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# Lifestyle Changes Normalize Serum Lactate Levels in an m.3243A>G Carrier

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Conflict of interest:** None declared

**Patient:** Female, 57-year-old
**Final Diagnosis:** Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
**Symptoms:** Fatigue • gastrointestinal
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Neurology

**Objective:** Challenging differential diagnosis

**Background:** The normalization of serum lactate levels in a patient with non-syndromic mitochondrial disorder due to the m.3243A>G mitochondrial DNA (mtDNA) variant has not been previously reported.

**Case Report:** A 57-year-old woman was diagnosed with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) due to the m.3243A>G variant, with low heteroplasmy rates (31%), at age 50. The initial manifestations were short stature, migraine, and diabetes. With progression of the disease, multisystem involvement developed, affecting the brain (stroke-like episode, mild cognitive impairment), eyes (pigmentary retinopathy), ears and the vestibular system (impaired hearing, tinnitus, imbalance, drop attacks, vertigo), intestines (constipation, distended abdomen, gastro-esophageal reflux, gastroparesis), and the muscles (muscle weakness). The gastrointestinal involvement was most prominent and most significantly lowered the patient's quality of life. The diabetes was well controlled with an insulin pump. Recurrent, acute deteriorations responded favorably to L-arginine. Owing to lifestyle and diet changes 2 years after diagnosis (start of art classes, increase in spin biking to 22.5 km 3 times per week, travel to Hawaii, adherence to low-carbohydrate high-protein diet), the patient managed to lower elevated serum lactate levels to largely normal values.

**Conclusions:** Gastrointestinal compromise may be the prominent manifestation of the m.3243A>G variant, lifestyle and diet changes may lower serum lactate in m.3243A>G carriers, and low heteroplasmy rates of the m.3243A>G variant in scarcely affected tissues do not exclude pathogenicity.

**Keywords:** MELAS Syndrome • Mitochondria • Mitochondrial Proton-Translocating ATPases

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/930175







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## Background

The m.3243A>G variant is one of the most common point mutations of mitochondrial DNA (mtDNA) [1]. The m.3243A>G variant is located within the mtDNA gene *MT-TL1*, which encodes the mitochondrial transfer ribonucleic acid (tRNA) leucine-1. Generally, tRNAs help assemble protein building blocks (amino acids) into functioning proteins. Leucine tRNA specifically attaches to the amino acid leucine and inserts it into the appropriate locations in the growing protein during protein assembly. The variant m.3243A>G manifests phenotypically in a broad spectrum of diseases. The most well-known phenotype is mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. In 80% of the cases, MELAS is due to the variant m.3243A>G [1]. More rarely, the m.3243A>G variant manifests as maternally inherited diabetes and deafness syndrome, myoclonic epilepsy with ragged red fiber syndrome, Leigh syndrome, progressive external ophthalmoplegia, or MELAS/Kearns-Sayre overlap syndrome [2]. In addition to these syndromic phenotypes, the variant m.3243A>G manifests with non-syndromic phenotypes, which do not fit to any of the more than 50 mitochondrial syndromes. Although gastrointestinal involvement is known in m.3243A>G carriers [3], predominant gastrointestinal compromise and normalization of serum lactate levels have not been reported in non-syndromic m.3243A>G carriers. This report presents a case of a woman with mitochondrial encephalopathy, lactic acidosis, and MELAS syndrome due to the m.3243A>G variant. This study was approved by the institutional review board.

