

ARC syndrome with high GGT cholestasis caused by *VPS33B* mutations

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Abstract

Arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome (OMIM 208085) is an autosomal recessive disorder that is caused by mutations in 2 interacting genes *VPS33B* and *VIPAS39*. Mutations in *VPS33B* gene account for most cases of ARC. As low or normal gamma-glutamyl transpeptidase (GGT) activity has been described in all patients with ARC syndrome identified so far, ARC syndrome is a possible diagnosis for low GGT cholestasis. Here we describe a Chinese patient with neonatal cholestasis and a high GGT level in three consecutive tests. She had other typical manifestations of ARC syndrome, including arthrogryposis multiplex congenita, renal involvement and ichthyosis. Genetic study of the *VPS33B* gene further confirmed the diagnosis by identification of compound heterozygosity of two known disease-causing mutations, c.403+2T > A and c.1509-1510insG. The mechanism of high GGT in this patient is unclear. Nevertheless, this case indicates

that ARC syndrome cannot be excluded from the differential diagnosis of neonatal cholestasis even if high GGT activity is found.

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Key words: Arthrogryposis, renal dysfunction and cholestasis syndrome; Cholestasis; Gamma-glutamyl-transpeptidase; *VPS33B*; Renal dysfunction; Glucosuria

Core tip: Neonatal cholestasis with low or normal gamma glutamyl transpeptidase (GGT) activity was regarded as a characteristic feature of arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome. Here we describe a patient who presented with neonatal cholestasis and high GGT activities. She had all other typical clinical manifestations of ARC syndrome. The diagnosis was finally confirmed by the presence of compound heterozygosity of two known *VPS33B* disease-causing mutations. Our case indicates that ARC syndrome cannot be excluded in neonatal cholestasis even with unexpected high GGT activity.

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INTRODUCTION

Arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome (OMIM 208085) is an autosomal recessive disorder that typically presents with neonatal cholestasis, renal tubular dysfunction and arthrogryposis multiplex congenita^[1]. Mutations in 2 interacting genes *VPS33B* and *VIPAS39* have been identified. Mutations in *VPS33B*

Table 1 Biochemistry of the proband and her past elder sister at different age of days

Age (d)	TBIL (mmol/L)	DBIL (mmol/L)	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TBA (mmol/L)	TP (g/L)	ALB (g/L)
The proband									
17	80.5	28.1	12	22	694	216	27.2	50.3	31.2
21	55.9	27.5	13	22	486	150	34.2	49.0	24.0
26	107.5	36.5	40	29	558	202	90.7	NA	NA
The past elder sister									
30	263.4	122	22	NA	576	48	NA	48.9	29.0
32	334.7	210.5	16	30	454	43	NA	46.4	30.2
34	271.3	162.9	17	40	419	37	NA	57.1	31.5
Reference range	5-21	0-6	0-40	0-40	0-500	3-50	0-10	60-85	35-55

TBIL: Total bilirubin; DBIL: Direct bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl-transpeptidase; TBA: Total bile acid; TP: Total protein; ALB: Albumin.

gene account for most cases of ARC^[2-5].

As low or normal gamma-glutamyl transpeptidase (GGT) activity has been described in all patients with ARC syndrome identified so far, ARC syndrome is one of the differential diagnosis for low GGT cholestasis^[6,7]. Recently we diagnosed a case with ARC syndrome caused by *VPS33B* mutations, but an unexpectedly high GGT level was noticed.

CASE REPORT

The proband is a female patient, the second child of a non-consanguineous *han* couple. Oligohydramnios, ascites and enhanced echo of the kidneys of the fetus were demonstrated by ultrasound in the 7th mo of pregnancy. She was born in good condition with a birth weight of 3400 g by a cesarean section at 39 wk of gestation, due to breech presentation. Her weight dropped to 2900 g by day 8 while on mixed formula and breast feeding. Hearing screening tests performed on day 7 yielded no definitive results.

Jaundice was first noticed on day 3 after birth and resolved spontaneously on day 10. It recurred from day 14 after birth and dark urine and light yellow colored stools were noticed thereafter. The investigations at the local hospital revealed mild cholestasis so the child was transferred to a children's hospital in Beijing at 21 d of age, when her body weight was 2900 g. She received blood transfusion because of anemia with a hemoglobin level of 71 g/L at 28 d of age, and was then referred to a hepatology centre at age 30 days for investigations of the cause of her cholestasis.

