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CASE REPORT
Medical management of arrhythmias

Successful treatment of frequent premature ventricular contractions and non-sustained ventricular tachycardia with verapamil and flecainide in *RYR1*-related myopathy: a case report

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Background Ryanodine receptor 1 (*RYR1*)-related myopathies are a group of congenital muscle diseases caused by *RYR1* mutations. These mutations may cause centronuclear myopathy, a congenital neuromuscular disorder characterized by clinical muscle weakness and pathological presence of centrally placed nuclei on muscle biopsy. Mutations in *RYR2* cause ventricular arrhythmias that can be treated with flecainide; however, reports of ventricular arrhythmias in *RYR1*-related myopathies are rare. Herein we report a case of centronuclear myopathy with *RYR1* mutations who exhibited frequent premature ventricular contractions (PVCs) and non-sustained ventricular tachycardia (NSVT), which was successfully treated with verapamil and flecainide.

Case summary At 7 months, the patient presented neurological manifestations of hypotonia and delayed motor development. A skeletal muscle biopsy performed at age 4 years led to the diagnosis of centronuclear myopathy. At age 15 years, frequent PVCs and NSVT were identified on the electrocardiogram and 24 h Holter monitoring. Treatment with verapamil was initiated; however, it was not beneficial. Therefore, flecainide was added to the treatment, decreasing the frequency of PVCs and NSVT. Non-sustained ventricular tachycardia disappeared at the age of 21, and PVCs almost disappeared at the age of 22. Genetic testing revealed c.13216delG (p.E4406Rfs*35), c.14874G>C (p.K4958N), and c.9892G>A (p.A3298T) in *RYR1*, and the compound heterozygosity of variants was confirmed by analysis of the parents.

Discussion This is the first report of ventricular arrhythmia associated with *RYR1*-related myopathy that was successfully treated with verapamil and flecainide. The combination of verapamil and flecainide may be a useful treatment option for ventricular arrhythmias in patients with *RYR1*-related myopathies.

Keywords *RYR1*-related myopathy • Centronuclear myopathy • Premature ventricular contraction • Ventricular tachycardia • Flecainide • Case report

ESC curriculum 5.8 Cardiac ion channel dysfunction • 5.6 Ventricular arrhythmia

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Learning points

- Patients with *RYR1*-related myopathies can present with potentially fatal ventricular arrhythmias in adulthood.
- Ventricular arrhythmias in *RYR1*-related myopathies may be effectively treated using verapamil and flecainide.

Introduction

Ryanodine receptor 1 (*RYR1*)-related myopathies are a group of congenital muscle diseases caused by *RYR1* mutations.[1] These mutations may cause myopathies classically defined according to skeletal muscle histopathology including central core disease, multi-minicore disease, centronuclear myopathy, core-rod myopathy, and congenital fibre-type disproportion.[2,3] Mutations in *RYR2* cause ventricular arrhythmias that can be treated with flecainide; however, reports of ventricular arrhythmias in *RYR1*-related myopathies are rare.[4–6] Herein we report a case of centronuclear myopathy, a congenital neuromuscular disorder characterized by clinical muscle weakness and the pathological presence of centrally placed nuclei on muscle biopsy in a patient with *RYR1* mutations who exhibited frequent premature ventricular contractions (PVCs) and non-sustained ventricular tachycardia (NSVT), which was successfully treated with verapamil and flecainide.

Summary figure

Age	Events
At birth	Delivered vaginally at 37-week gestational age weighing 2250 g with no neonatal asphyxia.
7-month-old	Hypotonia and delayed motor development appeared.
4-year-old	A skeletal muscle biopsy led to the diagnosis of centronuclear myopathy.
15-year-old	Frequent PVCs were identified on the electrocardiogram. Twenty-four-hour Holter monitoring revealed NSVT.
16-year-old	Verapamil was initiated; however, it was not beneficial. Flecainide was added to the treatment, decreasing the frequency of PVCs.
18-year-old	The patient self-discontinued the treatment. The PVCs frequency worsened; therefore, verapamil and flecainide were reinitiated.
21-year-old	Non-sustained ventricular tachycardia disappeared.
22-year-old	Premature ventricular contractions almost disappeared.

