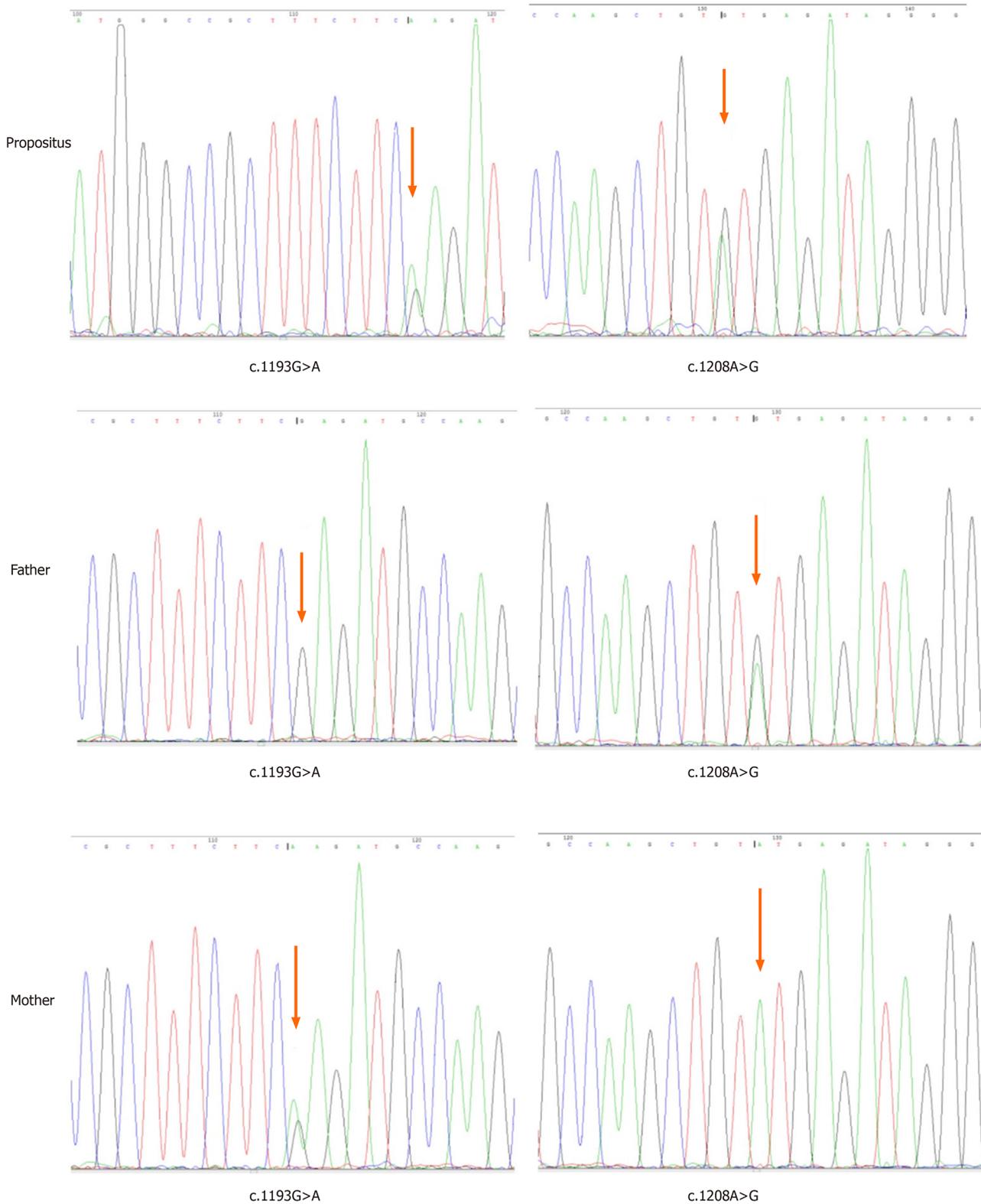


Figure 1 Genetic testing of the isovaleryl-CoA dehydrogenase gene. Sequence analysis of the isovaleryl-CoA dehydrogenase gene in the patient revealed the missense mutations, c.1193G>A (p.Arg398Gln) and c.1208A>G (p.Try403Cys).

database using the terms “isovaleric acidemia,” “isovaleric aciduria,” “organic acidemia” and “organic aciduria” in order to obtain comprehensive information on the clinical course of IVA from a larger number of patients. The clinical features are summarized in Table 1^[10-29].

