

Late-onset MELAS syndrome in a 46-year-old man with initial symptom of chest tightness: a case report

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Background

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome is a rare mitochondrial disorder caused by mutations in mitochondrial DNA, resulting in impaired energy production and affecting multiple organs. We present a suspected MELAS syndrome case with the initial symptom of chest tightness.

Case summary

A 46-year-old man sought medical attention due to progressively worsening chest tightness during physical activity. He had been receiving treatment for type 2 diabetes for 15 years. One year ago, he presented with symptoms of hearing impairment. Transthoracic echocardiography revealed increased thickness of the left ventricular wall. Serum protein electrophoresis showed no evidence of light-chain amyloidosis, and the ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scan showed no definite uptake in the heart muscle. The patient's head magnetic resonance imaging (MRI) indicated lacunar infarcts. The lactate threshold test was positive. The biopsy of the skeletal muscle showed broken red fibre infiltration on modified Gomori trichrome staining, and electron microscopy revealed signs of mitochondrial cardiomyopathy, including mild mitochondrial swelling, lipid accumulation, and myofibril damage. A whole-exome genetic test was used to detect the m.3243A>G mutation in the MT-TL1 gene. Based on these findings, MELAS syndrome was the most probable diagnosis.

Discussion

The patient presented with chest tightness in adulthood, without any accompanying psychoneurological symptoms. However, the patient presented with other symptoms, including diabetes mellitus, hearing loss, abnormal lactate levels, ischaemic lesions on head MRI, and left ventricular hypertrophy. By identifying a mutation in the MT-TL1 gene and conducting a muscle biopsy, the diagnosis of MELAS syndrome was definitively confirmed.

Keywords

Cardiomyopathy • MELAS syndrome • Mitochondrial disease • Case report

ESC curriculum

6.5 Cardiomyopathy • 8.4 Cardiovascular aspects in a diabetic patient • 9.9 Cardiological consultations • 2.3 Cardiac magnetic resonance

Learning points

- Not all MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) patients exhibit psychiatric symptoms. Endomyocardial biopsy and genetic testing can be useful in differentiating cases of idiopathic cardiomyopathy.
- It should be noted that some drugs such as metformin, phenobarbital, and statins may affect mitochondrial function, and their use needs to be carefully evaluated.

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Introduction

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome is a mitochondrial disorder caused by mtDNA mutations that affects energy metabolism and oxidative phosphorylation.¹ Symptoms vary and can include epilepsy, intellectual disability, dementia, hemiparesis, blindness, hearing impairment, and heart conduction block.² Diagnosis is based on clinical symptoms, histological findings, and genetic testing. We present a case of a 46-year-old man with chest tightness who was diagnosed with MELAS syndrome based on a musculus gastrocnemius biopsy and whole-exome sequencing (WES), despite the absence of neurological symptoms.

Summary figure

Time point	Clinical events
-15 years	Diagnosed with type 2 diabetes.
-2 years	Exertional chest tightness began.
-1 year	Onset of bilateral auditory impairment.
-6 months	Exertional angina worsened.
0 month	Visited the Cardiovascular Department outpatient clinic. Conducted examinations, including muscle biopsy and whole-exome sequencing.
2 months	Diagnosis of MELAS syndrome and discharge.
6 months	Improvement in chest discomfort and hearing impairment.

Case presentation

A 46-year-old man was referred to a clinic for chest discomfort. He has been experiencing exertional chest tightness for 2 years, which has gradually become more severe in the past 6 months. Prior to his clinic visit, he had been taking aspirin, clopidogrel, atorvastatin, metoprolol, metformin, and insulin. The tightness in his chest has deteriorated over the last two months, and he presently encounters breathlessness even after walking a mere 20 m. He had been receiving treatment for type 2 diabetes for 15 years. He has no history of hypertension, smoking, or drinking. The man is married and has two daughters, and there is no family history of cardiac disease. He has no history of surgery or trauma. On physical examination, his blood pressure was 102/66 mmHg, and his pulse rate was 77 b.p.m. No abnormalities were observed, and there was no Jugular-Venous Distention. A regular heart-beat without a murmur or extra heartbeat was observed, and his lung sounds were clear. No leg oedema was observed.