Case presentation

A male patient was born to non-consanguineous parents via vaginal delivery at 37-week gestational age, weighed 2250 g with no neonatal asphyxia. He had no family history of myopathies or arrhythmias. At 7 months, he presented neurological manifestations of hypotonia and delayed motor development. Magnetic resonance imaging of the brain at 11 months revealed no abnormalities.

A skeletal muscle biopsy from the biceps brachii performed at age 4 years revealed type 1 fibre atrophy (5–10 μm in diameter) and predominance (accounting for 85%), myofibres with centrally placed nuclei (accounting for 10%), and absence of nemaline bodies or core structures, leading to the diagnosis of centronuclear myopathy, albeit radial strands of myofibrils were not apparent (*Figure 1*). Although he experienced a delay in motor development, he attended to school and developed without regression during childhood. His activities of daily living such as personal hygiene, continence management, dressing, and feeding were independent, whereas ambulation required partial assistance.

The patient was referred to the Department of Paediatric Cardiology for frequent PVCs, which were first identified on the electrocardiogram at the age 15 years. He had symptoms of daytime drowsiness and fatigue. His blood pressure was 110/63 mmHg, and the pulse was regular with a rate of 96 b.p.m. Heart sounds were regular, and he had no murmur. Neurological examination showed mild muscle weakness with reduced deep tendon reflexes. Blood analysis showed mildly elevated brain natriuretic peptide value of 24.4 pg/mL (reference range: 0–18.4 pg/mL). Echocardiography showed normal cardiac structure and function. In electrocardiogram, two consecutive PVCs were observed (*Figure 2*). Twenty-four-hour Holter monitoring revealed 38 065 PVCs per day, which accounted for 27% of total QRS complexes (34 755 isolated PVCs, 1632 couplets, and 15 NSVT). When he was 16 years old, verapamil was initiated, and the dose was increased to 120 mg/day; however, it was not beneficial, and the frequency of NSVT increased to 2802 times per day and the total number of PVCs increased to 59 967 times per day. Therefore, flecainide was added to the treatment, and the dose was increased to a maximum of 200 mg/day, decreasing the frequency of PVCs and NSVT (*Figure 3*). Verapamil was tapered after flecainide was increased. The PVC frequency worsened when the patient self-discontinued the treatment due to an increase in drowsiness and fatigue at the age of 18. Therefore, flecainide monotherapy was reinitiated; however, PVCs did not decrease. At the age of 19, the frequency of NSVT increased, and Holter monitoring demonstrated a ventricular run of 19 beats (*Figure 4*); therefore, the combination of flecainide and verapamil was reinitiated, which decreased the frequency of PVCs and NSVT. Non-sustained ventricular tachycardia disappeared at the age of 21 (*Figure 3*). At patient's request, verapamil was discontinued at the age of 21. Premature ventricular contractions almost disappeared at the age of 22 (*Figure 3*). The drowsiness and fatigue improved over time.

A mutation screening for known causative genes of congenital myopathy using a custom-made panel revealed the novel pathogenic variants c.13216delG (p.E4406Rfs*35) and c.14874G>C (p.K4958N) in *RYR1* in the proband and in his father, and whole genome sequencing revealed the known pathogenic variant c.9892G>A (p.A3298T) in *RYR1* in the proband and in his mother.[7,8] Since centronuclear myopathy associated with *RYR1* mutations is known to have autosomal recessive inheritance,[9] and the compound heterozygosity of variants was confirmed by analysis of the parents, we concluded that these mutations caused the disease. In the most recent follow-up at 23 years of age, no life-threatening cardiac complications were observed; however, his motor function gradually regressed, and a wheelchair is needed for mobility.

Discussion

Ryanodine receptors are intracellular Ca^{2+} release channels embedded in the sarco/endoplasmic reticulum membrane, an intracellular calcium storage site that releases Ca^{2+} to activate muscle contraction and neurotransmitter release.[4] Mutations in RYR induce RYR-mediated Ca^{2+} handling dysfunction, causing heart failure, arrhythmias, myopathies, diabetes, and neurodegenerative disorders.[4] There are three isoforms of RYR in humans, RYR1, RYR2, and RYR3, with an ~65%