As shown in Table 1, 29 cases of clinically diagnosed IVA published between 2007 and 2020 were identified and reviewed, specifically focusing on patient age at disease onset, mortality and neurocognitive outcome. The clinical features included neonatal

Table 1 The features of 29 patients with isovaleric acidemia reported in China

Patient No.	Ref.	Sex	Age of symptom onset	Age at diagnosis	Clinical presentation	Urine isovaleryl-glycine	IVD gene mutations	Prognosis
1	Zhou <i>et al</i> ^[10]	Male	4 d	After death	Poor feeding, sweaty feet odor, thrombocytopenia, acidosis, coma, hypocalcemia	Increased	-	Died at 13 d after birth
2	Qiu <i>et al</i> ^[11]	Male	3 d	31 mo	Vomiting, acidosis, hyperglycemia, hypocalcemia	Increased	c.149G>A, c.466G>C	Intelligence and development retardation
3	Ren <i>et al</i> ^[12]	Female	3 d	After death	Poor feeding, low response, acidosis, hypoglycemia, coma, shock	Increased	-	Died at 7 d after birth
4	Wang <i>et al</i> ^[13]	Male	7 d	After death	Poor feeding, low response, acidosis, thrombocytopenia, anemia, lethargy	Increased	-	Died at 1 mo after birth
5	Wu <i>et al</i> ^[14]	Female	7 d	10 d	Rhinobyon, poor feeding, sweaty feet odor, coma, poor response, convulsion, hyperammonemia, thrombocytopenia	25.73	-	The patient showed normal growth and development after follow-up for 3 mo
6	Zhao <i>et al</i> ^[15]	Male	6 d	After death	Poor response, lethargy, sweaty feet odor, thrombocytopenia, leukopenia, shock	Increased	-	Died at 12 d after birth
7	Teng <i>et al</i> ^[16]	Male	3 mo	11 yr	Poor feeding, low response, lethargy, sweaty feet odor	1192.54	-	Delayed development after 2.5 yr follow-up
8	Long <i>et al</i> ^[17]	Female	68 d	70 d	Poor response, sweaty feet odor, anemia, thrombocytopenia, lethargy	Increased	-	Died at 78 d after birth
9	Shang <i>et al</i> ^[18]	Female	7 d	11 d	Lethargy, rhinobyon, convulsion, hyperammonemia, hypocalcemia, thrombocytopenia, sweaty feet odor	Increased	-	After treatment for 7 d, the patient was better and was discharged, reviewed urine isovaleryl-glycine decreased to 25.12
10	Shang <i>et al</i> ^[18]	Male (the older of twins)	5 d	After death	Lethargy, sweaty feet odor, leukopenia, thrombocytopenia, poor response, coma, shock, hyperammonemia	25.13	-	Died at 10 d after birth
11	Shang <i>et al</i> ^[18]	Male (the younger of twins)	5 d	10 d	Lethargy, sweaty feet odor, thrombocytopenia, poor response, hyperammonemia	25.73	-	Leukopenia, neutropenia, thrombocytopenia and hyperammonemia after follow-up for 1 wk, reviewed urine isovaleryl-glycine was slightly elevated
12	Zhu <i>et al</i> ^[19]	Male	6 d	After death	Poor feeding, poor response, lethargy, acidosis, hypocalcemia, urine ketone	Increased	-	Died at 12 d after birth
13	Xu <i>et al</i> ^[20]	Male	5 d	14 d	Poor response, poor feeding, sweaty feet odor, thrombocytopenia	1989.67	-	Better after treatment, sweaty feet odor disappeared
14	Xu <i>et al</i> ^[21]	Male	4 d	After death	Poor feeding, poor response, sweaty feet odor, thrombocytopenia, acidosis, hypocalcemia, ecchymosis	Increased	-	Died at 13 d after birth
15	Xu <i>et al</i> ^[21]	Male	4 d	After death	Lethargy, poor feeding, sweaty feet odor, acidosis, hypoxemia, thrombocytopenia, leukopenia	Increased	-	Died at 13 d after birth