Family history revealed that the mother was healthy and the father had polycystic kidney disease. The mother's first pregnancy produced a full-term girl weighing 3000 g, delivered by cesarean section for breech presentation and II° contaminated amniotic fluid. Enhanced echoes of the fetal kidneys were demonstrated by ultrasound at the 4th mo of pregnancy and oligohydramnios and ascites at the 7th mo of pregnancy. The limbs and skin of this elder sibling looked similar to those of the proband. Jaundice persisted from birth and stool color became lighter after 20 d of age. Laboratory tests at 1 mo of age revealed

persistent positive glucose and protein in the urine and moderate anemia. Liver function tests were listed in Table 1. Ultrasound of the abdomen revealed polycystic kidneys, but CT scan of the brain was normal. This first baby died at 8 mo from infection, anorexia, jaundice and poor weight gain.

On examination of the proband, obvious arthrogryposis multiplex, exfoliative skin (ichthyosis), mild jaundice and simian lines on the right palm were seen. A weak response to surrounding stimulus and no response to sound were noted. Liver was palpable 2 centimeters below the costal edge with normal texture. The spleen was not palpable.

Laboratory investigations of the proband showed mildly elevated conjugated bilirubin, raised alkaline phosphatase, elevated GGT and total bile acids, hypoalbuminemia but normal ALT and AST (Table 1). Proteinuria and glucosuria were present. There was a mildly elevated lactate level. The following results were normal or unremarkable: blood urea, creatinine, electrolytes, free T4 and thyroid stimulating hormone, ammonia, α 1-antitrypsin level, blood tandem mass spectrometry (MS/MS) study of amino acid and carnitine profile, serology for hepatitis A to E, blood immunoglobulin M antibodies to toxoplasma, rubella, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, blood cytomegalovirus DNA and chromosome G bands.

The proband's previous X-ray revealed pneumonia. Cardiac ECHO revealed patent foramen ovale. Abdominal ultrasound showed normally sized kidneys with multiple cysts of various sizes in both kidneys with the largest in the left kidney of 0.8 cm × 0.6 cm, and the largest in the right kidney, 0.6 cm × 0.5 cm. Granular high-echo spots in the medulla of kidneys were revealed. Ultrasound of the hip showed no sign of dislocation. Brain CT scan showed symmetric, bilateral hypodense white matter of the cerebral hemispheres with a CT number of about 14 HU on the Hounsfield scale. CT also revealed swollen bilateral frontal and temporal lobes, narrowed bilateral lateral and third ventricles, and basal ganglia of heterogeneous density.