## Case Report

The patient was a 57-year-old woman, with a height of 155 cm and weight of 56 kg, who was diagnosed with MELAS at the age of 50 years. The initial manifestations of MELAS were a short stature since early childhood and migraine since age 17 years. When the patient was between 20 and 35 years of age, she had recurrent lower urinary tract infections, which were repeatedly treated with ciprofloxacin (800 mg/day for 3 days). During her only pregnancy at age 30, she experienced gestational diabetes. Additionally, she experienced postpartum depression and transient weakness of the lower legs, after epidural anesthesia for Cesarean section, which was conducted in the absence of clinical indications for deep venous thrombosis or nerve injury. Since pregnancy, she had symptoms of a distended abdomen. Starting at age 38, she developed progressive impaired hearing, and diabetes was diagnosed, which was treated with metformin (up to 2000 mg/day). Starting at age 40, she began experiencing recurrent episodes of hearing loss, left ear tinnitus, imbalance, drop attacks, and occasional vertigo, which were interpreted as Meniere's disease. Since age 42, she had intermittent dysphagia. At age 48, an episode of depression developed following the deaths of her mother and brother. Insulin treatment was added to the metformin regimen at age 49 years. At age 50, sudden-onset weakness of the left upper limb, slurred speech, blurred vision, and tandem gait occurred, and were interpreted as a stroke-like episode. Cerebral magnetic resonance imaging (MRI), carried out within 6 h after onset, showed T1-hyperintensity of the globus pallidum bilaterally and the left posterior thalamus, but no stroke-like lesion was detected. Additionally, there were some non-specific, subcortical T2-hyperintense spots. The patient's lactate level was elevated, but L-arginine was not given. At age 51 years, pigmentary retinopathy ("speckled pigment" maculopathy) was diagnosed, and a genetic work-up revealed the common MELAS mutation m.3243A>G in *MT-TL1*, with a heteroplasmy rate of 31% in buccal mucosa cells. Two other mtDNA variants, m.5084A>G in *MT-ND2* and m.16362T>C in the D-loop, with heteroplasmy rates of 9% and 4%, respectively, were additionally detected. A muscle biopsy was not carried out. Instead, a second genetic test revealed the m.3243A>G variant, but in the blood lymphocytes, with a heteroplasmy rate of 14%. MELAS was diagnosed, and a mitochondrial cocktail was prescribed. The metformin was discontinued.

Since the first episode, the patient experienced recurrent episodes of slurred speech, imbalance, and left-sided weakness, lasting between a few minutes and a few hours, which always resolved with intravenous L-arginine. At age 52 years, the patient had recurrence of a distended abdomen and constipation, and gastro-esophageal reflux disease (GERD) and gastroparesis were diagnosed. Laxatives helped little, and probiotics were ineffective. Transient sinus tachycardia was recorded on an electrocardiogram (telemetry). Changes in lifestyle (start of art classes, increase in spin biking to 22.5 km 3 times per week, travel to Hawaii, and daughter moving out of state for new job) and adherence to a low-carbohydrate, protein-rich diet resulted in the normalization of the patient's serum lactate level (**Figure 1**). A cerebral MRI at age 53 years was unchanged from previous findings. The patient started recognizing weakness of the left lower leg upon exercising. Since age 54 years, the patient's creatine-kinase level had been slightly but constantly elevated. A cerebral computed tomography scan at age 57 years showed marked bilateral basal ganglia calcification. She had multiple allergies, including milk, corn, pork, lobster, mussels, monosodium glutamate, preservatives, sulfites, nitrates, pollen, ragweed, trees, grass, dust, mold, many chemicals, perfumes, cosmetics, and many drugs, particularly antibiotics. Her last medication included insulin in a pump, antihistamines, potassium, and magnesium. Additionally, she was taking liquid ubiquinol, citrulline, taurine, vitamin B complex (riboflavin, vitamin B12), vitamin D3, alpha-lipoic acid, nicotinamide riboside, and N-acetyl-cysteine. The patient was on a low-carbohydrate (30 g to 50 g daily) diet for diabetes and ate protein-rich food, healthy fats, and medium-chain triglyceride





