

CASE REPORT

ADVANCED

CLINICAL CASE

Novel Loss of Function in the *AGK* Gene

Rare Cause of End-Stage Heart Failure



Bibhuti B. Das, MD,^a Lazaro E. Hernandez, MD,^a Parul Jayakar, MD,^b Kathryn C. Chatfield, MD, PhD,^c
Maryanne Chrisant, MD^a

ABSTRACT

The authors present a case of mitochondrial cardiomyopathy due to a novel mutation of *AGK* gene that led to progressive heart failure. The cardiac magnetic resonance image findings of diffusely elevated relaxation time and increase in extracellular volume in the myocardium without early or late gadolinium enhancement may suggest mitochondrial cardiomyopathy. The authors emphasized the multidisciplinary team approach in the care of patients with mitochondrial cardiomyopathies. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2019;1:11-6)
© 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation.
This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HISTORY OF PRESENTATION

A 13-year-old Hispanic female patient presented with complaints of nausea, vomiting, and abdominal pain for 2 days. Additionally, she was complaining of difficulty in breathing and being unable to lie flat due to orthopnea. Her weight was 24 kg (<3rd percentile), height 134 cm (<3rd percentile), and body mass index 13 kg/m². Her vital signs were significant for tachycardia (134 beats/min) and hypotension (88/64 mm Hg). She had bilateral cataracts and mild pallor without icterus or cyanosis. Her cardiovascular

examination was notable for soft S1 and S2, a systolic murmur grade 3/6 best heard at right sternal border with gallop rhythm, and no pericardial rub. She was tachypneic (46 breaths/min) and had rales bilaterally on auscultation of chest. Her liver edge was palpable 4 cm below her right costal margin. She had 2+ pedal edema and her capillary refill was 4 s. Her sensorium was intact but she was wheelchair bound with generalized muscle weakness.

PAST MEDICAL HISTORY

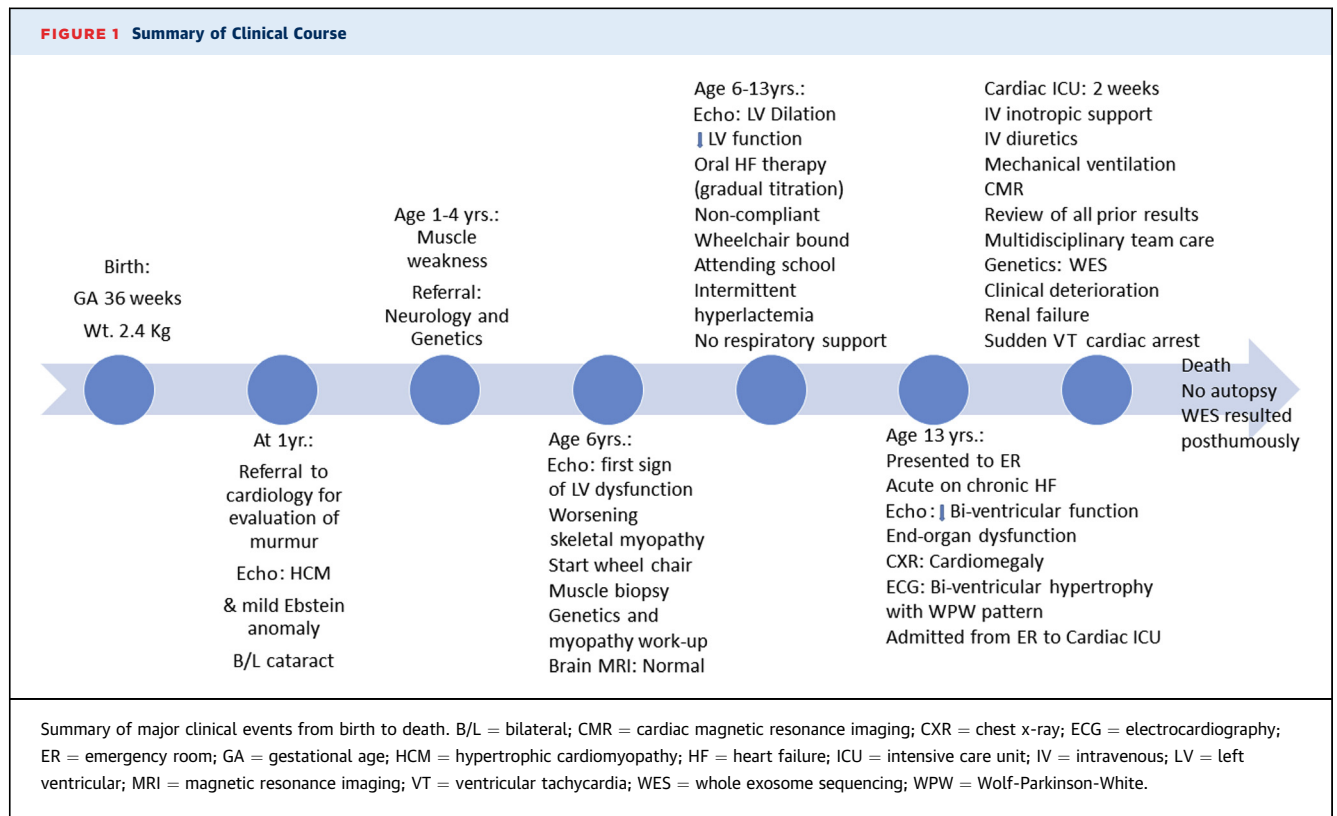
She was born at 36 weeks of gestation and was small for gestational age. She had the findings of bilateral cataracts was previously known and discovered at age 1 year (**Figure 1**). Her hypertrophic cardiomyopathy was diagnosed at age 1 year. She was wheelchair bound due to progressive muscle weakness since age 6 years. At age 6 years, she was noted on routine cardiac surveillance to have reduced global left ventricular (LV) systolic function and dilatation of LV for which she was started on oral heart failure therapy: carvedilol; lisinopril; and furosemide. She had history

