Cardiology in the Young

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Desmin-related cardiomyopathy in a young woman presented with an infra-Hisian atrioventricular block

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Brief Report

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Abstract

A 17-year-old woman was admitted due to a complete atrioventricular block. Comprehensive analytic and imaging studies were conducted to determine the aetiology. Cardiac magnetic ressonance imaging revealed concentric hypertrophy of the left ventricle and diffuse intramural late enhancement gadolinium. Genetic testing identified a heterozygous pathogenic variant in the desmin gene. To manage atrioventricular block, a dual-chamber pacemaker was implanted. During follow-up, no spontaneous ventricular activity was detected.

Clinical report

Patient presentation and initial work-up

The authors present the case of a 17-year-old woman, followed up by rheumatology due to polyarthralgia and general weakness, with an inconclusive immunological study. She had no smoking or drinking habits and no drug abuse. Her grandfather died suddenly at the age of 49 years, but there was no family history of cardiomyopathy.

She presented at the Pediatric Emergency Department after experiencing an episode of post-prandial syncope with prodromal symptoms. There was no sphincter incontinence or tonic or myoclonic movements.

At initial evaluation, the patient had low blood pressure (87/50 mmHg), bradycardia, hypoxaemia (pO2 58 mmHg), and normoglycemia. The electrocardiogram revealed a third-degree atrioventricular block with a ventricular rate of 35 bpm and an associated right bundle branch block morphology (Figure 1). Blood tests showed normal ionic values, slight elevation of high sensitivity troponin I (14.1 pg/mL, normal value under 11.6 pg/mL), creatine kinase (261 UL/, normal value under 145 U/L), and N-terminal pro-B-type Natriuretic Peptide (3000 pg/mL, normal value under 133 pg/mL). Renal function was also exhibited a mild decline.

A bedside transthoracic echocardiogram revealed slight left ventricular concentric hypertrophy with normal ejection fraction, normal morphological and functional valves, and no pericardial effusion.

Diagnosis and management

The patient experienced progressive clinical and haemodynamic deterioration, requiring the implantation of a temporary transvenous pacemaker.

The patient was admitted to the Pediatric Intensive Care Unit (ICU). Forty-eight hours later, sinus rhythm was achieved and the temporary transvenous pacemaker was removed. The electrocardiogram revealed sinus rhythm with a right bundle branch block. A 48-hour Holter monitoring showed no relevant abnormalities. Immunological and serological studies were unremarkable, ruling out active autoimmune disease, as well as acute infection from *Borrelia spp.*, group A streptococcus (as in rheumatic fever), or Chagas disease. Thyroid function, angiotensin I-converting enzyme levels, and galactosidase activity were all within normal ranges.

Despite the absence of a definitive underlying cause, a watchful waiting approach was adopted, as the possibility of viral acute myocarditis, drug or medication abuse, or cardioinhibitory reflex was not excluded. The patient was discharged symptom-free, pending further evaluation with cardiac magnetic ressonance imaging (MRI) and follow-up consultation in the near term. A positron emission tomography scan was also scheduled to rule out cardiac sarcoidosis.

About one month later, she experienced a new episode of syncope without prodromes. The electrocardiogram revealed a complete atrioventricular block and a temporary transvenous pacemaker was implanted. She was readmitted to the Pediatric ICU.

The cardiac MRI showed a maximal thickness of 16 mm in the mid-ventricular segment of the interventricular septum; non-specific segmental contractility changes; and left ventricular ejection