The patient had two instances of abnormally elevated cardiac troponin I (cTNI) levels with experiencing apparent chest pain (cTNI = 0.086 ng/mL; reference range, <0.03 ng/mL). The patient's red blood cell (RBC) count and haemoglobin (HGB) levels were within the normal range (RBC $4.55 \times 10^{12}/L$; reference range, $4.30\text{--}5.80 \times 10^{12}/L$; HGB 134 g/L; reference range, 130–175 g/L), and his electrolyte, renal, and liver functions were normal. His glucose, HBA1C, and glycated albumin levels were also normal. However, the patient's N-terminal pro-B-type natriuretic peptide (115 pg/mL; reference range, 0–100 pg/mL) and troponin-T (0.082 pg/mL; reference range, 0–0.03 pg/mL) levels were elevated. The D-dimer level was 0.18 mg/L (reference range, 0–0.8 pg/mL).

The transthoracic echocardiography revealed a left ventricular wall thickness of 16 mm and normal left ventricular diameter (see [Supplementary material online, Material S1](#)). The estimated left ventricular ejection fraction

was 57%. Coronary angiography revealed no significant stenosis in coronary artery systems (see [Supplementary material online, Material S2](#)). Cardiac magnetic resonance imaging (MRI) revealed abnormal signal in the front wall of the left ventricle, but the signal was not related to the heart's blood supply ([Figure 1](#)). In addition, ^{99m}Tc-PYP imaging indicated low likelihood of myocardial ATTR amyloidosis with a myocardial uptake ratio of 0.88 in the left ventricle. Serum immunoglobulin levels were normal. Serum immunofixation tests also showed no evidence of monoclonal gammopathy (κ : 21.3 mg/L, normal range 6.7–22.4 mg/L; λ : 24.4 mg/L, normal range 8.3–27.0 mg/L).

The patient lacked a history of stroke-like episodes, yet displayed abnormal serum lactic acid levels (pre-exercise: 3.5 mmol/L, immediate post-exercise: 9.25 mmol/L, and 10 min post-exercise: 6.97 mmol/L; reference range, 0.7–2.1 mmol/L). Cranial MRI exhibited punctate high signals on T2WI and T2-FLAIR, signifying lacunar infarction ([Figure 2](#)). Cardiac symptoms, hearing loss, diabetes, and abnormal cardiac MRI findings suggest a greater MELAS syndrome likelihood. Subsequently, a right musculus gastrocnemius tissue biopsy provided deeper insight. Transmission electron microscopy disclosed local myofibril fragmentation, disorderly arrangement, sarcomere disappearance, apoptotic bodies, and a significant amount of collagen. While mitochondrial swelling was mild, lipid droplet accumulation was notable ([Figure 3](#)). Modified Gomori trichrome staining of the skeletal muscle biopsy revealed broken red fibre infiltration ([Figure 4](#)).

The WES analysis has confirmed the presence of a m.3243A>G mutation in the MT-TL1 gene, with a mutation abundance of 14.2% detected in the blood sample. Five family members underwent WES. Two daughters of the index case and one of the three nephews have a normal genotype, while the remaining two nephews (III-1 and III-2) carry the m.3243A>G transition mutation without clear symptoms ([Figure 5](#)). No mutations associated with other diseases, including Anderson–Fabry disease, were identified in the family. Upon discharge, the patient was prescribed empagliflozin (15 mg, orally once daily) and dapagliflozin (10 mg, orally once daily) for blood sugar control, along with coenzyme Q10 capsules (10 mg, three times daily after meals), and a complex vitamin B tablet (two tablets, three times daily) containing vitamin B1 (3 mg), vitamin B2 (1.5 mg), vitamin B6 (0.2 mg), niacin (10 mg), and calcium pantothenate (1 mg). The patient was advised to monitor blood sugar levels and consult the endocrinology department for diabetes medication adjustments. Four months post-discharge, we conducted a telephone follow-up with the patient. The patient reported that both the discomfort in the chest and the hearing impairment have shown some degree of improvement.

