Case Report

A Case Report of a Rare Heterozygous Variant in the Desmin Gene Associated With Hypertrophic Cardiomyopathy and Complete Atrioventricular Block

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the primary cause of sudden cardiac death in children and adolescents. Patients with HCM frequently have ventricular tachycardia and ventricular fibrillation, although complete atrioventricular block (CAVB) is very rare. We report a case of HCM with CAVB in an 8-year-old girl who underwent transvenous implantable cardioverter-defibrillator placement after resuscitation. In this patient, we identified a de novo heterozygous missense variant, Arg406Trp (c.1216C>T), in the desmin (DES) gene. Pathogenic variants in the DES gene result in cardiomyopathy, conduction disorders, and skeletal muscle weakness. This recently identified variant may cause HCM with CAVB.

Hypertrophic cardiomyopathy (HCM) is a genetic disorder affecting primarily the heart muscle. Half the cases of HCM are familial, and most are due to genetic abnormalities, predominantly those affecting sarcomere proteins. HCM is also the primary cause of sudden cardiac death in children and adolescents. Risk factors for sudden cardiac death in children include age at diagnosis, non-sustained ventricular tachycardia, unexplained syncope, and septal and left ventricular posterior wall diameter. Ventricular tachycardia and ventricular fibrillation are common causes of sudden death in patients with HCM. However, complete atrioventricular block (CAVB) is a very rare complication of HCM, and its exact frequency is unknown.

Desmin is an intermediate filament protein involved in cell–cell adhesion. It is found in cardiomyocytes and skeletal muscles, and its dysfunction can lead to various cardiac and muscular disorders.

RÉSUMÉ

La cardiomyopathie hypertrophique (CMH) est la première cause de mort subite d’origine cardiaque chez les enfants et les adolescents. Les patients atteints de CMH présentent fréquemment une tachycardie ventriculaire et une fibrillation ventriculaire, bien que le bloc atrioc-ventriculaire complet (BAVC) soit très rare. Nous rapportons un cas de CMH avec BAVC chez une fillette de 8 ans qui a reçu un défibrillateur cardiovertedeimplantable par voie transveineuse après réanimation. Chez cette patiente, nous avons isolé un variant faux sens hétérozygote de novo, Arg406Trp (c.1216C>T), dans le gène de la desmine (DES). Les variants pathogènes du gène DES entraînent une cardiomyopathie, des troubles de la conduction et une faiblesse des muscles squelettiques. Ce variant récemment identifié peut causer une CMH avec BAVC.

Novel Teaching Points

- HCM with CAVB may be caused by DES variants.
- The possibility of DES variants should be considered when nonspecific ECG findings are observed in patients with HCM.
- Genetic testing for genes such as DES is useful for making predictions about quality of life for patients with HCM.

Ethics Statement: Informed consent was obtained from the family of the patient.

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muscle cells. Pathogenic variants in the desmin (DES) gene lead to poor mechanochemical signaling, transport processes between the extracellular and nuclear matrix, and crosstalk between different cellular organelles. Consequently, cardiomyopathy, conduction disorders, and skeletal muscle weakness can occur. There are few reports of DES variants in patients with HCM, and a heterozygous DES variant of HCM has not been reported.

We report a case of HCM with CAVB in an 8-year-old girl who underwent transvenous implantable cardioverter–defibrillator (ICD) placement after resuscitation, and in whom a rare DES variant was identified. This is the first case of HCM to be reported with a heterozygous DES variant.

Case

A 7-year-old Japanese girl was diagnosed with left ventricular hypertrophy during a school-screening electrocardiogram (ECG) for first-grade students. She was referred to a nearby hospital for further examination. Echocardiography showed left ventricular hypertrophy with an interventricular septal wall thickness of 14 mm (Supplemental Fig. S1). An ECG showed right bundle branch block, left-axis deviation, and high-voltage R waves in lead V5, and ST−T changes in leads V3–V6 (Fig. 1). The patient had no metabolic or neuromuscular disorders based on the results of the blood and urine tests, and there was no family history of HCM or arrhythmia. The patient also had no complaints of skeletal muscle weakness. The serum creatine kinase level was within normal limits at 82 U/L, and physical exam suggested normal skeletal muscle strength. She was diagnosed with HCM and started outpatient visits for regular monitoring.

In the year following diagnosis, the patient fainted twice. However, the HCM findings had not worsened, and monitoring continued. Holter monitoring also showed no arrhythmia. At the age of 8 years, the patient lost consciousness while walking. Her father immediately performed cardiopulmonary resuscitation. Approximately 3 minutes later, her consciousness was restored and she was brought to our hospital by ambulance.