Management

From the clinical manifestations and previously per-

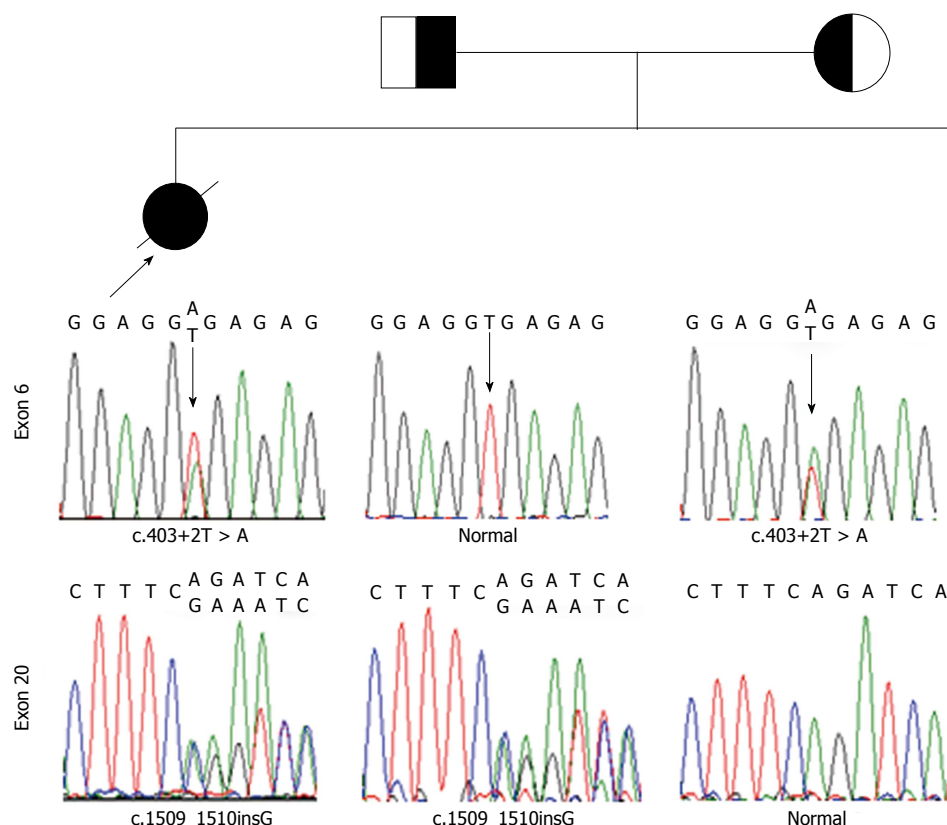


Figure 1 Genomic DNA sequences of the exons 6 and 20 of *VPS33B* gene from the proband and her parents. The arrows in exon 6 indicate T/A heterozygous (c.403+2T > A) in the proband and her mother, but normal sequence (T) in her father. The arrows in exon 20 indicate heterozygous insertion of G (c.1509-1510insG) in the proband and her father, but no change in her mother. These confirmed the proband was a compound heterozygote for c.403+2T > A and c.1509-1510insG in *VPS33B* gene.

formed investigations, the diagnosis of ARC syndrome was suspected. In view of the bad prognosis, the parents were not willing to allow the child to undergo any further tests. However they consented to genetic analysis to help with future prenatal diagnosis. Ursodeoxycholic acid and fat-soluble vitamins were prescribed and follow-up was made over the telephone or by email. Her ichthyosis got much better with olive oil massage after bathing and the patient attained her birth weight at 67 d of age. Facial eczema developed from about 5 mo of age and she died at 7.5 mo of age.

Molecular genetic techniques

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki of 1975. With the approval by the Ethics Committee on human research of the Children's Hospital of Fudan University and informed consent of the parents, 1 mL of whole blood was drawn from the proband and her parents. DNA was extracted routinely and all the coding exons together with adjacent intronic sequence of the *VPS33B* gene were amplified and sequenced according to Gissen P *et al* with modifications (detailed primers, PCR and sequencing condition are available upon request)^[2,3].

Result of molecular genetic studies

In the proband, compound heterozygosity for c.403+2T

> A and c.1509-1510insG mutations was revealed. The parents were found to be heterozygous (Figure 1).

DISCUSSION

ARC syndrome is known to be caused by *VPS33B* and *VIPAS39* mutations and has been reported to occur in many ethnic groups^[3,8]. Normal or low GGT is one of the characteristics of neonatal cholestasis in ARC syndrome and it was listed as one of the four diagnostic features of the syndrome (arthrogryposis, renal tubular dysfunction and cholestasis with a low GGT activity)^[3]. By reviewing the literature to date, none of the cases reported manifested cholestasis with significantly high GGT. Therefore, the proband case here is the first report that ARC syndrome could present as neonatal cholestasis with significantly high GGT activities.

The patients had three major diagnostic features: arthrogryposis multiplex congenita, renal involvement and cholestasis. The genetic study of *VPS33B* gene of the proband further confirmed the diagnosis by identification of two mutations previously reported in the East Asians^[8]. c.1509-1510insG is a frame-shift mutation. c.403+2T > A mutation disrupts the original donor site following new donor site creation and therefore, a 16 bp intronic sequence that contains a stop codon is inserted into the mRNA sequence and results in a truncated

Table 2 Gamma-glutamyl transpeptidase level in arthrogryposis, renal dysfunction and cholestasis patients previously reported