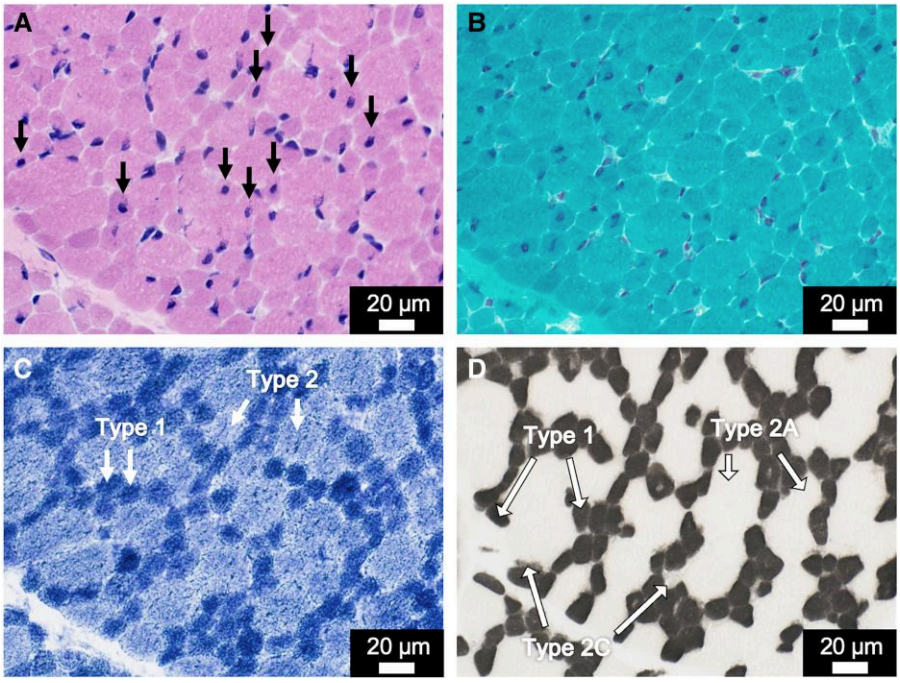

Figure 1 Pathological findings of biopsied biceps brachii. (*A*) On hematoxylin–eosin staining, there is a bimodal fibre size. No apparent necrotic and regenerating fibres are seen. No mononuclear cell infiltration is seen. Fibres with centrally placed nuclei (arrowheads) accounted for 10% of all fibres. Mild endomysial fibrosis is seen. (*B*) On modified Gomori trichrome staining, no nemaline bodies, cytoplasmic bodies, rimmed vacuoles, or ragged red fibres are seen. Peripheral nerve bundles are well myelinated. (*C*) On NADH staining, intermyofibrillar networks are well organized, except in dark-centred fibres. Fibres with radial sarcoplasmic strands are not apparently seen. (*D*) On ATPase staining (pH 4.6), type 1 fibre (dark stain) atrophy and predominance are seen. Some type 2C fibres (intermediate stain) are observed. Type 2B fibres are deficient.