LEARNING OBJECTIVES

- Detailed history, physical examination, and multimodality imaging can significantly narrow down the differential diagnosis of pediatric cardiomyopathy.
- Mitochondrial diseases are rare causes of cardiomyopathy, and a collaborative multidisciplinary team approach is required in the care of this complex group of patients.

From the ^aDepartment of Pediatric Cardiology, Joe DiMaggio Children's Hospital Heart Institute, Memorial Health Care, Hollywood, Florida; ^bDivision of Genetics and Metabolism, Nicklaus Children's Hospital, Miami, Florida; and the ^cDivision of Cardiology, Children's Hospital Colorado, Aurora, Colorado. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

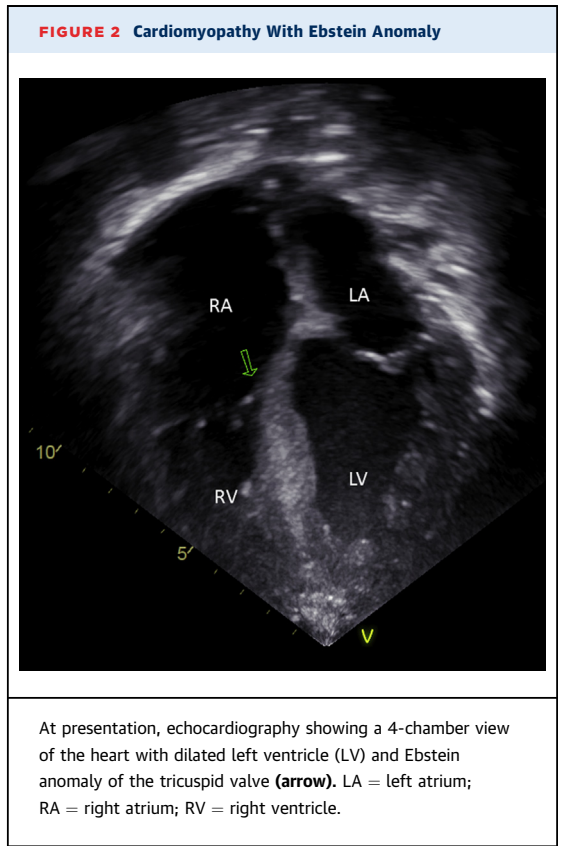
Manuscript received March 22, 2019; revised manuscript received May 2, 2019, accepted May 7, 2019.

