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Case Report

Arrhythmia as a cardiac manifestation in MELAS syndrome☆

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ABSTRACT

A 44-year-old female with a diagnosis of mitochondrial myopathy, encephalopathy and stroke-like episodes (MELAS) syndrome had progressive left ventricular hypertrophy (LVH) on echocardiogram. A Holter monitor demonstrated episodes of non-sustained atrial tachycardia, a finding not been previously described in this population. This unique case of MELAS syndrome demonstrates the known associated cardiac manifestation of LVH and the new finding of atrial tachycardia which may represent the potential for subclinical arrhythmia in this population.

Case report

SH is a 44-year-old female diagnosed with mitochondrial myopathy, encephalopathy and stroke-like episodes (MELAS) at age 32 after suffering a fall at her job that was thought to be secondary to a seizure. After her diagnosis was made, she was initially followed by Neurology; however she was subsequently referred to our cardiomyopathy clinic secondary to progressive left ventricular hypertrophy (LVH) on echocardiogram and the known association between MELAS and cardiac disease. Prior to evaluation by our clinic, she had a clinical diagnosis of MELAS but evaluation by our cardiovascular genetics team yielded positive results for the A-to-G transition at nucleotide 3243 (m.3243A>G) of the mitochondrial genome, with 25% heteroplasmic deleterious mutation in MT-TL1, a mitochondrial leucine transfer RNA gene, the most common mutation underlying MELAS.

At the time of presentation to our clinic, SH had carried the diagnosis of MELAS for 11 years and her symptoms had progressed significantly so that she was no longer able to be employed and her husband became her primary caretaker. Her clinical status included multiple medical problems related to her MELAS diagnosis: sensorineural hearing loss, myopathy, bilateral ophthalmoplegia, ptosis, seizures and stroke-like episodes with concern for dementia. Her family history is significant for a 12-year-old daughter who is currently asymptomatic and a sister who also carries the diagnosis of MELAS but is less severely affected with symptoms mainly of diabetes mellitus and hearing loss.

In addition to a clinical exam and genetic evaluation, cardiac work-up included an EKG which showed sinus rhythm with frequent normally conducted premature atrial contractions and a Holter monitor that demonstrated episodes of non-sustained atrial tachycardia (Fig. 1). From a cardiac imaging perspective, an echocardiogram demonstrated symmetric left ventricular hypertrophy with normal ventricular systolic function, and her cardiac MRI showed extensive positive late gadolinium enhancement in the sub-epicardium of approximately 25–50% in thickness in the inferior segment at the base, inferior to lateral segments at the mid-ventricle and lateral segment of the apex, with sparing of the endocardium and septum (Fig. 1A and 1B). Her brain MRI demonstrated extensive cerebral atrophy especially involving the temporal lobes (R > L), and moderate cerebellar atrophy with extensive white matter disease. Monitoring laboratory evaluation yielded no significant abnormalities with the exception of a slightly elevated brain natriuretic peptide of 305 (normal <200 ng/L). Her liver and kidney functions were normal and there was no hyperglycemia. From a cardiac management perspective, she has been maintained on Atenolol 25 mg twice daily and aspirin 325 mg once daily.

Discussion

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a disease belonging to a group of heterogeneous disorders that result from abnormalities in mitochondrial DNA (mtDNA) within a cell [1]. Each cell, with the exception of mature red blood cells, harbors hundreds to thousands of copies of mtDNA. mtDNA mutations such as MELAS syndrome show a matrilineal pattern of inheritance since all mitochondria are transmitted to offspring only through the egg. Eighty percent of MELAS cases are due to a mutation