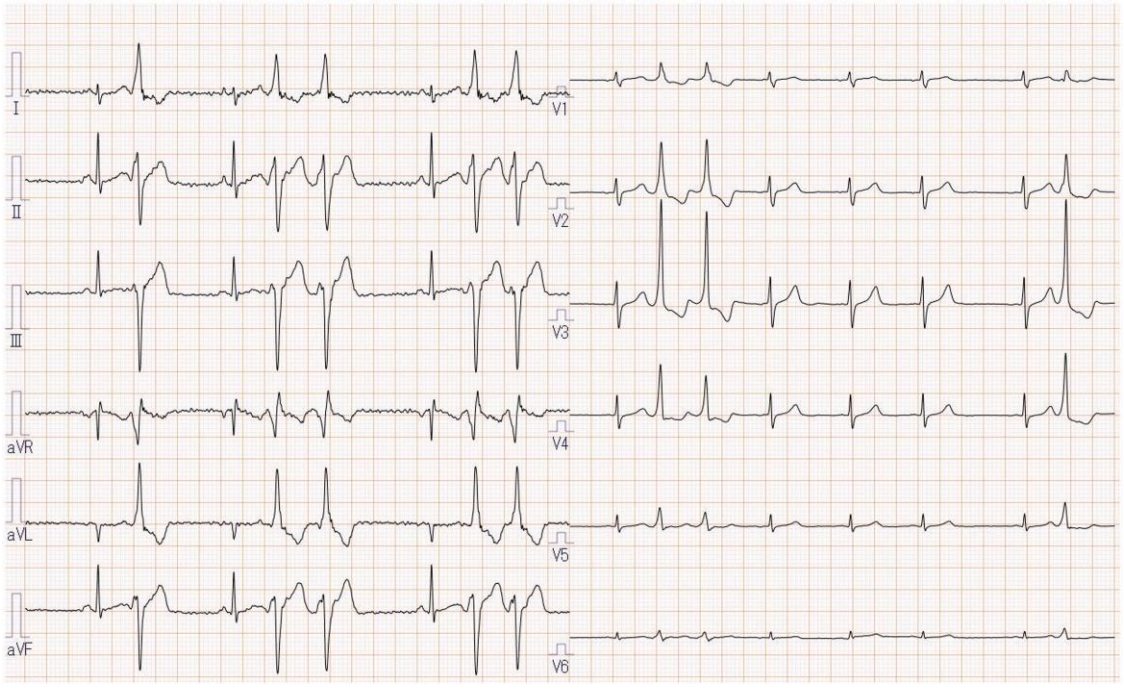

Figure 2 Electrocardiogram at the age of 15. Electrocardiogram was recorded at a speed of 25 mm/s and a voltage of 1.0 mm/mV in limb leads and 2.5 mm/mV in precordial leads. Two consecutive premature ventricular contractions were observed.

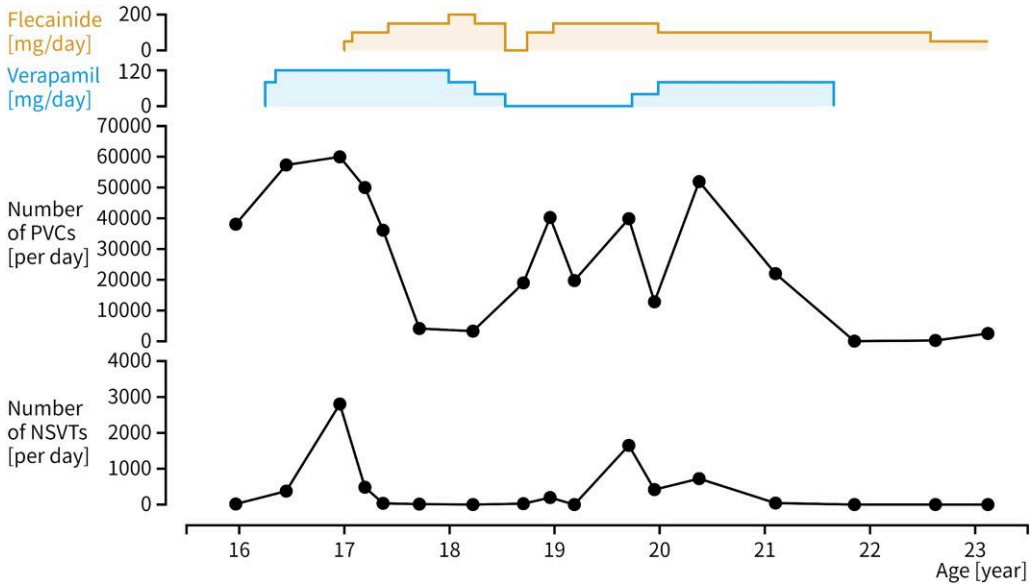

Figure 3 The clinical course. Horizontal axis shows age in years. Vertical axis shows the daily dosage of flecainide and verapamil, the number of premature ventricular contractions per day, and the number of non-sustained ventricular tachycardia per day. PVCs, premature ventricular contractions; NSVT, non-sustained ventricular tachycardia.