On arrival, her blood pressure was 67/48 mm Hg, and ECG revealed CAVB with a heart rate of 30 beats per minute (Supplemental Fig. S2). The patient underwent echocardiography in the emergency room, which did not show left ventricular outflow tract obstruction or pericardial effusion. Thus, the loss of consciousness was due to the combination of CAVB with HCM. Temporary cardiac pacing was initiated immediately, to stabilize her condition. Cardiac catheterization showed normal coronary arteries and no left ventricular outflow tract pressure gradient. After temporary cardiac pacing, echocardiography showed that the interventricular septal wall thickness was 15.5 mm. A few days later, a transvenous ICD was placed due to the possibility that the prior syncopal episode was due to ventricular tachycardia or ventricular fibrillation. Subsequent ICD interrogations did not reveal any evidence of malignant ventricular arrhythmias.

We performed genetic testing after obtaining informed consent from the patient and her parents. A rare novel missense heterozygous variant, Arg406Trp (c.1216C>T), in the DES gene was identified. The Arg406Trp (c.1216C>T) variant may disrupt the function of desmin, based on in silico analysis including SIFT (http://sift.jcvi.org/) and Mutation

|    | 7 yr | 7yr 4m | 8yr 2m | 8yr 7m |
|----|------|--------|--------|--------|
| PR interval (ms) | 140  | 160  | 180  | 200  |
| QRS dur (ms) | 100  | 100  | 100  | 120  |
| RV5 (mV) | 5.2  | 4.0  | 5.0  | 3.8  |
| RV6 (mV) | 2.2  | 1.6  | 2.6  | 2.8  |

Figure 1. Changes in electrocardiography during the clinical course. Right bundle branch block and left-axis deviation were observed when the patient was 7 years old, and a prolonged PR interval and QRS durations were observed. dur, duration. RV5, R wave in lead V5; RV6, R wave in lead V6.
Taster (http://www.mutationtaster.org/). This DES variant is absent from gnomAD (https://gnomad.broadinstitute.org) and was not identified in either parent, consistent with a de novo variant (Fig. 2).

Discussion

Cases of HCM are rarely associated with CAVB and are reported only in short case reports, leaving the exact pathological mechanisms underlying CAVB unclear. CAVB may be caused by fibrosis of the atrioventricular node and bundle of His. However, in this case, we hypothesize that CAVB was caused by a variant of the DES gene. The DES gene is located on chromosome 2q35, and its variants cause cardiomyopathy, conduction disorders, and skeletal muscle weakness. These findings are most often observed in adults, whereas restrictive cardiomyopathy or HCM has been reported in younger patients. Conduction disorders were reported in approximately 60% of carriers of DES variants, and CAVB is characteristic of desmin-related cardiomyopathy. Desmin is abundant in cardiomyocytes, especially in Purkinje fibers, suggesting that the disruptions of desmin may cause abnormalities in the conduction system.

In our case, the Arg406Trp (c.1216C > T) variant may disrupt the function of desmin. The Arg406Trp variant has been found previously in patients with sporadic cardioskeletal DES disease, CAVB, and cardiomyopathies such as dilated cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy, but not HCM. This residue is highly conserved and is located at the C-terminal of the core domain in desmin (2B segment) that is critically relevant for filament assembly. The Arg406Trp variant compromises the attachment of the desmin filament to the intercalated discs, resulting in structural changes within the intercalated discs. Therefore, we hypothesize that this DES variant is involved in the pathogenesis of cardiomyopathy and CAVB.

In this case, right bundle branch block and left-axis deviation were observed during the first consultation, and prolonged PR and QRS durations were observed during the clinical course (Fig. 1). Desmin is found in abundance in the Purkinje fibers and cardiomyocytes and is responsible for the network formation among cardiomyocytes. Thus, the most common conduction disorders caused by variants in the DES gene are CAVB, right bundle branch block, and prolonged PR and QRS durations. These electrocardiographic findings are not commonly observed in HCM. Therefore, when conduction disturbances, such as right bundle branch block and prolonged PR and QRS durations, are observed in patients with HCM, a desmin variant should be considered.

Additionally, it was reported that many patients with variants in the DES gene had skeletal muscle weakness several years after the onset of cardiomyopathy. The Arg406Trp variant is also known to be a cause of myofibrillar myopathy. It is useful to be able to make predictions about a patient’s quality of life based on genetic test results relating to these variants. Differentiating DES variants in patients with HCM is very useful for future follow-up.
In conclusion, this report discusses a *de novo* DES variant (desmin protein) in a case of HCM complicated by CAVB. We hypothesize that desmin variants may be a cause of HCM with CAVB. ECG findings can help differentiate this condition from typical HCM.

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**Supplementary Material**

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at doi:10.1016/j.cjco.2021.05.003.