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Journal
BMJ Case Reports, 14(1)

ISSN
1757-790X

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Publication Date
2021

DOI
10.1136/bcr-2020-237592

Peer reviewed

Kickboxing a cardiomyopathy: mitochondrial sequencing provides answer for young athlete and her family

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Accepted 19 December 2020

To cite: Dineen EH, Torkamani A, Muse ED. *BMJ Case Rep* 2021;**14**:e237592. doi:10.1136/bcr-2020-237592

SUMMARY

Mitochondrial diseases are rare, often go undiagnosed and can lead to devastating cascades of multisystem organ dysfunction. This report of a young woman with hearing loss and gestational diabetes illustrates a novel presentation of a cardiomyopathy caused by a previously described mutation in a mitochondrial gene, MT-TL1. She initially had biventricular heart dysfunction and ventricular arrhythmia that ultimately recovered with beta blockade and time. She continues to participate in sport without decline. It is important to keep mitochondrial diseases in the differential diagnosis and understand the testing and management strategies in order to provide the best patient care.

BACKGROUND

Mitochondrial diseases are often suspected if multiple organ systems are affected without a unifying diagnosis, but without a high clinical suspicion, diagnosis and appropriate care can be delayed.[1] Routine selective panel-based genetic testing is often unrevealing, and although whole exome sequencing improves diagnostic yield,[2] it may not provide answers. We present a case of a mitochondrial disorder in a woman presenting with chest pain where routine genetic testing was negative for an arrhythmogenic cardiomyopathy-related gene despite high clinical suspicion.

CASE PRESENTATION

A 43-year-old woman recreational kickboxer presented to the emergency department for evaluation of a few weeks of chest pain during exercise. These episodes were occasionally associated with lightheadedness and diaphoresis. She denied oedema, orthopnoea or recent illness. She appeared well and had a benign physical examination, including absence of cardiac murmurs, no jugular venous pressure elevation, rales or peripheral oedema. She had a normal blood pressure and pulse rate and was saturating well on room air. Initial laboratory investigations revealed an elevated troponin (troponin: 1.9 ng/mL, normal <0.100 ng/mL) and T wave inversions on surface ECG (figure 1). She was admitted to the hospital for further monitoring and evaluation. Her pertinent medical history included sensorineural hearing loss with hearing aids, gestational diabetes (G2P2) and Grave's hyperthyroidism. Family history was negative for any known cardiac diseases.

INVESTIGATIONS

An echocardiogram revealed biventricular dysfunction. Left ventricular ejection fraction was 40% with evidence of global dysfunction and the right ventricular ejection fraction was severely decreased with an RV S' of 6.8 cm/s (normal 9.5 cm/s). Interestingly, the right ventricle was initially dilated but the left ventricle was normal in size, with RVDd1=5.1 cm (normal <4.2 cm) and RVDd2=4.0 cm (normal <3.6 cm) (figure 2).

Coronary angiogram revealed normal coronary artery anatomy without evidence of coronary artery disease or other acute pathology. She was started on carvedilol at the maximum tolerated dose, though other guideline-directed medical therapy for cardiomyopathy could not be initiated given low resting blood pressure. Cardiomyopathy of arrhythmogenic or idiopathic aetiology was top in the differential, and cardiac MRI was suggested as the next step; however, it was unable to be obtained at the preferred timing due to logistics. Given frequent premature ventricular contraction (PVC) on telemetry, she was discharged with a cardiac event monitor. At home, she had a presyncopal event that correlated with sustained ventricular tachycardia (figure 3), which heightened suspicion for an arrhythmogenic cardiomyopathy.

Cardiac MRI revealed global right ventricular hypokinesis with decreased right ventricular ejection fraction (28%, normal 56%–78%), not meeting diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC), as well as right ventricular transmural delayed gadolinium uptake at the apex. Right ventricular volumes were normal at 80 mL (normal 77–195 mL) and 57 mL (19–72 mL) for end diastolic and end systolic volumes, respectively.

Subsequent electrophysiology testing revealed PVCs that were successfully targeted for ablation in the right ventricular outflow tract. She received an implantable cardioverter defibrillator (ICD) for secondary prevention.