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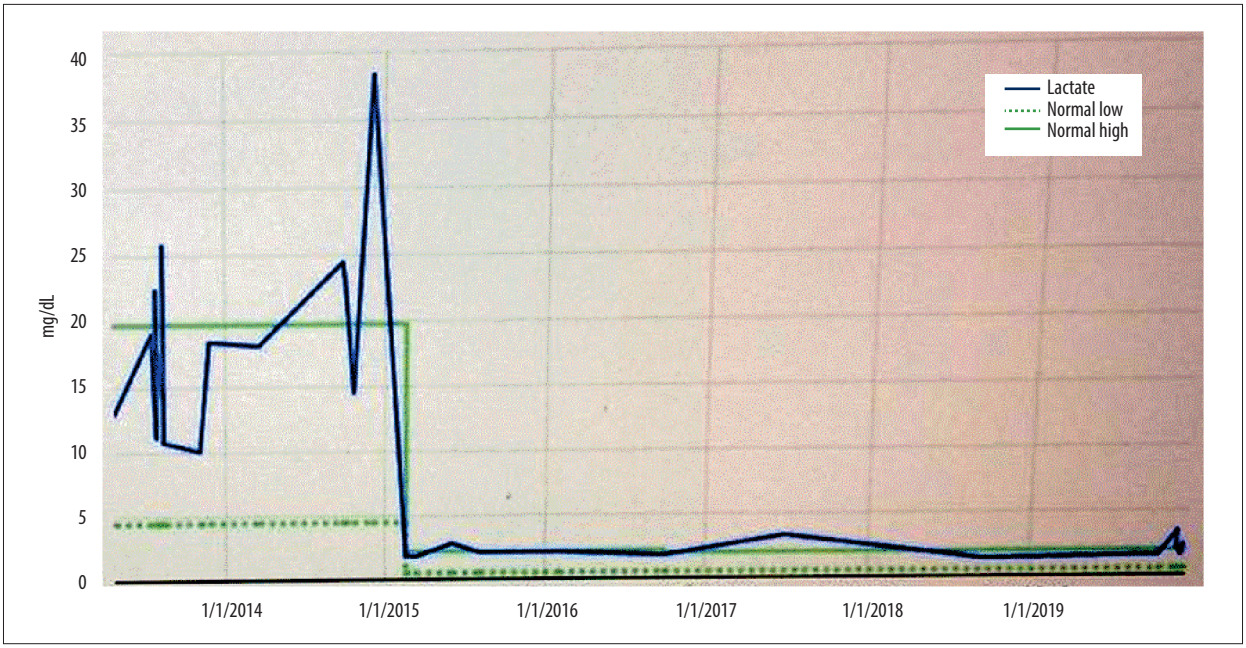


**Figure 1.** Serum lactate values over 5 years showing improvement upon changes in the patient's lifestyle and diet at the end of 2014.

