



## *Kidney Transplantation in a Patient with MELAS: A Case Report and Review of the Literature on Medication Use*

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### Abstract

*MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke like episodes) is an inherited mitochondrial disorder that can have renal manifestations. These manifestations can consist of proteinuria, glomerular injury or focal or global glomerulosclerosis on biopsy. Ongoing renal injury can result in end stage kidney disease and need for kidney transplantation. Kidney transplantation in MELAS patients is not well described and medication management can be difficult. We describe a recent successful case of kidney transplantation in a patient with MELAS and review the available literature for management in the peri and post-operative setting.*

*Keywords: Mitochondria; Nervous system; Myopathy; Diabetes; Lactic Acidosis*

### Introduction

Mitochondria are responsible for generating cellular energy. Their function is particularly critical in high energy organ systems such as the nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine systems. When mutations occur in mitochondrial DNA, impaired energy production, microvasculature angiopathy, and nitric oxide deficiency can result [1]. In such circumstances, patients may present with an array of multi-organ dysfunction including stroke-like episodes, dementia, epilepsy, lactic acidemia, myopathy, recurrent headaches, hearing impairment, diabetes, and short stature [2].

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) is one of the most frequently inherited mitochondrial disorders [3]. It involves a mutation in the MT-TL1 gene encoding mitochondrial tRNA. This is most often substitution of a guanine nucleotide for an adenine at position 3243 [4]. Patients with MELAS often require a multi-disciplinary team that includes neurologists, metabolic geneticist, cardiologists, endocrinologists, audiologists, ophthalmologists, physical and occupational therapists,

psychologists, and social workers. And, because MELAS can be exacerbated by various common medications that interfere with oxidative phosphorylation or impair mitochondrial activity. Surgical procedures and post-operative management with these patients can be difficult [5]. While neurologic and muscular manifestations of MELAS are well-known, renal manifestations are less commonly identified.

Generally, the most common mtDNA mutation associated with MELAS and renal manifestations is a base change at m.A3243G [6]. However, mitochondrial mutations do not always lead to the same clinical manifestations in each patient making it more difficult to associate renal manifestations with specific mitochondrial mutations [7]. Renal manifestations that have been associated with MELAS consist of proteinuria, glomerular injury, or focal or global glomerulosclerosis on biopsy [8-10]. Renal tubular dysfunction and tubulointerstitial nephritis may less commonly be seen on biopsy as well [6,7].

In the following case, we share our recent experience preparing for, and ultimately performing a kidney

transplant in a patient with MELAS. There is little published literature examining in a comprehensive way the use of immunosuppressive medications or post-operative management of transplant recipients with mitochondrial disorders. We hope that our experience offers guidance to others considering solid organ transplantation in this patient population, particularly regarding the selection and use of transplant related medications.

### Case Report

A 36-year-old Caucasian male with a history of end-stage kidney disease secondary to focal segmental glomerulosclerosis, on peritoneal dialysis, was evaluated for potential kidney transplant. He had a past medical history significant for failure to thrive as a child, chronic kidney disease, external strabismus, unexplained syncopal episodes, and progressive hearing loss. He was ultimately diagnosed with MELAS at the age of 32 year via a mitochondrial genome sequencing that was positive for m.13513G>A mutation in the MT-ND5 gene and was started on a medication regimen targeted towards improving mitochondrial function, including co-enzyme Q (Co-Q10), L-arginine, and vitamin B complex.

To assess the safety of kidney transplantation in a patient with MELAS, and ultimately to plan for the patient's perioperative and post-transplant care, all commonly used transplant medications were reviewed by members of the transplant team, including medications required for surgery, immune suppression, infection prophylaxis, and those used for the most common post-transplant complications. Members of the pharmacy team put together a master list of these medications, and then following consultation with the patient's sub-specialists and a detailed literature search, compiled a list of medications that would be safe to use throughout the patient's anticipated clinical course. Prior to transplant the patient was receiving L-arginine, carvedilol, cinacalcet, Co-Q 10, epoetin, folic acid, fosrenol, lactobacillus, bactroban, riboflavin, vitamin B complex, albuterol inhaler, and sevelamer.

The patient was admitted for a deceased donor kidney transplant in the spring of 2017. He received dextrose 5% in sodium chloride 0.9% solution at 30 mL/hour pre-operatively to maintain normal blood glucose and lactate levels. Peri-operatively, the patient received midazolam. He received propofol 120 mg and fentanyl 150 mcg for sedation and anesthesia induction. He then received isoflurane 0.7%-0.9% for maintenance induction and was subsequently intubated. The patient's

hemodynamics, lactate, and electrocardiography were monitored throughout the procedure. Throughout the procedure, the patient received phenylephrine and dopamine to maintain hemodynamics, cisatracurium to maintain neuromuscular blockade, and sodium bicarbonate.