Genetic testing was pursued using commercial panel testing that checked coding regions and splice junctions of 13 genes as part of an ARVC panel, which were negative. Next, despite normal routine genetic testing, with increased clinical suspicion given her multiorgan system involvement, we pursued whole exome sequencing. However, no likely pathogenic variants were discovered. Still with high suspicion for genetic pathology, we went one step further to assess the mitochondrial genome, identifying a

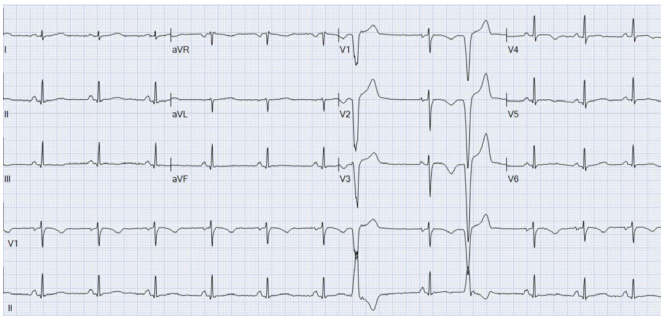

Figure 1 ECG demonstrating sinus rhythm, T wave inversions in leads V1–V4 and right ventricular outflow tract morphology premature ventricular contractions, which can be characteristic of arrhythmogenic right ventricular cardiomyopathy.

pathogenic MT-TL1 variant (m.3243A>G). The mutation had the following level of heteroplasmy based on sampling location: 28% blood (mesoderm), 58% urinary bladder cells (endoderm) and 0% buccal swab (ectoderm).

DIFFERENTIAL DIAGNOSIS

Based on her initial presentation, the top differential diagnoses for exertional chest pain, troponin elevation and ECG changes were myo-pericarditis, non-ST-elevation myocardial infarction with acute plaque rupture and spontaneous coronary artery dissection. However, after further investigations, she was found to have a new cardiomyopathy with biventricular dysfunction and a dilated right ventricle as well as PVCs, which led the differential to that of an idiopathic, familial or arrhythmogenic cardiomyopathy. Subsequent genetic testing revealed a mitochondrial variant that could explain her findings, and the possibility of inborn errors of metabolism, such as carnitine uptake deficiency, were thus included in the differential.

TREATMENT

Close outpatient monitoring was arranged with periodic echocardiograms and device interrogations, with treatment guided by inherited cardiomyopathy and mitochondrial disease specialists.

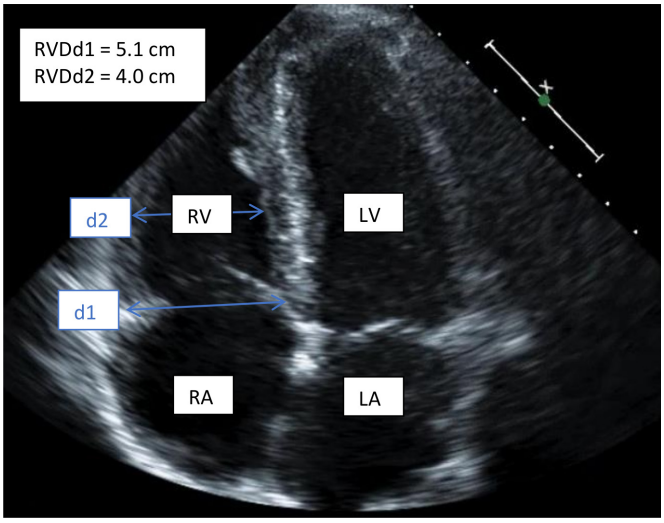

Figure 2 Transthoracic echocardiogram, apical four-chamber view, revealing a dilated right atrium and ventricle. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; RVDd1, right ventricle diameter at d1, RVDd2, right ventricle diameter at d2.

