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CASE REPORT

Novel mutations of the Alström syndrome 1 gene in an infant with dilated cardiomyopathy: A case report

Ping Jiang, Liang Xiao, Yuan Guo, Rong Hu, Bo-Yi Zhang, Yi He

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Ping Jiang, Yuan Guo, Yi He, Department Of Cardiology, Zhuzhou Central Hospital, Zhuzhou 412000, Hunan Province, China

Liang Xiao, Department of Pediatric, Zhuzhou Central Hospital, Zhuzhou 412000, Hunan Province, China

Rong Hu, Bo-Yi Zhang, Department of Medical Ultrasonics, Zhuzhou Central Hospital, Zhuzhou 412000, Hunan Province, China

Corresponding author: Yi He, MBBS, Chief Physician, Department Of Cardiology, Zhuzhou Central Hospital, No. 118 South Changjiang Road, Zhuzhou 412000, Hunan Province, China. heyicardiology@163.com

Abstract

BACKGROUND

Alström syndrome (AS) is a rare autosomal recessive disease that is generally induced by mutations of the Alström syndrome 1 *(ALMS1)* gene. We report a case of AS, extend the spectrum of *ALMS1* mutations and highlight the biological role of *ALMS1* to explore the relationship between dilated cardiomyopathy (DCM) and mutations in *ALMS1*.

CASE SUMMARY

We present the case of an infant with AS mainly manifesting with DCM that was caused by a novel mutation of the *ALMS1* gene. Whole-exome sequencing revealed a simultaneous large deletion and point mutation in *ALMS1,* leading to frameshift and missense mutations, respectively, rather than nonsense or frameshift mutations, which have been reported previously. Upon optimized anti-remodeling therapy, biohumoral exams and arrhythmic burden of the infant were alleviated at follow-up after 6 mo.

CONCLUSION

We identified novel mutations of *ALMS1* and extended the spectrum of *ALMS1* mutations in an infant with AS.

Key Words: Alström syndrome; Dilated cardiomyopathy; Alström syndrome 1; Missense mutation; Frameshift mutation; Case report

Core Tip: We present the case of an infant with dilated cardiomyopathy (DCM) who was diagnosed with Alström syndrome at the early stage of the disease. Whole-exome sequencing revealed that a large deletion and point mutation simultaneously occurred in the Alström syndrome 1 *(ALMS1)* gene, leading to frameshift and missense mutations, respectively, rather than nonsense or frameshift mutations, which have been reported previously. Likewise, to date, few interpretations have been made of the related mechanism of the novel *ALMS1* gene mutation to induce DCM in infants.

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INTRODUCTION

Alström syndrome (AS; MIM# 203800) is an unusual autosomal recessive genetic disorder that involves multiple systems and progressive dysfunction and is characterized by visual disturbance, hearing impairment, cardiomyopathy, hypertriglyceridemia, accelerated nonalcoholic fatty liver disease, and recurrent respiratory disease[1]. It is caused by mutations of the Alström syndrome 1 *(ALMS1)* gene, which is located on chromosome 2p13. The *ALMS1* gene contains 23 exons and encodes a 461.2-kDa protein of 4169 amino acids[2]. To date, over 268 variants in *ALMS1* have been identified[2]. The ALMS1 protein localizes to centrosomes and the base of cilia[3]; however, the function of the protein is not clear, and the explicit molecular pathological mechanisms of dilated cardiomyopathy (DCM) have not been fully demonstrated. Here, we present the case of a 1-month-old girl who was initially diagnosed with DCM induced by a novel mutation of the *ALMS1* gene and describe the likely pathogenesis of DCM as a result of variants in *ALMS1*.

CASE PRESENTATION

Chief complaints

A 1-month-old girl was brought to the hospital because of cyanosis and dyspnea.

History of present illness

She had a persistent cough with recurrent choking for 4 d, and the symptoms deteriorated in the last 12 h, manifesting with cyanosis and dyspnea.

History of past illness

She had a history of recurrent respiratory infections and had nystagmus at birth.

Personal and family history

Her parents denied a family history of cardiomyopathy and genetic disease.

Physical examination

Her body weight was 4.5 kg, and her body length was 50 cm. Her heart border was enlarged to the left midaxillary line, and she had a few rales in both lower lungs.