16	Bei <i>et al</i> ^[22]	Female	4 d	11 d	Poor response, poor feeding, dyspnea, sweaty feet odor, shock, acidosis, hyperammonemia	1488.78	c.39G>A, c.597C>G	Died at 12 d after birth
17	Fu <i>et al</i> ^[23]	Male	7 d	11 d	Lethargy, sweaty feet odor, poor response, poor feeding, hyperammonemia, thrombocytopenia, leukopenia, urine ketones, urine protein	Increased	c.1016G>A	Died at 14 d after birth
18	Fu <i>et al</i> ^[23]	Male	2 mo	7 d	Hyperammonemia, sweaty feet odor	Increased	c.1016G>A	Due to timely detection and treatment, the patient's growth and development were normal after follow-up of 2 yr
19	Li <i>et al</i> ^[24]	Female	4 d	20 mo	Vomiting, coma, thrombocytopenia, acidosis, hyperammonemia	2535.76	c.1193G>A, c.1208A>G	Normal development after follow-up of 3 yr
20	Li <i>et al</i> ^[24]	Male	1 d	25 d	Vomiting, poor feeding, hypothermia, coma, acidosis, hyperammonemia	1537.94	c.145C>T	Mild development retardation after follow-up of more than 3 yr
21	Li <i>et al</i> ^[24]	Female	3 d	4 yr	Vomiting, acidosis	858.51	c.611A>G, c.1183C>T	Normal development after follow-up of 10 yr
22	Li <i>et al</i> ^[24]	Male	2 d	After death	Vomiting, poor feeding, coma, leukopenia, thrombocytopenia, hyperammonemia	258.30	c.158G>A, c.676-677insA	Died at 15 d after birth
23	Zhang <i>et al</i> ^[25]	Male	6 d	After death	Tachypnea, hypothermia, leukopenia, acidosis, poor response, hypocalcemia, hyperammonemia, septicemia	Increased	-	Died at 11 d after birth
24	Wang <i>et al</i> ^[26]	Male	1 d	33 mo	Recurrent vomiting, acidosis, leukopenia, elevated urine ketones and urine acid, hypokalemia, hyponatremia, thrombocytopenia	576.181	-	Severe mental retardation
25	Tan <i>et al</i> ^[27]	Male	1 d	9 d	Cough, somnolent, delirious, pneumonia, sweaty feet odor, acidosis, anemia, leukopenia, thrombocytopenia, hyperglycemia	2122.18	c.1208A>G	Died at 16 d after birth
26	Mei <i>et al</i> ^[28]	Male	5 d	8 d	Poor response, sweaty feet odor, leukopenia, hypoglycemia, hyperammonemia, acidosis, hypocalcemia	Increased	c.1195G>C, c.466-3_466-2delinsGG	Died at 14 d after birth
27	Sun <i>et al</i> ^[29]	Male	1 d	5 d	Poor response, anemia, leukopenia, thrombocytopenia, sweaty feet odor, hyperammonemia, urinary ketones and protein, hypermyotonia	623.4	c.158G>A, c.1195G>C	The patient's growth and development were normal after follow-up of 1 yr
28	Sun <i>et al</i> ^[29]	Female	20 d	3 d	Hyperammonemia	58.73	c.214G>T	Magnetic resonance imaging of the brain showed abnormal signals at the right parietal lobe and left thalamus at 21 mo old, intelligence retardation after follow-up of 26 mo
29	Sun <i>et al</i> ^[29]	Female	1 mo	1 mo	No obvious abnormalities were found in routine blood work, biochemistry and blood ammonia	41.32	-	Normal development after follow-up of 6 mo

-: The examination was not performed. IVD: Isovaleryl-CoA dehydrogenase.

onset (25 cases), acute episode (24 cases), sweaty feet odor (17 cases), pancytopenia (19 cases) and hyperammonemia (14 cases), and 15 deaths were reported. Through the literature review, we found that most cases occurred during the neonatal period, and

the mortality rate was high. Thus, it is important for clinicians to be aware of this disease.