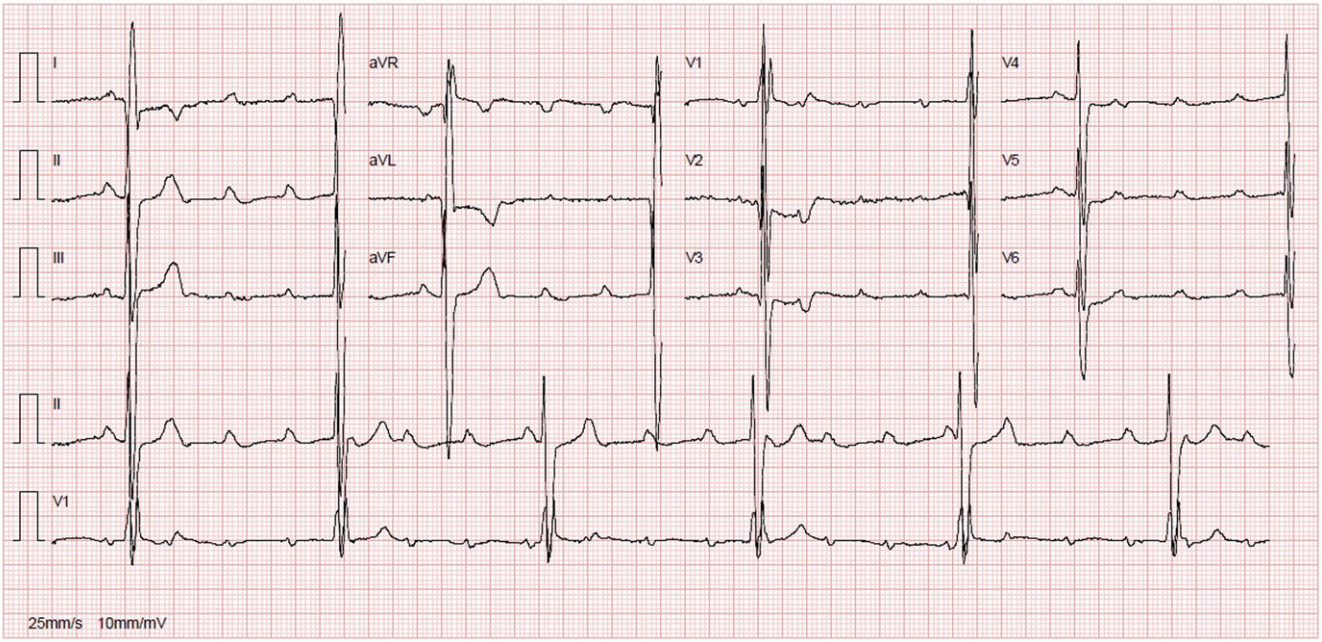

Figure 1. Twelve-lead electrocardiogram showing third-degree atrioventricular block with a ventricular frequency of 35 bpm, associated with a right bundle branch block pattern.

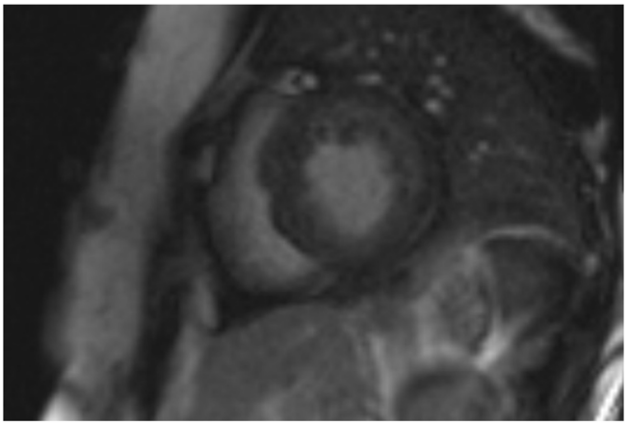

Figure 2. Cardiac MRI showing concentric left ventricular hypertrophy.

fraction of about 54% (Figure 2). The T2-weighted imaging excluded the presence of myocardial oedema and perfusion imaging presented diffuse, non-specific, intramural delayed enhancement in the mid-ventricular location. The positron emission tomography scan ruled out cardiac sarcoidosis. The electrophysiology study indicated an infra-Hisian block and low voltage near the *crista terminalis*, without induction of tachycardia under isoprenaline. Given the recurrent complete atrioventricular block with no identifiable reversible cause, a permanent dual-chamber pacemaker was implanted.

Follow-up

Later, a genetic study revealed the pathogenic variant NM_001927.4(desmin):c.1216C>T (p. Arg406Trp) (R406W) in the desmin gene, in heterozygosity. The patient and their family underwent genetic counselling. Electrocardiogram and transthoracic echocardiogram were performed for all first-degree relatives, with no abnormalities.