Laboratory examinations

Clinical laboratory tests indicated a plasma triglyceride level of 3.17 mmol/L (normal < 1.7 mmol/L), high-density lipoprotein (HDL) cholesterol level of 0.99 mmol/L (normal 1.15–2.25 mmol/L), serum cardiac troponin T (cTnT) level of 0.05 μg/L (normal< 0.024 μg/L) and N-terminal pro-brain natriuretic peptide level of 23 681 pg/mL (normal < 125 pg/mL).

Imaging examinations

Twelve-lead ECG documented high voltages in the left precordial leads and diffuse T wave inversion (Figure 1A). There were two episodes of paroxysmal atrial tachycardia in 24-h Holter ECG monitoring, and the maximum heart rate was 180 beats/min, whereas ventricular arrhythmia was not recorded. Chest radiography demonstrated cardiac enlargement and pulmonary congestion (Figure 1B). Transthoracic echocardiography (TTE) indicated severe left ventricular dilatation and heart failure with reduced ejection fraction (Figure 1C).

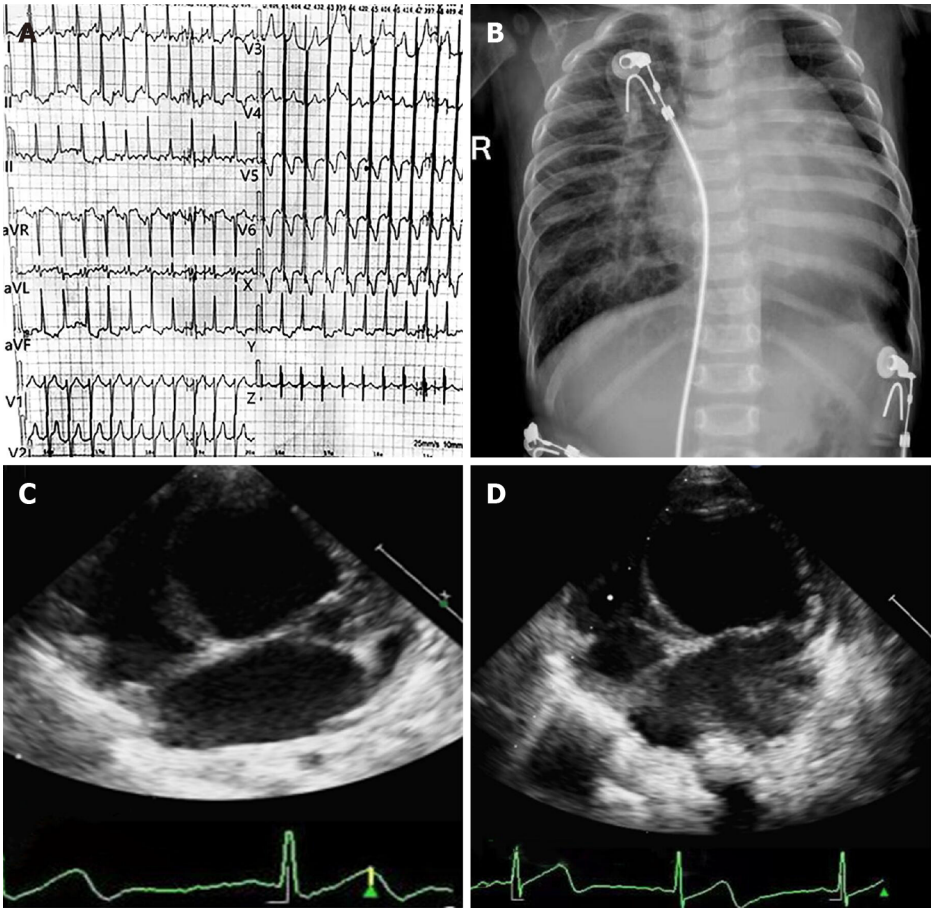

Figure 1 Electrocardiography and imaging examinations of the patient. A: Abnormal 12-lead electrocardiography indicated high voltages in the left precordial leads and diffuse T wave inversion; B: Chest radiography demonstrated cardiac enlargement and pulmonary congestion; C: Dilated left ventricle approximately 43 mm in late diastole and reduced ejection fraction approximately 26% (echocardiography at admission); D: Dilated left ventricle approximately 46 mm in late diastole, reduced ejection fraction approximately 27% (echocardiography at a follow-up of 6 mo).