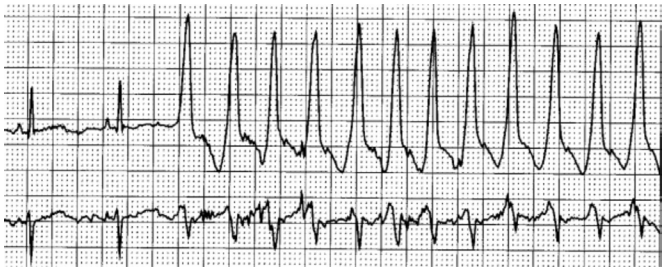

Figure 3 Cardiac event monitor strip demonstrating sinus rhythm with initiation of non-sustained ventricular tachycardia.

After the mutation was identified, on further questioning, she endorsed a history of sensorineural hearing loss. Given her prior arrhythmia burden and ARVC-like ventricular morphology, she was counselled on the potential risk of accelerating the progression of her degree of cardiomyopathy with continued exercise. In addition, she was counselled on the risk of possibly increasing number of shocks given the dynamic metabolic changes of exercise in her class IIIa (high static, low dynamic) sport[3] and the potential for ICD damage in the setting of her high-impact activity.[4] Through shared-decision-making, her passion for sport guided her decision to continue exercising. She understood the lack of disease-specific treatment for MT-TL1-related mitochondrial disorders. Given the difference in this novel presentation from typical mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), the usual medication suggestions for mitochondrial diseases postdiagnosis were not recommended.

In light of the maternal inheritance pattern associated with mitochondrial disorders, our patient was encouraged to speak with the mitochondrial specialist about the utility of testing her children. Her children ultimately underwent genetic counselling and subsequent testing revealed the same mutation.

OUTCOME AND FOLLOW-UP

Our patient initially required hospitalisations for symptomatic ventricular arrhythmia and heart failure exacerbation, but after continued medical management for cardiomyopathy and with close clinical follow-up in the outpatient department, her echo parameters have remained stable. She continues to work and exercise without limitation.

DISCUSSION

Mitochondrial diseases are rare, but if undiagnosed, multisystem organ dysfunction can go unmonitored and untreated for years. Mitochondria play a key role in the body's energy production, and when malfunctioning, the higher energy consuming organ systems generally manifest the most dysfunction, importantly skeletal and cardiac muscle.[5] In this case, the presence of a cardiomyopathy, hearing loss and gestational diabetes should prompt the astute provider to consider and test for a mitochondrial disease. Notably, our patient did not have short stature, renal impairment, diffuse myopathy or prior stroke, all elements that can also suggest a mitochondrial disorder.

In our case, we identified a pathogenic gene variant MT-TL1, which is typically associated with MELAS,[6] maternally inherited diabetes and deafness (MIDD)[7] or a mixture of phenotypes from both syndromes. MELAS rarely has cardiac involvement, but if present, then hypertrophic cardiomyopathy or dilated cardiomyopathy have been described.[6] MT-TL1 is often linked with dilated cardiomyopathy,[8] but to the authors' knowledge, we

Central Illustration

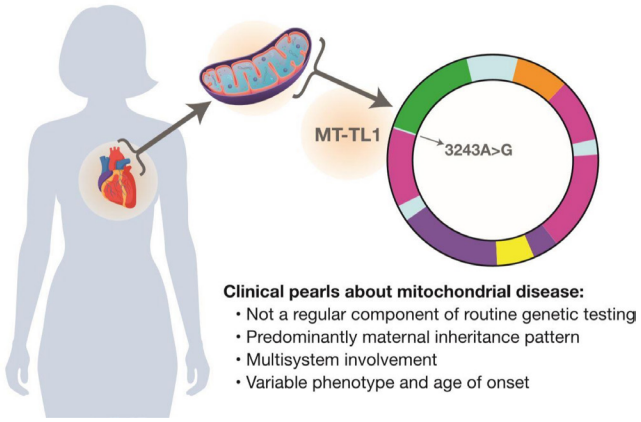

Figure 4 Faith Hark, Visual Communications Lead at Scripps Research, created this central illustration.

describe the first case of ARVC-like non-dilated cardiomyopathy associated with this specific MT-TL1 variant. Furthermore, it is important to note the contrast in presentation with overt deafness and diabetes seen with MIDD compared with the more subtle findings of hearing loss and gestational diabetes as seen with our patient, the latter initially invoking a lesser degree of clinical suspicion for a mitochondrial disorder.