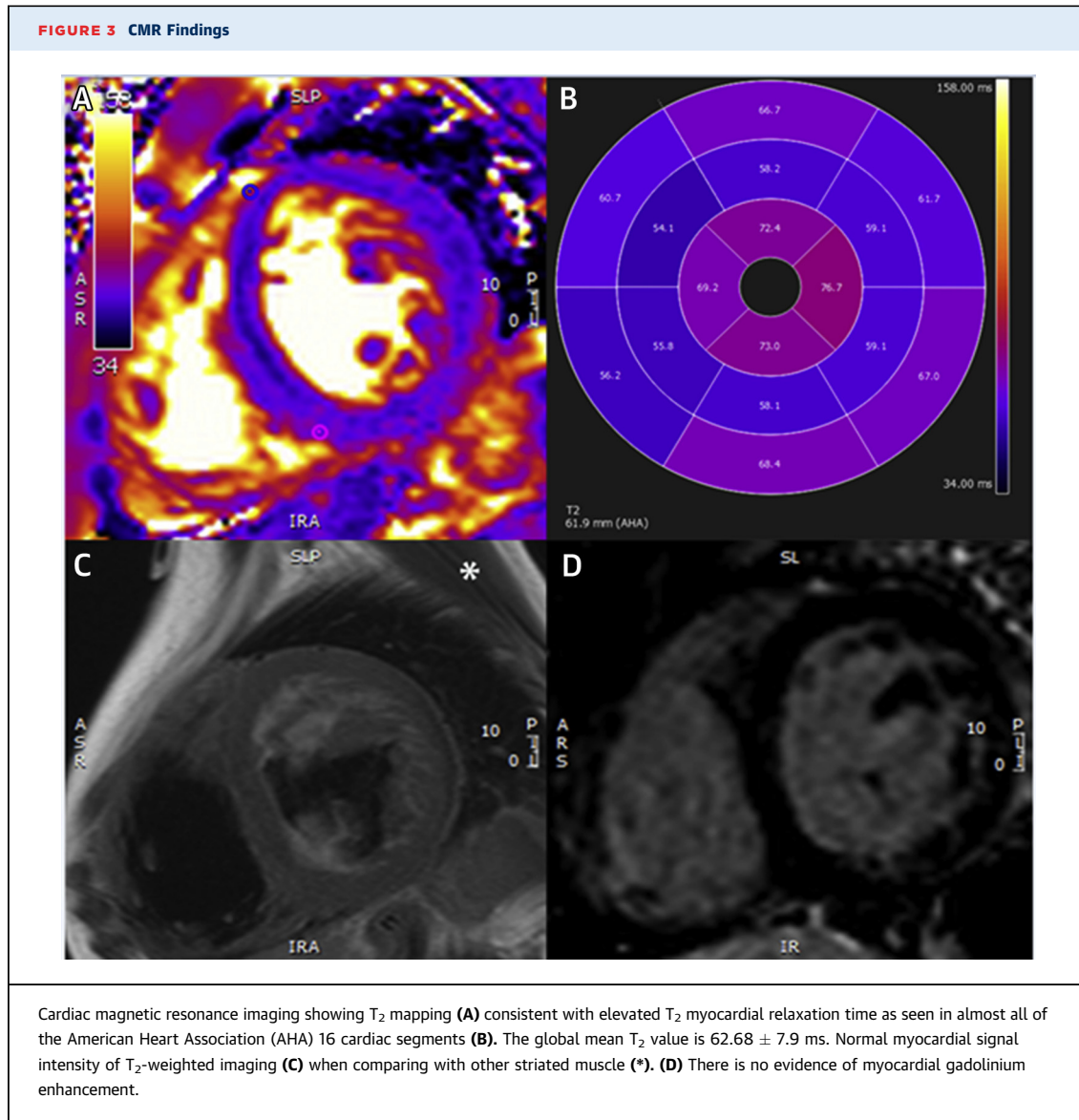


of hyperlactemia intermittently that did not require intervention. She had no history of hearing loss, seizure, syncope, stroke, or ataxia. Between ages of 6 and 13 years, she followed-up with her pediatric cardiologist, neurologist, and geneticist intermittently, with a history of noncompliance with recommended medical therapy. The detail sequence of her clinical course and events since birth is summarized in **Figure 1**. On family history, her parents were consanguineous; biological father of the patient was her mother's uncle. There was no family history of cardiomyopathy or related diseases or sudden death.