Further diagnostic work-up

Nuclear genomic DNA was extracted from peripheral blood samples of the infant and her parents for amplification with targeted capture of the coding regions of the genome. Then, amplicons were subjected to whole-exome sequencing by a NextSeq500 sequencer (Illumina, San Diego, CA, United States). Novel genetic mutations in *ALMS1* were identified, and genetic analysis showed that the *ALMS1* gene (NM_015120) had two mutations on chr2: 73829360 (c.12160C>G, p.R4054G) in exon 20 and chr2: 73827805-73830431 deletion in exons 18-21 (Figure 2). The mutations were confirmed by the Sanger sequencing method, which revealed that c.12160C>G (p.R4054G) and a deletion removing the entire exons 18-21 were acquired by paternal and maternal inheritance, respectively.

FINAL DIAGNOSIS

According to diagnostic criteria for AS[4], the infant met two major criteria and one minor criterion. The mutation sites associated with clinical features were in favor of the diagnosis of AS.

TREATMENT

Both sacubitril/valsartan and dapagliflozin are strongly recommended for adult patients with heart failure with reduced ejection fraction, according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[5], but not in infants, because the safety and efficacy of both have not been confirmed in infants, and further study is needed for evaluation[6,7]. Therefore, drug therapies such as angiotensin-converting enzyme inhibitors, beta blockers, spironolactone, digoxin and diuretics were administered according to consensus clinical management guidelines for AS[1].