Ref.	GGT level
Di Rocco <i>et al</i> ^[10] (1995)	Normal (3 patients)
Franceschini <i>et al</i> ^[11] (1997)	Normal (3 patients)
Papadia <i>et al</i> ^[12] (1996)	Normal (1 patient)
Coleman <i>et al</i> ^[13] (1997)	Normal (2 patients, 60-70 U/L)
Abdullah <i>et al</i> ^[14] (2000)	Normal (3 patients)
Denecke <i>et al</i> ^[15] (2000)	Normal (2 patients), mildly elevated (1 patient 78 U/L)
Eastham <i>et al</i> ^[16] (2001)	Normal (4 patients)
Howells <i>et al</i> ^[17] (2002)	Normal (1 patient)
Gissen <i>et al</i> ^[23] (2004)	Normal (29 patients)
Abu-Sa'Da <i>et al</i> ^[18] (2005)	Normal (2 patients)
Choi <i>et al</i> ^[19] (2005)	Normal (1 patient)
Tekin <i>et al</i> ^[20] (2005)	Normal (2 patients)
Bull <i>et al</i> ^[21] (2006)	Normal (1 patient)
Gissen <i>et al</i> ^[3] (2006)	Normal (9 patients)
Taha <i>et al</i> ^[22] (2007)	Normal (1 patient)
Hershkovitz <i>et al</i> ^[23] (2008)	Normal (2 patients, 35-83 U/L)
Arhan <i>et al</i> ^[24] (2009)	Normal (1 patient)
Jang <i>et al</i> ^[8] (2009)	Normal (6 patients)
Kim <i>et al</i> ^[25] (2010)	Normal (10 patients)

GGT: Gamma-glutamyl transpeptidase.

VPS33B protein^[9]. Based on this, a diagnosis of ARC syndrome caused by *VPS33B* mutations in the proband case could be confirmed.

An interesting finding is the parallel increase in serum levels of GGT and total bile acids in the proband. Her elder sister demonstrated a typical neonatal cholestasis with low GGT, who should have same genetic background of *VPS33B*, indicating that the high GGT in the proband could not be explained by the specific mutations.

The normal reference range of GGT is age dependent^[7]. It could be quite high in newborns and then decreased to adult range. In Mainland China, because of the lack of age specific data, 50 U/L is widely used as the upper normal limit regardless of age. 93 U/L is defined as the upper normal limit of GGT in infants less than 6 mo of age in National Taiwan University Hospital^[6]. One feature of this proband is that she went to see a doctor much earlier than her elder sister, so the elevation of GGT might be explained as an age-related evolution of normal GGT activity. The limitation of this case report is the lack of follow-up of her liver function test beyond neonatal stage. As a result, we do not know whether the elevated GGT activity would reduce as age advances. However, all cases with available data on GGT activity reported until now had GGT activity labeled normal or with a peak level no more than 83 U/L (Table 2). Her elder sister's GGT activity tested at 30 days of age was also below 50 U/L (Table 1). However, the proband had a GGT activity over 200 U/L at 26 days of age, making it unlikely that it can be fully explained by the specific age.

This case shows that the presence of high GGT activity cannot exclude ARC if the diagnosis is strongly suspected due to the presence of other cardinal features such as ichthyosis, arthrogryposis, agranular platelets, fail-

ure to thrive, and renal tubular acidosis. It indicates that ARC syndrome should be considered as a diagnostic possibility in various populations and a cholestasis with significantly high GGT activity, especially in the early stage after birth, should not exclude the diagnosis.

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COMMENTS

Case characteristics

Arthrogryposis multiplex congenita and ichthyosis were found in a cholestatic infant with high gamma-glutamyl transpeptidase (GGT) activity.

Clinical diagnosis

Arthrogryposis multiplex congenita, renal dysfunction and cholestasis.

Differential diagnosis

Biliary atresia, progressive familial intrahepatic cholestasis, citrin deficiency, idiopathic neonatal cholestasis, etc., should be considered.

Laboratory diagnosis

Genetic study revealed compound heterozygote with known disease-causing mutations in *VPS33B*.

Imaging diagnosis

Multiple cysts in kidneys and patent foramen ovale were revealed by ultrasound.

Treatment

Ursodeoxycholic acid and fat-soluble vitamins were prescribed.

Related reports

Cholestasis of arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome has never been associated with significantly high GGT activities.

Term explanation

ARC refers to arthrogryposis multiplex congenita, renal dysfunction and cholestasis.

Experiences and lessons

ARC syndrome should not be excluded from the list of differential diagnoses in a cholestatic infant with high GGT activity, especially in the first months after birth.

Peer review

This article indicated that ARC syndrome cannot be excluded from the differential diagnosis of neonatal cholestasis based on serum levels of GGT activity.

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