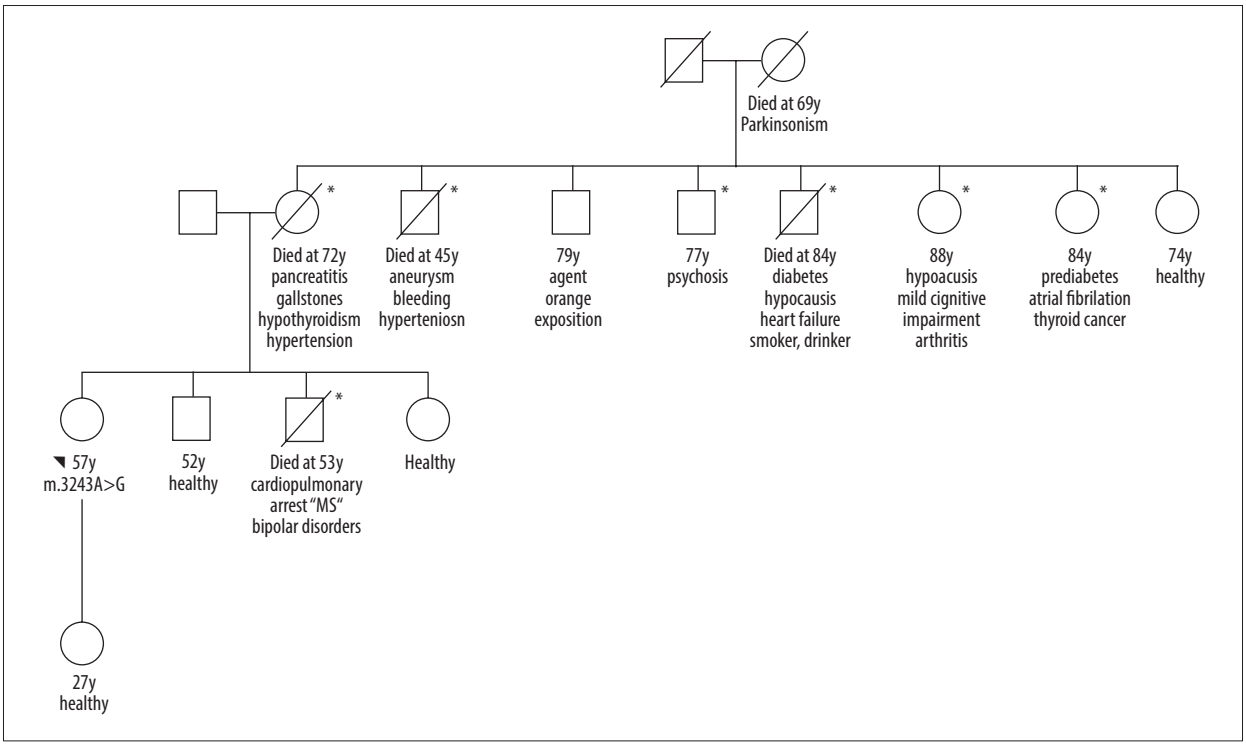


**Figure 2.** Pedigree of the family of the index patient, with possibly affected family members.

oil. She tolerated soft foods and liquids better than she did solid foods. A clinical neurologic exam at age 57 years revealed mildly delayed recall, hypoacusis, mild dysarthria, microphonia, and weakness of the left deltoid (M4+), left hip flexors (M4), and left plantar flexors (M4+).

The patient's family history was positive for suspected mitochondrial disorder; however, none of the index patient's relatives had been genetically tested (**Figure 2**). Her daughter's history included hypoacusis, migraine, attention deficit disorder, and a depressive episode. Her mother had mononucleosis, hypothyroidism, arterial hypertension, 1 stillbirth, and





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gallstones and died at 72 years of age from pancreatitis, which had been attributed to the gallstones (**Figure 2**). The grandmother from the mother's side had Parkinsonism and died at age 69 years. The index patient had 1 sister and 2 brothers (**Figure 2**). One brother had a history of severe mononucleosis, bipolar disorder, psychosis, several suicide attempts, and alcohol and drug misuse. At age 48 years, the brother was diagnosed with multiple sclerosis. He died from cardiopulmonary arrest at 53 years of age, but an autopsy was not performed. The other brother was healthy, as was the sister, who had a history of smoking and alcohol abuse. The index patient's mother had 7 siblings. An 88-year-old sister of the mother had mild memory impairment, hypoacusis, Brown-Sequard syndrome, and arthritis. One brother of the mother presumably died from a heart attack at 45 years of age. He had a history of alcohol abuse, smoking, and arterial hypertension. An 84-year-old sister had prediabetes since age 80 years, atrial fibrillation, and a history of thyroidectomy because of malignancy. One brother drank alcohol and smoked, developed diabetes, hypoacusis, and heart failure, and died at 84 years of age. A 79-year-old brother was exposed to Agent Orange during the Vietnam War, which caused long-term pulmonary compromise. A 77-year-old brother had psychosis and had also been exposed to Agent Orange in Vietnam. A 74-year-old sister of the mother was healthy. Among 3 cousins of the index patient (children of the 84-year-old aunt), a 60-year-old woman had Hashimoto's disease, Graves' disease, and a hip replacement; a 58-year-old woman had anosognosia and a history of smoking and alcohol and drug misuse; and a 52-year-old man had an intestinal carcinoid (**Figure 2**).

## Discussion

The presented patient is interesting for the non-syndromic, multisystem nature of the phenotype, normalization of serum lactate upon lifestyle and diet changes, predominant gastrointestinal manifestations, and the low heteroplasmy rate of the variant, which was responsible for the phenotype.