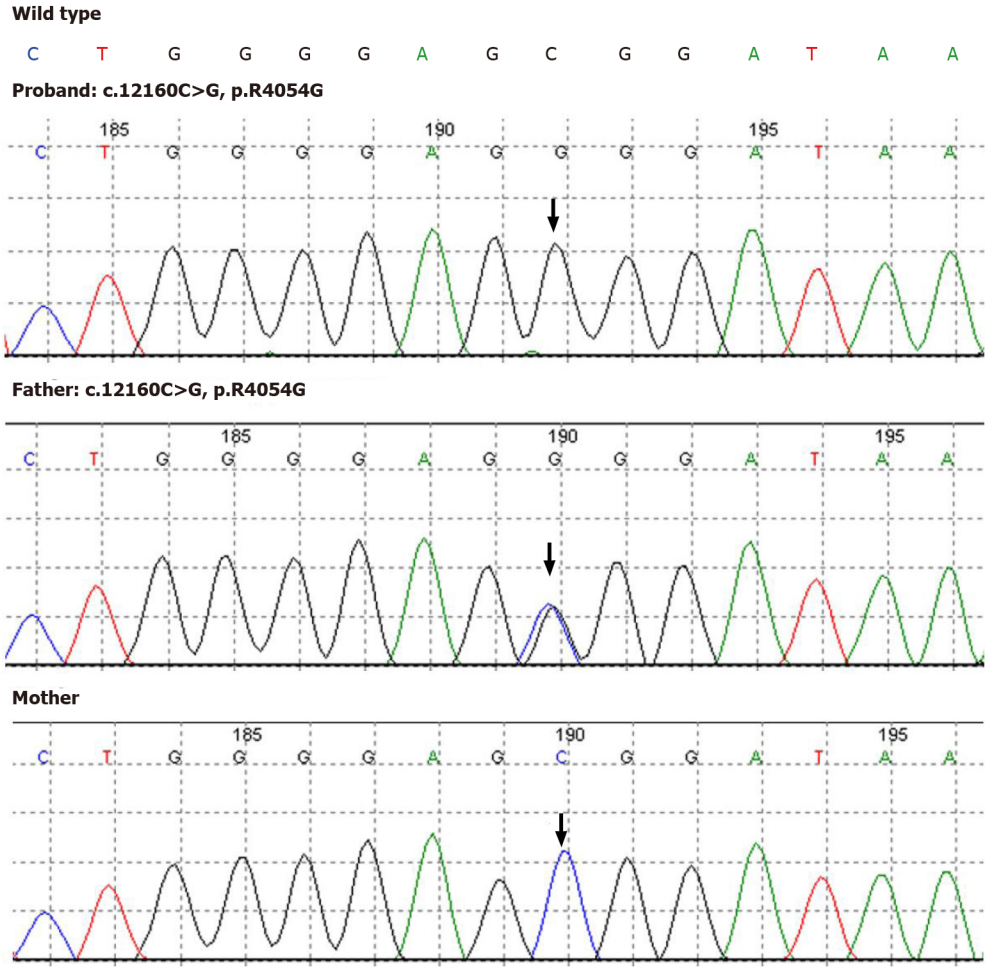

Figure 2 Sanger sequencing at the position of c.12160C>G, p.R4054G on the Alström syndrome 1 gene. The proband carried a homozygotic mutation of c.12160C>G, p.R4054G in exon 20 inherited from her father, while her mother had normal sequence in exon 20 on one chromosome and a deletion of exons 18-21 on the other chromosome.

OUTCOME AND FOLLOW-UP

In follow-up at 6 mo, clinical laboratory tests indicated that the N-terminal pro-brain natriuretic peptide level decreased to 1879 pg/mL, the cTnT concentration declined to normal, and there was no arrhythmic burden in repeated 24-h Holter ECG monitoring. Further, TTE revealed that cardiac function of the infant had not deteriorated with the current medication (Figure 1D).

DISCUSSION

AS is an extremely rare autosomal recessive disease induced by a mutation of the *ALMS1* gene, with an estimated incidence of 1 case per 1000000 live births[1]. In the present case, the patient had mutations in *ALMS1* and visual symptoms, DCM, repeated respiratory infection, and hypertriglyceridemia with low HDL levels, which conformed to the diagnostic standard for AS[4]. Mutations in *ALMS1* are associated with AS in the individual, and both DCM and visual symptoms are cardinal manifestations of AS[1]. Consequently, the classic phenotype in infants with AS is closely related to the genotype. Mutations in exons 18-21 of *ALMS1* were not identified in the mutational hotspots located in exons 8, 10 and 16. Variants in non-hotspot exons could result in classical phenotype deficiency or atypical phenotypes, such as the delayed age of obesity and diabetes onset. In contrast, most of the variants in *ALMS1* in previous reports were nonsense and frameshift mutations[8], but a large deletion and point mutation simultaneously occurring in the infant caused frameshift and missense mutations, respectively, both of which are reported for the first time. Casey and colleagues[9] also identified two infant siblings with DCM who were finally diagnosed with AS as a result of mutant alleles in exons 20 and 5 rather than in the mutational hotspots. Thus, an increasing number of diseases are caused by variants in the *ALMS1* gene outside the recognized mutational hotspots.

To date, little is known about the mechanism by which *ALMS1* gene mutation can lead to DCM in infants. In our case, the mutations that affected ALMS1 protein expression were missense and frameshift mutations in exons 20 and 18-21, respectively, which can lead to abnormal structure of the ALMS1 protein and subsequent loss of function. A previous study showed that the ALMS1 protein plays an important role in postnatal cardiomyocyte mitosis by affecting centrosomes and regulating cell cycle arrest, and ALMS1 protein deficiency can impair the terminal differentiation of cardiomyocytes[10], leading to cardiac dysfunction or progressive functional deterioration. Additionally, deficiency of the ALMS1 protein can activate β-catenin-dependent WNT signaling[10], which has been demonstrated to contribute to the inflammatory response and fibrosis in tissues and cells in animal experiments[11]. The local cardiac inflammatory response and cardiac fibrosis may be important mechanisms in the process of DCM.

CONCLUSION

We identified novel mutations of the *ALMS1* gene and extended the spectrum of known *ALMS1* mutations. It is essential to perform *ALMS1* gene sequencing in infants with DCM.

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FOOTNOTES

Author contributions: Jiang P and He Y reviewed the literature and contributed to manuscript drafting; Hu R and Zhang YB performed follow-up work and interpreted the data; Xiao L and Guo Y analyzed and interpreted the gene sequencing; all authors approved the final version to be submitted.

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ORCID number: Ping Jiang 0000-0002-4097-5115; Liang Xiao 0000-0003-2035-9697; Yuan Guo 0000-0002-3850-4664; Rong Hu 0000-0002-4226-8246; Bo-Yi Zhang 0000-0001-7008-3452; Yi He 0000-0002-5607-950X.

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