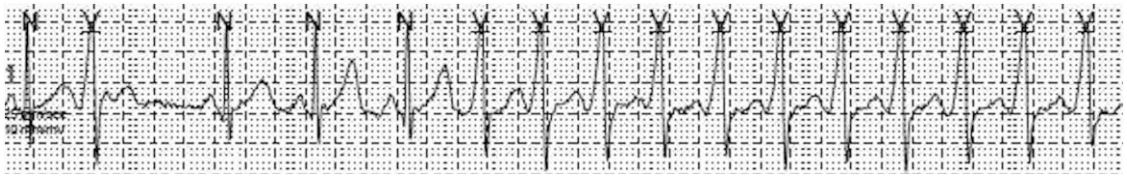

Figure 4 Holter monitoring demonstrating a ventricular run of 19 beats at 146 b.p.m. Holter monitoring was recorded at a speed of 25 mm/s and a voltage of 1.0 mm/mV.

homology between these isoforms.[4,9,10] *RYR1* is mainly expressed in the skeletal muscle, and its mutations are known to cause *RYR1*-related myopathy and malignant hyperthermia.[4] *RYR2* is mainly expressed in the myocardium, and its mutations cause heart failure, atrial fibrillation, and catecholaminergic polymorphic ventricular tachycardia.[4,5] There is a report of *RYR1*-related myopathy complicated by atrial tachycardia and sinus node dysfunction[11]; however, there are no reports of ventricular arrhythmias. Furthermore, to the best of our knowledge, this is the first report of ventricular arrhythmia associated with *RYR1*-related myopathy that was successfully treated with verapamil and flecainide.

Ventricular tachycardia is associated with a risk of syncope and sudden cardiac death. In our case, frequent couplets and NSVT were observed, which had the risk of causing sudden death. The symptoms of drowsiness and fatigue observed in our case may have been caused by ventricular arrhythmias. Catheter ablation was also considered as a treatment option; however, since the patient was not experiencing syncope, drug therapy was chosen as the initial treatment. The PVCs and NSVT in our case showed a right bundle branch block with left axis deviation, also known as the verapamil-sensitive ventricular tachycardia[12]; however, verapamil monotherapy showed no therapeutic effects.

Flecainide is an approved anti-arrhythmic drug that blocks sodium channels. Recently, flecainide has been reported to directly block RYR2 channels, inhibit Ca^{2+}-induced Ca^{2+} release, and prevent catecholaminergic polymorphic ventricular tachycardia, which is not mediated by Na^{+} channel blockade.[6,13] All individuals with *RYR1*-related myopathy are considered potentially susceptible to malignant hyperthermia triggered by volatile anaesthetics and muscle relaxants induced by hyperstimulation of the Ca^{2+}-induced Ca^{2+} release mechanism.[9] There are reports that RYR1 is expressed not only in skeletal muscles but also in cardiac muscles.[14] In our case, the Ca^{2+}-induced Ca^{2+} release mechanism may have been enhanced, causing ventricular arrhythmia, which was ameliorated by flecainide directly blocking RYR1 channels in the heart. The exacerbation of drowsiness and fatigue after initiating flecainide in our case may have been due to flecainide blocking of RYR1 channels and the inhibition of Ca^{2+} release in the skeletal muscle.

In our case, verapamil or flecainide monotherapy did not reduce the frequency of PVCs; however, the combination of verapamil and flecainide reduced PVCs. Furthermore, after PVCs decreased, flecainide monotherapy remained effective even after verapamil was discontinued. The combination of verapamil and flecainide may be effective in treating ventricular arrhythmias in *RYR1*-related myopathies, and flecainide alone may also be effective for sustained effects.

The cardiac manifestations of muscular diseases vary from asymptomatic to severe heart failure or sudden death.[15] Since cardiac complications may cause fatal outcomes, early recognition and appropriate treatment of cardiac manifestations in patients with myopathy are essential. In our case, cardiac arrhythmias were first identified during a school electrocardiographic examination at the age of 15 years and not during regular hospital check-ups. If not properly treated, sudden cardiac death due to ventricular arrhythmia could have occurred. Both cardiologists and neurologists should be aware of the possibility of arrhythmias in cases of myopathy, and regular cardiac examinations should be performed in such patients.

Conclusion

In summary, we report a case of *RYR1*-related myopathy complicated by frequent PVCs and NSVT that was successfully treated with verapamil and flecainide. Therefore, the combination of verapamil and flecainide may be a useful treatment option for ventricular arrhythmias in patients with *RYR1*-related myopathies.

Lead author biography

Dr Yuji Maruo has been working at the Department of Pediatrics, Hokkaido University Graduate School of Medicine. His research topic is paediatric cardiology and drug delivery system targeting mitochondria.

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Consent: The authors confirm that written informed consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available within the article.

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