The phenotype was definitively non-syndromic because it did not fulfill the Japanese or Hirano criteria for diagnosing MELAS [4,5]. The patient never experienced an MRI-confirmed stroke-like episode. The phenotype was too broad for diagnosing maternally inherited diabetes and deafness syndrome. Myoclonic epilepsy with ragged red fiber syndrome was excluded upon the absence of myoclonic epilepsy [6], and there were no typical diagnostic features allowing the diagnosis of Kearns-Sayre syndrome.

There was definitively multisystem involvement in the patient, as the variant manifested in the brain (migraine, basal ganglia calcification), eyes (pigmentary retinopathy), ears and vestibular system (hypoacusis, tinnitus, nausea, vertigo), endocrine organs (diabetes, short stature), intestines (dysphagia, nausea, vomiting, gastroparesis, bloating, GERD, constipation, distended abdomen), and muscles (myopathy, creatine-kinase elevation). Whether there was also involvement of the immune system remains speculative, but the patient's multiple allergies and the recurrent urinary tract infections suggest it.

Normalization of the patient's serum lactate values were achieved by avoiding physical and psychological stress and by the strict adherence to a low-carbohydrate, protein-rich diet. Although serum lactate levels occasionally slightly increased thereafter, they never reached values that were as high as before. Explanations other than lifestyle changes for lowering the patient's serum lactate level could include ramping up the mitochondrial cocktail the patient received since age 50 at age 53 and improved control of her diabetes with insulin. It is also conceivable that repeated L-arginine infusions had a lactate-lowering effect. Discontinuation of metformin was excluded as a cause of lactate normalization because it had happened 1 year earlier. Nevertheless, it has been reported that carriers of the m.3243A>G variant require a non-stressful life, discontinuation of mitochondrion-toxic drugs, ketogenic-like diet, and a clean environment [7].

Gastrointestinal involvement is not uncommon in carriers of the m.3243A>G variant and has been previously reported [3,8,9]. Gastrointestinal involvement was the phenotypic feature that most significantly affected our patient's quality of life. She had the feeling of a lump in her throat when swallowing and was afraid that hard food might get stuck. She had recurrent nausea and progressive dysphagia since age 50. However, she had no pseudo-obstruction, as has been previously reported [10]. She reported some relief from dysphagia from pureeing food and the use of stool softeners. However, probiotics, antacids, antiflatulent agents, and polyethylene glycol were ineffective. Gastrointestinal involvement was attributed to affection of smooth muscle cells rather than to autonomic neuropathy because no other clinical manifestations of an autonomic involvement were found. The patient's diabetes was well controlled. A brainstem/cerebellar lesion was excluded as the cause of nausea or dysphagia by MRI. Lactic acidosis was excluded because the patient's serum lactate values were largely within normal limits beyond age 52.

Whether the variant m.3243A>G was truly responsible for the phenotype remains speculative; however, low heteroplasmy rates detected in blood and buccal mucosa are not unusual and can nonetheless explain the phenotype. Low heteroplasmy rates of 14% and 31% can be explained by investigations of scarcely affected tissues. Most likely, heteroplasmy rates would be higher if more severely affected tissues, such as gastrointestinal smooth muscle cells, myocytes, beta cells,





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or cochlear cells, were investigated. Whether the 2 variants additionally detected played a pathogenic role in this patient remains speculative. Variant m.5084A>G in *MT-ND2* has not been previously reported as pathogenic. Variant m.16362T>C in the D-loop is regarded as a variant of unknown significance. Nonetheless, these variants may have modified the phenotypic expression of the m.3243A>G mutation.

There were some limitations to the study. None of the affected or unaffected family members were genetically tested and the mtDNA copy number was not determined. A further limitation is that the index patient had never undergone a muscle biopsy or electroencephalogram recordings. An additional limitation is that cerebral MRIs were not always immediately carried out in the acute stage of a clinical deterioration.

## Conclusions

This case shows that gastrointestinal compromise may be the prominent manifestation of the m.3243A>G variant, serum lactate may normalize upon changes in lifestyle and diet, and low heteroplasmy rates of the m.3243A>G variant in scarcely affected tissues do not exclude pathogenicity.

### Conflicts of Interest

None.

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