Discussion

The MELAS syndrome is a rare genetic disorder that affects mitochondrial function in the body's energy-producing cells, resulting in a range of symptoms that can include muscle weakness and pain, seizures, stroke-like episodes, headaches, nausea and vomiting, hearing loss, cognitive impairment, cardiac abnormalities, and diabetes.^{1,3} The m.3243A>G transition is the most frequent mutation associated with MELAS syndrome, accounting for 80% of cases, and its prevalence is at least 3.5 out of 100 000 individuals.⁴ When this mutation causes deficiencies in the oxidative phosphorylation system, it can lead to increased production of harmful molecules called reactive oxygen species,⁵ causing damage to macromolecules and dysfunction in multiple organs. The presence of cardiac symptoms such as chest tightness, endocrine disorders such as diabetes mellitus, and sensorineural hearing loss are pathognomonic features of MELAS syndrome.

In this case, apart from cardiac symptoms, the patient also exhibits hearing loss and diabetes. Additionally, the elevation of his lactic acid level makes a clinical diagnosis of MELAS more likely. The cranial MRI showed lacunar infarcts, but they are not characteristic of MELAS. There is no direct association between the patient's hearing loss with the observed infarcts. The patient lacks typical neurological symptoms of MELAS syndrome, such as headaches, stroke-like episodes, and seizures, which are reported in over 90% of cases.^{6,7} This aligns with some previously reported cases,^{8,9} where

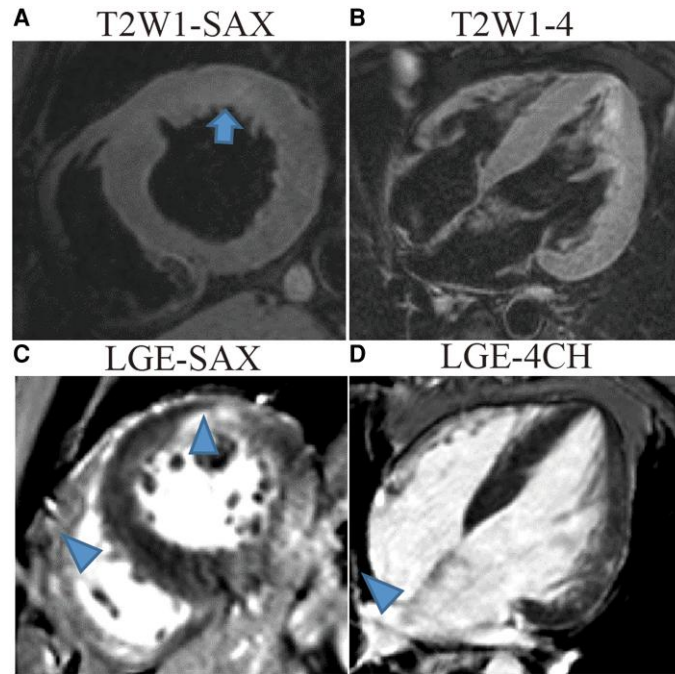


Figure 1 (A and B) T2-weighted imaging reveals patchy, slightly high signal (indicated by arrows) in the anterior wall of the left ventricle. (C and D) Delayed enhancement appears as stripes, patches, and granular distribution mainly in the anterior and inferior walls of the left ventricle (indicated by triangles), with transmural distribution.