The clinical manifestations vary, and disease onset can range from the neonatal period to the adult period. The clinical presentation of IVA is classified into two types: classic acute neonatal episodes and chronic intermittent episodes^[30]. The typical clinical manifestations are severe metabolic acidosis and encephalopathy, often accompanied by leukopenia, neutropenia and thrombocytopenia due to bone marrow suppression and other abnormal blood systems in the neonatal period, and hypocalcemia, hyperglycemia, coma and death may occur if appropriate treatment is not initiated. Therefore, the fatality rate is very high^[5]. These clinical manifestations often lack specificity, and the symptoms are similar to feeding intolerance and neonatal infection, which often cause diagnostic difficulties. Patients with the chronic intermittent form develop intermittent metabolic derangement during episodes of stress, such as infections and developmental delays. Due to the accumulation of isovaleric acid in the body, the patient's body and urine will have an odor similar to sweaty feet, which is an important clue for clinical diagnosis. Our patient demonstrated classical IVA features: Pancytopenia, hypocalcemia, acidosis and hyperammonemia. The characteristic "sweaty feet odor" should enable this condition to be easily recognized clinically.

Plasma isovaleryl carnitine and urine isovaleryl glycine are IVA biomarkers, and the levels of these biomarkers can increase several hundred-fold during acute episodes. Since the implementation of expanded newborn screening by MS/MS in many countries, IVA can be diagnosed presymptomatically^[31]. Molecular genetic analysis helps to further confirm the clinical diagnosis of IVA. To date, more than 70 heterogeneous mutations in the IVD gene have been reported in patients with IVA, including point mutations, frameshift mutations and splice-site mutations (<http://www.hgmd.org/>). Missense and splicing mutations are the most common, but a small number of frameshift mutations have been reported^[3]. Recently, a novel mild and potentially asymptomatic form of IVA and its association with a common missense mutation, c.932C>T (p.A282V) was identified in two-thirds of patients^[32]. The missense mutations, c.149G>A (p.R21H) and c.1199A>G (p.Y371C), are common in Han Chinese subjects, especially the latter^[1,33,34]. In the present study, the patient had compound heterozygous mutations: c.1193G>A (p.Arg398Gln) and c.1208A>G (p.Try403Cys), and both were missense mutations in accordance with an autosomal recessive inherited disease, which have been previously reported^[4,5].

Early diagnosis and treatment are necessary to prevent neonatal mortality and improve the neurologic and cognitive outcomes. Grünert *et al*^[8] investigated 155 IVA patients and found that the survival rate was higher in the group diagnosed early (*i.e.* diagnosed in the first 5 wk) than in the group diagnosed later (33% and 3%, respectively), and the rate of normal cognitive outcome followed a similar pattern (85% *vs* 45%, respectively). These data emphasize that early diagnosis and treatment play a vital role in the outcome of IVA. Therefore, early diagnosis is crucial, and asymptomatic detection is possible with expanded neonatal screening. In newborns or older babies who present with multiple symptoms such as poor feeding, vomiting, drowsiness, coma, metabolic acidosis, ketosis, hyperammonemia, hypocalcemia, neutropenia, thrombocytopenia and a decrease in whole blood cells at the same time, or other diseases of unknown causes, IVA should be considered. Relevant examinations should be carried out to establish a diagnosis as early as possible. We summarized characteristics of the IVA cases reported over a 14-year period using the Wanfang database, CNKI and the VIP database and found that neonatal morbidity was prevalent in the vast majority of cases. The patient's clinical symptoms and laboratory examinations were typical in the acute type, and the chronic intermittent type was not easily identified at an early age. When certain clinical manifestations occur in children, the disease can be diagnosed by blood and urinary organic acid or acyl carnitine analysis. However, there are few reported gene mutations related to this disease in China, and there is also a lack of long-term follow-up study data on IVA children.

An early diagnosis leads to early treatment and subsequently results in normal development of the children. Mild protein restriction and glycine and carnitine are recommended to remove toxic metabolites, in addition to antibiotics and supportive care. If untreated, patients may die or show significant developmental delay. The use of glycine has been effective in the treatment of IVA, and it has been shown that glycine administration reduced the rise in serum isovaleric acid produced by a leucine load^[35]. The measurement of disease-specific metabolites in the amniotic fluid and [¹⁴C] IVA incorporation in cultured amniocytes could help prenatal diagnosis^[36]. It is also important for the mother to undergo detection of metabolites in amniotic fluid during

future pregnancies for prenatal diagnosis of IVA.

CONCLUSION

The case of IVA reported herein showed that the mutations were not polymorphic. The frequency of occurrence in the population is extremely low. The clinical and genetic features of this patient help to further expand our knowledge of IVA. Moreover, most cases occur during the neonatal period, and the mortality rate is high. Thus, clinicians should be aware of this disease. Early diagnosis as well as the detection of genetic metabolic diseases may improve patient outcomes.

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