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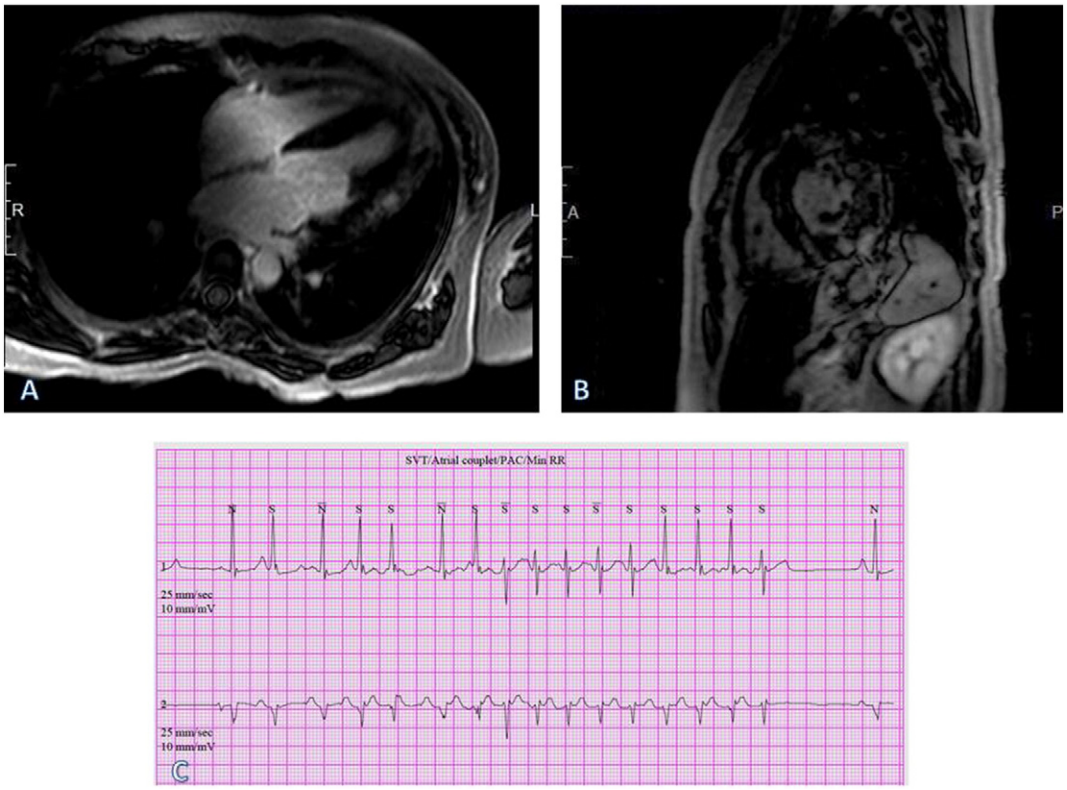

Fig. 1. Findings from cardiac magnetic resonance (CMR) imaging and Holter monitor recording. (A) Four chamber CMR image demonstrating extensive positive late gadolinium enhancement (LGE) in the subepicardium (25–50% thickness) in the lateral and apical segments with sparing of the endocardium and septum. (B) Short axis CMR image at the mid-ventricular level demonstrating extensive positive LGE in the subepicardium in the lateral and inferior segments, again, with sparing of the endocardium and septum. (C) Holter monitor recording of a 10 beat episode of non-sustained atrial tachycardia at a rate of 174 beats per minute.

in $tRNA^{Leu}$, m.3243A>G, leading to abnormal protein translation of the 13 mtDNA-encoded proteins that function within the mitochondrial respiratory chain complexes. While this mtDNA mutation can manifest clinically from newborns to old age, symptoms typically develop in late childhood to early adulthood, depending on the proportion of mutant mtDNA in any given tissue, a concept termed heteroplasmy.

The clinical manifestations include symptoms such as seizures, muscle weakness, vision and coordination problems, dementia-like changes, hearing loss, diabetes mellitus and other endocrinopathies, and cardiomyopathy [2]. Although most patients with MELAS syndrome carry the tRNA (Leu) A3243G mutation, the phenotypic manifestation of the disease is quite variable and dependent on the proportion of mutant mtDNAs [3], which can vary from tissue to tissue. While multiple cardiac manifestations have been previously reported in association with MELAS syndrome including hypertrophic cardiomyopathy, which can progress to a dilated phenotype, rhythm disturbances such as ventricular pre-excitation [4], and pulmonary hypertension [1], atrial tachycardias have not previously been reported. While atrial arrhythmias have been commonly described in other genetically driven cardiac phenotypes including dilated and hypertrophic forms, they have not previously been described in MELAS patients with or without a concomitant cardiomyopathy phenotype [5,6]. Although ventricular pre-excitation is a known MELAS association, it produces an AV node dependent supraventricular tachycardia via an accessory pathway, however, the mechanism of action of a primary atrial arrhythmia does not require the AV node for conduction. Therefore, whether or not atrial tachycardias are truly a rare entity, or are more commonly associated with MELAS and go under detected remains to be determined.

In summary, this is the unique case of a 44-year old female with a genetic diagnosis of MELAS syndrome with the associated cardiac manifestations of left ventricular hypertrophy and atrial tachycardia. This case demonstrates both the spectrum of associated cardiac disease in MELAS syndrome and the genetic component, and the potential association with subclinical atrial arrhythmias may advocate for routine ambulatory heart rate monitoring in this cohort of patients.

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