The evoked electromyography showed signs of abnormal electrical activity of the right iliopsoas muscle fibre, being under clinical surveillance in a specialised neuromuscular consultation.

The last pacing consultation follow-up revealed atrium sensing and ventricle pacing, with no spontaneous ventricular activity during the sensing test at VVI 30 bpm. The ventricular pacing was 99%, and the auricular pacing was 2.1%. No ventricular dysrhythmia was reported.

She is clinically stable and medicated with spironolactone 25 mg, valsartan 40 mg, dapagliflozin 10 mg, magnesium, and creatine supplementation. Blood tests showed a decrease of N-terminal pro-B-type Natriuretic Peptide (3000 to 1240pg/mL) and an elevation of creatine kinase (261 to 491U/L), with normalisation of renal function.

Discussion/Conclusion

The authors describe the case of a young woman presenting with a symptomatic complete atrioventricular block. In young patients with conduction abnormalities needing pacemaker implantation, recommendations address the importance of a thorough work-up, including multimodality imaging and molecular-genetic testing.[1,2]

In our case, a mutation was identified in the DES gene, which encodes desmin, a protein beloging to the intermediate filament family and an essential component of the extra-sarcomeric cytoskeleton in muscle cells.[3]

Mutations in the desmin gene can cause a range of general myopathy and/or cardiomyopathy, including dilated, restrictive, or less frequently hypertrophic or arrhythmogenic cardiomyopathy.[4,5] Due to the large presence of desmin protein in the conduction system, atrioventricular conduction abnormalities are frequent in desminopathies, affecting around 30–40% of desmin mutation carriers.[3,6] Ventricular arrhythmias occur in about 5% of carriers, and an implantable cardioverter defibrillator is needed in around 4% of all.[3,6]

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Phenotypic variability depends on the type of inheritance and the specific locations of mutations within the desmin molecule, which is structurally and functionally complex.[7] In this case, the patient presented with general weakness, with the complete atrioventricular block as the first cardiovascular manifestation. Imaging criteria for hypertrophic cardiomyopathy were met, indicated by wall thickness exceeding two standard deviations above the mean for age, gender, and body size, with no other causes for left ventricular hypertrophy (like arterial hypertension or valvular disease) and a compatible pathogenic genetic mutation. Typically, cardiomyopathy onset occurs at a younger age and is associated with a poorer prognosis.[7,8]

Regarding treatment, there is currently no specific cure for desminopathies; prevention remains the cornerstone of management.[8] Early detection and treatment of conduction defects and cardiac arrhythmias are essential.[8] In our case, the permanent pacemaker was implanted after the second episode of transient atrioventricular block. The implantable cardioverter defibrillator has not yet been considered due to the absence of documented ventricular dysrhythmia and preserved biventricular systolic function. However, despite the lack of specific recommendations, the authors believe that the threshold for implantation should be low, given the presence of late enhancement on cardiac MRI. Finally, timely detection and treatment of heart failure is indispensable.[9]

To date, it is unclear whether physical activity is beneficial or harmful for individuals with desminopathy.[10] It has been hypothesised that stiffness and mechanical stress are probably not responsible for disease progression.[11] This fact is supported by the evidence that a third of patients with manifest skeletal muscle disease reported normal creatine kinase serum levels, a classic but unsensible marker of muscle damage.[11] Then, reported cases demonstrated that a nutritional intervention, including creatine supplementation, and exercise training could minimise disease progression and improve quality of life.[10]

In conclusion, this case highlights a rare cause of complete atrioventricular block, underscoring the crucial role of genetic testing. Clinicians should consider pathogenic mutations in the desmin gene in patients with conduction abnormalities, cardiomyopathy, or muscular involvement.[12] More comprehension of desminopathies and heterogenicity of different mutations must be further elucidated to find potential target treatments.

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Competing interests. None.

Ethical standard. Authors declare that personal protection and data confidentiality are assured. The authors confirm that informed consent has been obtained from the involved patient.

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