The initial evaluation for mitochondrial disease includes basic laboratory panels, lactate and creatine kinase (CPK) to look for evidence of end-organ perfusion and muscle breakdown.[1] In our patient's case, some of the initial history suggestive of mitochondrial disease were not uncovered until later; thus, lactate, CPK and other metabolic investigations were not obtained. Infantile onset MELAS can be detected by newborn screening; however, given that our patient's symptoms manifested later in life and the more modern newborn screening of inborn errors of metabolism were not available at the time of her birth, her condition likely would not have been detected during infancy. In our case, mitochondrial disease diagnostic algorithms can be complicated if concomitantly presenting with acute cardiac pathology, such as acute decompensated heart failure, since lactate can be elevated in both conditions.[9]

If suspicion is high, then genetic testing is key and should include next-generation sequencing of the mitochondrial DNA genome.[1] As in our case, most commercial genetic panel tests, including whole exome sequencing, will not automatically perform mitochondrial testing. While some are identified at a young age, many are not detected until years later, highlighting the importance of understanding the variable presentations and testing cascade for mitochondrial diseases (figure 4). Improving access to genetic testing and consultation and education of providers as to when to engage these specialists will help patients in securing a diagnosis and treatment plan.

Genetic counselling is a critical component to couple with genetic testing. Mitochondrial diseases are predominantly maternally inherited and can equally affect all children. Our patient had a maternal family history of diabetes but did not have a family history of known mitochondrial or other mitochondrial-related disease, including, but not limited to stroke and deafness. Women of childbearing age must receive preconception counselling to understand the possibility of passing along the disorder and inherent pregnancy risks, including an increased risk of pre-eclampsia, gestational diabetes and preterm delivery.[10]

Learning points

- To increase awareness of mitochondrial diseases for differential diagnosis.
- To gain appreciation for heterogeneity of mitochondrial disease presentations.
- To understand that genetic testing is often tailored to answer a specific question, such as with mitochondrial disease testing.

Treatment for mitochondrial disease largely remains supportive, for example, in the case of MELAS, CoQ10, L-carnitine and creatine can be suggested as daily maintenance therapy, while intravenous arginine can be used in acute stroke-like episodes,[6] granted there is yet to be strong evidence for these therapies in clinical trials. While mitochondrial disease-specific treatments are lacking, knowledge of genotype-positive status can help guide earlier referral to specialists, closer monitoring and consideration of earlier initiation of medications like beta-blockers and angiotensin-converting enzyme inhibitors or earlier use of pacemakers, given the appropriate clinical context.[8]

Mitochondrial diseases are just one example of inborn errors of metabolism. In the right clinical context of unexplained cardiomyopathy, especially in the young, the astute practitioner should consider other metabolic pathology such as disorders of fatty acid oxidation, lysosomal or glycogen storage.[11] These inborn errors of metabolism have been implicated in 5%–26% of cases of cardiomyopathy in the infant.[11]

CONCLUSION

Mitochondrial diseases have multisystem organ manifestations and implications for disease monitoring and family planning. Initial genetic testing may be negative. If suspicion is high, then more comprehensive genetic testing should be pursued. We present the first case of ARVC-like morphology due to a novel presentation for mitochondrial gene variant MT-TL1 (m.3243A>G).

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Acknowledgements The authors would like to thank the patient for which this case report is based, whereby allowing this publication, she is helping the medical community better understand mitochondrial diseases. Faith Hark, Visual Communications Lead at Scripps Research, seamlessly translated our vision to a meaningful central illustration.

Contributors EHD: conception and design, acquisition of data, interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version published. AT: conception and design, acquisition of data, interpretation of data, revising the article critically for important intellectual content, final approval of the version published. EM: conception and design, acquisition of data, interpretation of data, revising the article critically for important intellectual content, final approval of the version published. All authors are in agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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