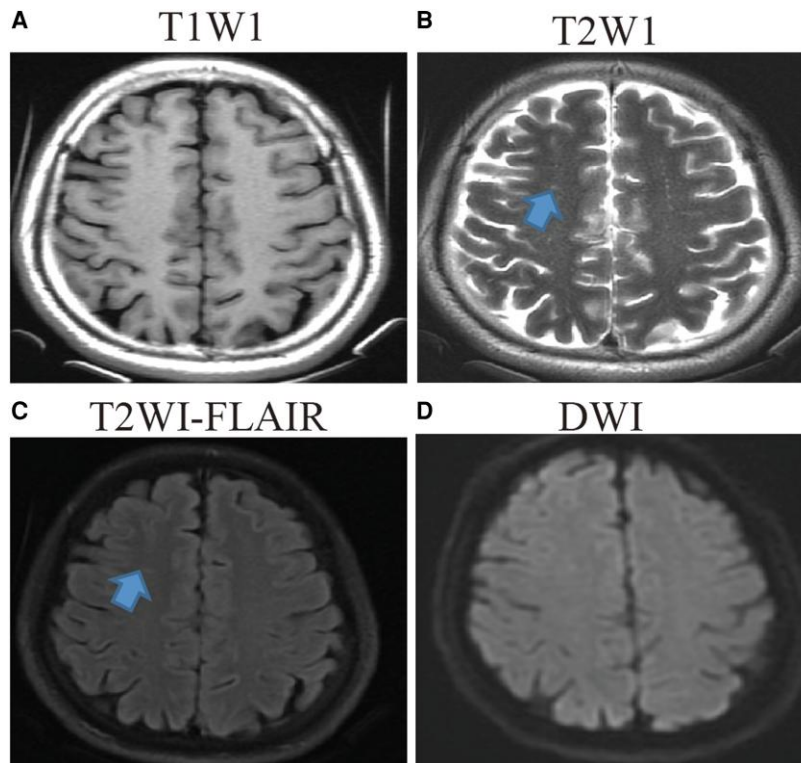


Figure 2 (A and B) Punctate high signals are observed on T2WI and T2-FLAIR images. (C and D) No significant abnormal signals are seen on T1WI and DWI. Abbreviations: T2WI, T2-weighted imaging; T2-FLAIR, T2-fluid attenuated inversion recovery; T1WI, T1-weighted imaging; DWI, diffusion weighted imaging.

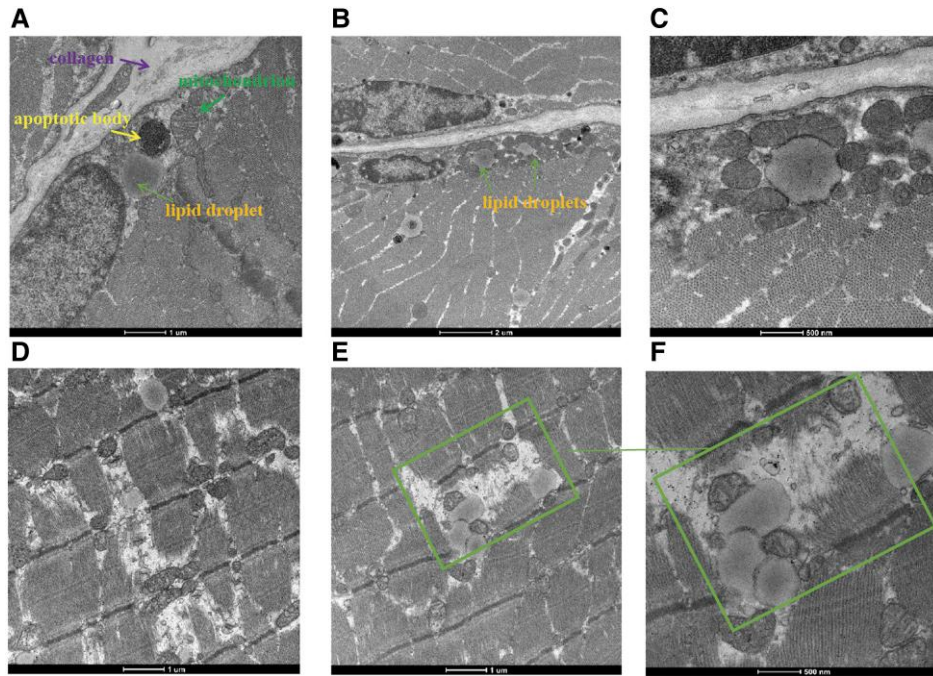


Figure 3 (A) Apoptotic bodies are observed near the nuclei of muscle cells in other parts of the biopsy tissue. There is a large amount of collagen between muscle cells. (B and C) The mitochondria show slight swelling, and there is still a significant amount of lipid droplet accumulation in the tissue. (D, E, and F) Local muscle filaments are broken, arranged disorderly, and sarcomeres disappear.