DIFFERENTIAL DIAGNOSIS

Sengers syndrome was first considered in this patient with history of hypertrophic cardiomyopathy, mitochondrial myopathy, hyperlactatemia, and bilateral cataract. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes were a possibility, but in the presence of normal cognition were unlikely. Kearns-Sayre syndrome was considered due to short stature and myopathy, but in the absence of ophthalmoplegia and cerebellar signs was unlikely. Similarly, myoclonus epilepsy and ragged red fibers syndrome was in differential diagnosis due to cardiomyopathy, muscle weakness, and hyperlactemia, but



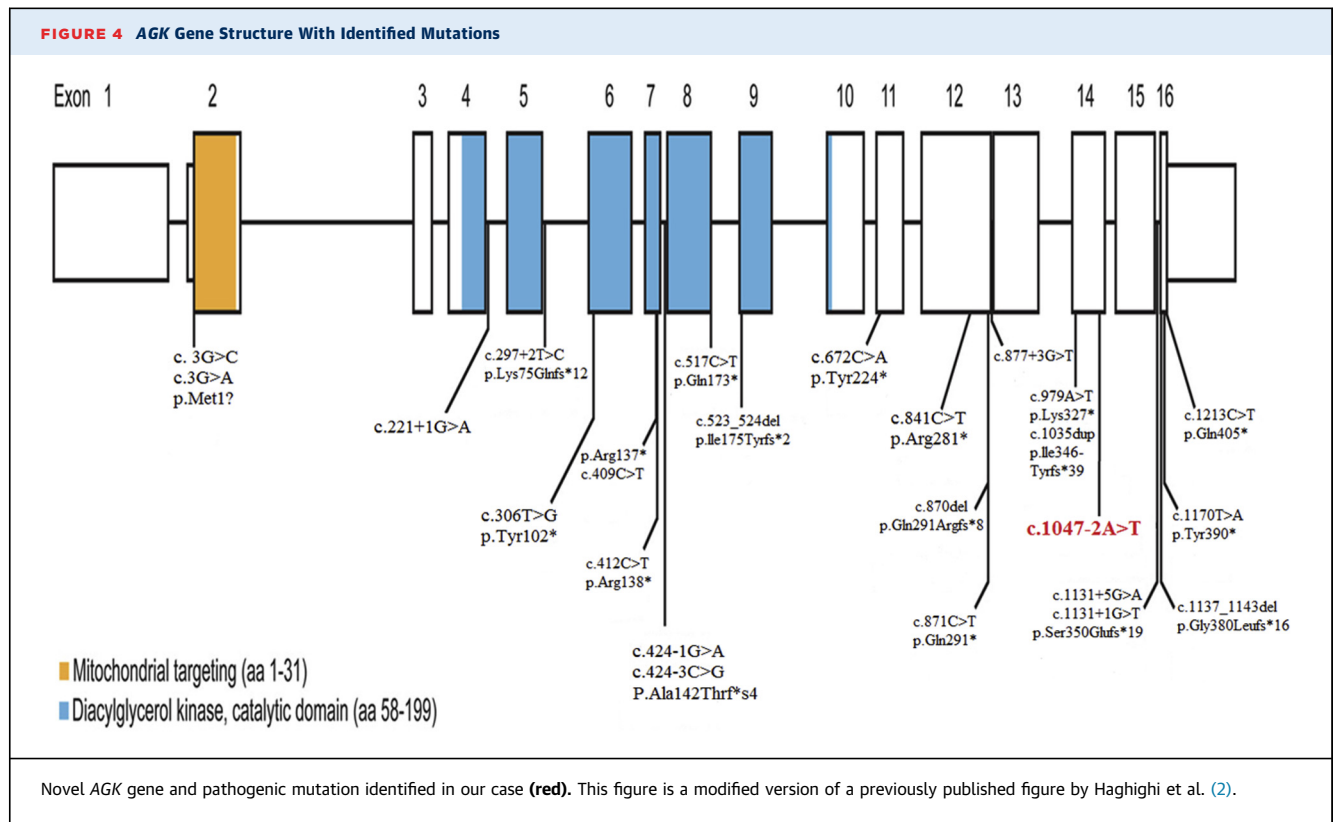


was unlikely due to absence of seizures and no ragged red fibers were present on muscle biopsy. Alpers syndrome, Leigh syndrome, ceroid lipofuscinosis, and Vici syndrome were unlikely due to normal mental status. To go along with her abnormal urine organic aciduria, she could have 3-methylglutaconic aciduria with cataracts, but without neurologic involvement and neutropenia, this was unlikely.

INVESTIGATIONS

Before her presentation to our center, she had an electromyography that showed a myopathy pattern. Her muscle biopsy suggested mitochondrial myopathy with vacuolar changes in the myocytes and no

ragged red fibers were present on muscle biopsy performed at age 6 years (Figure 1). No electron microscopic study was performed. Her blood acid-alpha-glucosidase and urine oligosaccharide levels were normal, suggesting no evidence of storage diseases. Urine organic acids were notable for increased 3-methylglutaconic, 3-methylglutaric, and hydroxybutyric acids. Serum acyl carnitine and biotinidase levels were normal. Her mitochondrial deoxyribonucleic acid depletion studies were negative for *DGUOK*, *POLG*, *TK2*, *SCO1*, *SCO2*, *SURF1*, and *COX13* gene mutations. Genetic testing for spinal muscular atrophy was normal. Her brain magnetic resonance imaging was normal. She had normal cognitive development.



At presentation, her chest x-ray showed cardiomegaly. Echocardiogram demonstrated mild mitral regurgitation, severely dilated LV (end-diastolic diameter: 52.7 mm, z-score = 4.9) with a shortening fraction of 8% and biplane ejection fraction of 17% and decreased LV peak longitudinal average global strain, -6.8% (normal mean: -20.2%) (1). There was an Ebstein anomaly of the tricuspid valve with a moderate degree of septal leaflet displacement (displacement index = 18.5 mm/m²) (Figure 2). Her right ventricle was enlarged with severely reduced systolic function with right ventricular fractional area change of 0.13 (normal: >0.35). Coronary arteries had normal origins and no pericardial effusion was noted. Her electrocardiogram showed Wolf-Parkinson-White pattern due to accessory pathway related to Ebstein anomaly and biventricular hypertrophy. Laboratory testing showed pro-B-type natriuretic peptide level of 43,400 pg/ml, elevated transaminases (alanine aminotransferase 395 U/l and aspartate aminotransferase 410 U/l), bilirubin 2.4 mg/dl, lactate 6.5 mmol/l, hyponatremia (126 mEq/l), anion gap (-12), troponin T 0.8 µg/l, creatinine kinase-MB 420 IU/l, and creatinine 1.4 mg/dl.

MANAGEMENT

The patient was intubated and intravenous vaso-pressors and diuretics were started for advanced heart failure after admission to the cardiac intensive care unit. Coenzyme Q10 and carnitine were added as a part of dietary supplements for primary mitochondrial disorders. Cardiac magnetic resonance imaging (CMR) was performed to characterize the myocardium, revealing a diffusely increased T₂ myocardial relaxation time (global mean T₂: 62.68 ± 7.9 ms) (Figures 3A and 3B). However, T₂-weighted imaging showed qualitatively normal myocardial signal intensity (Figure 3C). No early (3 min) or late gadolinium enhancement (10 min) was noted (Figure 3D). Native myocardial T₁ and calculated extracellular volume were also diffusely elevated with values of 1,056 ± 34 ms and 34% (normal: 25.3 ± 3.5%) respectively, suggesting extracellular space expansion.

Her heart failure clinically worsened despite support with intravenous inotropes (milrinone 0.75 µg/kg/min and epinephrine 0.03 µg/kg/min) and mechanical ventilation. The patient was discussed in multidisciplinary care conference and was not

considered for ventricular assist device support and heart transplantation due to her underlying respiratory disease, extreme debilitation, and history of noncompliance in the past. Her condition gradually deteriorated and she suffered a ventricular tachyarrhythmic arrest, resulting in death. No autopsy was performed. The whole exome sequencing testing was posthumously resulted. Whole exome sequencing detected a homozygous mutation in *AGK* gene c.1047-2A>T: IVS14-2A>T in intron 14 (Figure 4) and no other variant of unknown significance was present. Parents did not have genetic testing.

DISCUSSION

In this case, the revealing clinical findings were bilateral cataracts, severe skeletal myopathy, initial presentation of hypertrophic cardiomyopathy, and the patient was subsequently noted to have LV dilation, likely due to end-stage (i.e., burnt-out) hypertrophic cardiomyopathy, lactic acidosis, and elevated 3-methylglutaconic acid. These are characteristic of Sengers syndrome, which is caused by homozygous or compound heterozygous mutation in *AGK* gene on chromosome 7q34 (2). Mutation of *AGK* gene destroys the canonical splice acceptor in intron 14, causing abnormal gene splicing, leading to an abnormal message leading to nonsense-mediated messenger ribonucleic acid decay or abnormal protein product (3). The defect found in our patient, c.1047-2A>T: IVS 14-2A>T mutation of *AGK* gene, has not been previously reported in association with Sengers syndrome. The finding of Ebstein anomaly and associated Wolf-Parkinson-White pattern on electrocardiogram is not historically associated with Sengers syndrome and may have been an isolated finding.