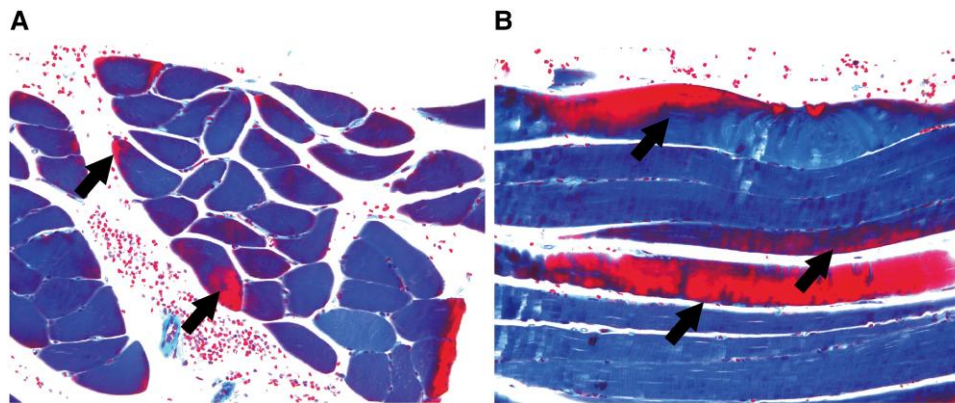


Figure 4 (A) Cross-sectional muscle fibre under a 20 \times objective lens, with the arrow indicating representative fragmented red fibre infiltration. (B) Longitudinal muscle fibre under a 20 \times objective lens, with the arrow indicating fragmented red fibre infiltration.

cardiac symptoms are often accompanied by hearing impairment and endocrine system disorders, rather than neurological impairments.

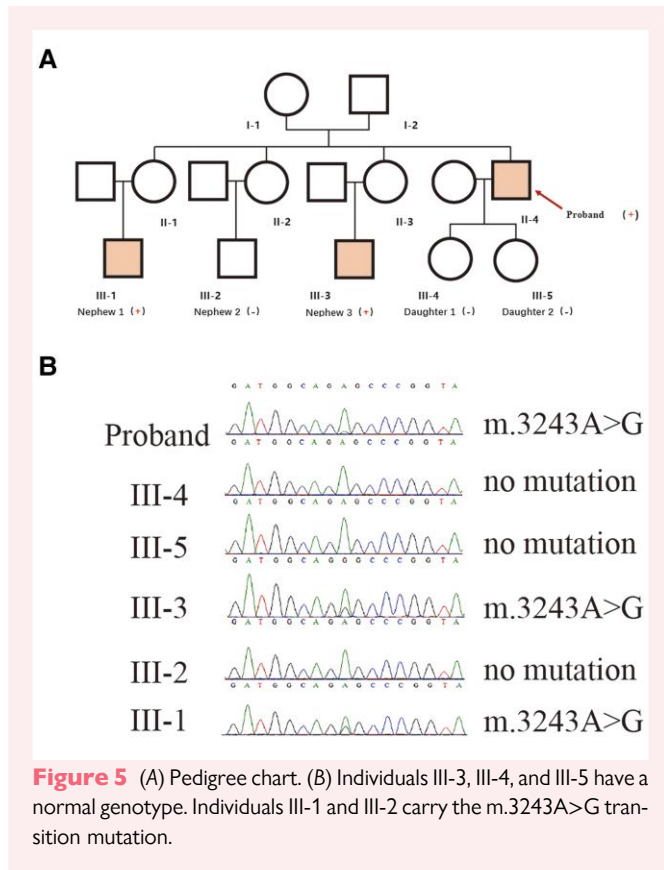
In mitochondrial diseases, mutant and wild-type mtDNA coexist within the same cell, leading to variability in the clinical presentation of MELAS syndrome. Within an individual, different cells and organs can have varying mutational loads, resulting in different degrees of dysfunction.¹⁰ This explains why clinical manifestations can vary even within families carrying the same mutation.

As MELAS is a maternally inherited mitochondrial disease, affected mothers transmit the disease to all of their children due to the exclusive maternal inheritance of mitochondrial DNA in the zygote. Conversely,

males do not transmit mitochondrial diseases.⁴ Genetic testing has significant implications for guiding eugenic reproduction in female patients with MELAS. Therefore, it is crucial to diagnose MELAS in the offspring of affected female patients.