The common cause of death in Sengers syndrome is heart failure as the result of severe cardiomyopathy. Two distinct forms of Sengers syndrome are described (4). An infantile form of Sengers syndrome is caused by homozygous *AGK* nonsense mutation with onset in infancy of cardiomyopathy and lactic acidosis leading to early death. Some patients who carry at least 1 *AGK* splice site variant or a start codon mutation develop a milder form of Sengers syndrome characterized by cardiomyopathy and cataracts, but have normal mental development.

Diagnosis of mitochondrial disease currently depends on a combination of clinical suspicion supported by biochemical or histochemical demonstration of abnormal mitochondria in the affected tissue. Due to the potential risks of obtaining an endomyocardial biopsy, as well as the small sample size,

skeletal muscle biopsy is typically obtained for tissue diagnosis.

The myocardial tissue characterization by CMR with expansion of extracellular volume without late gadolinium enhancement is also informative, because two-thirds of cases of mitochondrial cardiomyopathy do not show late gadolinium enhancement (5,6). Another interesting finding on CMR was the diffusely elevated T₂ myocardial relaxation time. Although this is commonly seen with elevated myocardial water content, as in myocarditis, the presence of normal myocardial signal intensity on T₂-weighted imaging and absence of early gadolinium enhancement make myocardial edema very unlikely. Instead, elevation of T₂ values has been previously reported in mitochondrial cardiomyopathy as a consequence of intracytoplasmic vacuoles (6).

Management of Sengers syndrome is mostly individualized and requires a multidisciplinary team approach, because it is a heterogeneous disorder with different phenotypical manifestations (7). Ventricular assist device support for destination therapy or a bridge to heart transplantation is an option for patients who have significant heart failure with a relatively preserved constitution and respiratory muscle function. Survival after heart transplant in patients with mitochondrial disorders, compared with other patients with cardiomyopathy, was not found to be different in a recent multicenter analysis; however, patients with mitochondrial disorders do suffer from higher morbidity, especially higher incidence of strokes (8). It may be reasonable to consider heart transplantation in patients with Sengers syndrome without significant neurological disease, though as with our patient, multiorgan involvement is regarded as contraindication.

CONCLUSIONS

Patients with mitochondrial disorders are at increased risk of cardiomyopathy. CMR can provide clues to the diagnosis of mitochondrial cardiomyopathy. Cardiac function may deteriorate rapidly in a previously diagnosed mitochondrial disorder and can lead to death as in our patient. Transplant may be a reasonable option for patients with mitochondrial cardiomyopathy, but it must be emphasized that such a decision needs to be taken after careful multidisciplinary discussions.

ADDRESS FOR CORRESPONDENCE: Dr. Bibhuti B. Das, Joe DiMaggio Children's Hospital Heart Institute, Memorial Health Care, 1150 North 35 Avenue, Hollywood, Florida 33021. E-mail: bdas99@hotmail.com.

REFERENCES

1. Levy PT, Machefsky A, Sanchez AA, et al. Reference ranges of left ventricular strain measures by two-dimensional speckle-tracking echocardiography in children: a systematic review and meta-analysis. *J Am Soc Echocardiogr* 2016;29:209-25.
2. Haghighi A, Haack TB, Atiq M, et al. Sengers syndrome: six novel AGK mutations in seven new families and review of phenotypic and mutational spectrum of 29 patients. *Orphanet J Rare Dis* 2014;9:119-31.
3. Kang Y, Stroud DA, Baker MJ, et al. Sengers syndrome-associated mitochondrial acylglycerol kinase is a subunit of the human TIM22 protein import complex. *Mol Cell* 2017;67:457-70.
4. Holmgren D, Wahlander H, Eriksson BO, Oldfors A, Holme E, Tulinius M. Cardiomyopathy in children with mitochondrial disease: clinical course and cardiological findings. *Eur Heart J* 2003;24:280-8.
5. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. *J Cardiovasc Magn Reson* 2012;14:63.
6. Lee KH, Park HS, Park CH, et al. Extracellular volume imaging and quantitative T2 mapping for the diagnosis of mitochondrial cardiomyopathy. *Circulation* 2014;130:1832-4.
7. Limongelli G, Masarone D, D'Alessandro R, Elliott PM. Mitochondrial diseases and the heart: an overview of molecular basis, diagnosis, treatment and clinical course. *Future Cardiol* 2012;8:71-88.
8. Weiner JG, Lambert AN, Thurm C, et al. Heart transplantation outcomes in children with mitochondrial disorders (abstr). *Circulation* 2018;138 Suppl 1:10706.

KEY WORDS acylglycerol kinase, AGK, mitochondrial cardiomyopathy, Sengers syndrome