In conclusion, for adult patients with suspected MELAS, evaluation should begin with a thorough medical history and physical examination, followed by appropriate laboratory investigations.¹¹ When fulfilling the diagnostic criteria for certain cases becomes challenging, the implementation of muscle biopsy and WES analysis remains a vital approach in diagnosing MELAS syndrome.

Currently, there is no specific and effective treatment for MELAS syndrome. Treatment aims to manage symptoms, improve quality of



life, and slow disease progression through various therapies such as nutritional support, muscle training, and medications. In severe cases where heart damage is present and symptoms persist despite other treatments,¹² heart transplantation may be considered.¹³ Medication mainly focuses on symptomatic relief, such as supplementing with L-arginine and coenzyme Q10, which can help improve energy metabolism and quality of life for patients.¹⁴ It should be noted that some drugs, such as metformin, phenobarbital, and statins, may affect mitochondrial function, and their use needs to be carefully evaluated.^{15,16}

Lead author biography



Yan Yan is a cardiology professor at Zhongshan Hospital, Fudan University. He completed his post-doctoral training at Cleveland Heart Center. He has authored over 30 publications including *Cell Research*. He served as a senior evaluation expert for Shanghai Science and Technology Commission.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Consent: The written consent for submission and publication of this case report containing images, videos, and laboratory data was obtained from the patient in line with COPE guideline.

Conflict of interest: None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

- El-Hattab AVW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab* 2015;**116**:4–12.
- Tetsuka S, Ogawa T, Hashimoto R, Kato H. Clinical features, pathogenesis, and management of stroke-like episodes due to MELAS. *Metab Brain Dis* 2021;**36**: 2181–2193.
- Koopman WJ, Willems PH, Smeitink JA. Monogenic mitochondrial disorders. *N Engl J Med* 2012;**366**:1132–1141.
- Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann Neurol* 2015;**77**:753–759.
- Pagliarini DJ, Calvo SE, Chang B, Sheth SA, Vafai SB, Ong SE, et al. A mitochondrial protein compendium elucidates complex I disease biology. *Cell* 2008; **134**:112–123.
- Wu G, Shen Y, Zhu F, Tao W, Zhou Y, Ke S, et al. Comprehensive diagnostic criteria for MELAS syndrome; a case study involving an elderly patient with MT-TWm.5541C>T mutation. *Neurologist* 2023;**28**:190–194.
- Sunde K, Blackburn PR, Cheema A, Gass J, Jackson J, Macklin S, et al. Case report: 5 year follow-up of adult late-onset mitochondrial encephalomyopathy with lactic acid and stroke-like episodes (MELAS). *Mol Genet Metab Rep* 2016;**9**:94–97.
- Brambilla A, Favilli S, Olivetto I, Calabri GB, Porcedda G, De Simone L, et al. Clinical profile and outcome of cardiac involvement in MELAS syndrome. *Int J Cardiol* 2019; **276**:14–19.
- Lee SH, Lee CJ, Won D, Kang SM. Adult-onset MELAS syndrome in a 51-year-old woman without typical clinical manifestations: a case report. *Eur Heart J Case Rep* 2023;**7**:ytad028.
- Kärppä M, Herva R, Moslemi AR, Oldfors A, Kakko S, Majamaa K. Spectrum of myopathic findings in 50 patients with the 3243A>G mutation in mitochondrial DNA. *Brain* 2005;**128**:1861–1869.
- Lorenzoni PJ, Werneck LC, Kay CS, Silvado CE, Scola RH. When should MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes) be the diagnosis? *Arq Neuropsiquiatr* 2015;**73**:959–967.
- Limongelli G, Tome-Esteban M, Dejthevaporn C, Rahman S, Hanna MG, Elliott PM. Prevalence and natural history of heart disease in adults with primary mitochondrial respiratory chain disease. *Eur J Heart Fail* 2010;**12**:114–121.
- Di Toro A, Urtis M, Narula N, Giuliani L, Grasso M, Pasotti M, et al. Impediments to heart transplantation in adults with MELAS(MT-TL1:m.3243A>G) cardiomyopathy. *J Am Coll Cardiol* 2022;**80**:1431–1443.
- Santa KM. Treatment options for mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. *Pharmacotherapy* 2010;**30**: 1179–1196.
- Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* 2000;**22**:685–708.
- Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2010; **2010**:Cd002967.