As a Caucasian male with no history of sensitization and a PRA of zero, he was deemed low immunologic risk per Duke University Hospital kidney transplant protocol and given basiliximab for induction per surgeon preference. He received a standard maintenance immunosuppression regimen of tacrolimus, mycophenolate mofetil, and prednisone. For pneumocystic jiroveci prophylaxis, the patient received sulfamethoxazole/trimethoprim and for Herpes Simplex Virus (HSV) prophylaxis he received acyclovir for 3 months.

He had immediate graft function with an unremarkable early post-transplant course and underwent removal of his peritoneal dialysis (PD) catheter 1-month after kidney transplant. His transplant wound healed without incident, but he developed focal subcutaneous fluid collections concerning for abscesses at the PD catheter entrance and exit sites requiring incision, drainage, and later, a course of cephalexin. He is now 6-months post-transplant with a baseline creatinine between 1.2-1.3mg/dL, without proteinuria, requiring no medications for blood pressure or blood glucose control.

### Discussion

A search using PubMed revealed limited published reports describing transplantation in patients with MELAS. There was a single case report published by Lederer and colleagues that focused on the difficulty of diagnosing patients with MELAS [11]. Another article published by Parikh and colleagues evaluated the outcomes of solid organ transplant recipients with primary mitochondrial disease [12]. Patients that required a kidney transplant most frequently in their cohort had a m.3243A>G mutation.

They did not see any correlation between need for transplant and severity of organ involvement. Patients that underwent liver transplant had a lower survival rate compared to other organs (heart 82%, kidney 100%, liver 75%) with mean follow-up time frame of 6-9 years. However, the researchers concluded that patients with mitochondrial disease should not be excluded from transplantation [12]. Finally, an article published by Vater and colleagues reviewed existing literature on transplantation patients with mitochondrial disorders and reported a case of an emergent liver transplant [13].

The article discussed both the paucity of literature on perioperative management of transplant recipients with mitochondrial disorders as well as the conflicting nature of reports with safety of anesthesia and perioperative drugs. While there have been a few case reports published reviewing various induction and sedation agents for surgical procedures, there is still a significant lack of information discussing the safety of commonly used medications post-transplant. Similar to other surgical procedures, transplant recipients require perioperative management with induction agents,

neuromuscular blockers, and sedation. Additionally, the use of vasopressors, anti-arrhythmic agents, beta-blockers, and steroids may be required to maintain hemodynamics throughout the procedure. Post-transplant complications include pain, hypertension, constipation, hyperglycemia, electrolyte disturbances, nausea, and infection. Therefore, an in-depth literature review was performed to identify a perioperative and postoperative management plan identifying medication as safe, likely safe, and unsafe/to be avoided (Tables 1 and 2).

**Table 1:** Peri-Operative Management.

<b>Peri-operative management</b>			
	Safe to Use	Likely Safe to Use	Should be Avoided
Induction/Neuromuscular Blockers	Propofol	Lidocaine/ropivacaine	Halothane
	Etomidate	Succinylcholine	Thiopental
		Isoflurane/sevoflurane	Nitrous oxide
		Cisatracurium, Vecuronium, Rocuronium	
Sedation/Pain	Ketamine		Barbiturates
	Midazolam		
	Fentanyl, morphine, oxycodone		
Cardiac	Beta-blockers		Amiodarone
	Non- dihydropyridine calcium channel blockers		
	Vasopressors (epi, NE, vasopressin, DA, PE)		
Miscellaneous	Insulin		Lactated ringers'
	Neostigmine, atropine, glycopyrrolate		

**Table 2:** Post-operative management.

<b>Post-operative Management</b>			
	Safe to Use	Likely Safe to Use	Should be Avoided
Immunosuppression	Tacrolimus		
	Mycophenolate		
	Methylprednisolone Prednisone		
Antibiotics/Prophylaxis	Penicillins, Cephalosporins		Aminoglycosides
	Vancomycin		
	Antifungals		
	Bactrim		
Miscellaneous	Acyclovir/valganciclovir		
	Magnesium, potassium, calcium, vitamin D supplements	Acetaminophen	Aspirin

	Pantoprazole		Metformin
	Insulin		
	Opiates		
	Anti-emetics		
	Laxatives, stool softeners		

The clinical issue of medication use in patients with mitochondrial disorders is widely discussed. There have been no clinical trials investigating the role of anesthetic agents in patients with mitochondrial dysfunction. Existing articles are limited to case reports and case series.

Additionally, there have been adverse effects of varied anesthetic agents identified in vitro but this has not translated when used in vivo. There are no guidelines published that specify which agents are safe to use for anesthesia due to the lack of evidence [14]. General anesthetic agents can act on the mitochondria and therefore, there is a concern that patients with mitochondrial dysfunction may respond differently [15].

One case report discussed the successful anesthetic management of a patient with MERFF (a mitochondrial disorder, myoclonic epilepsy with ragged red fibers) [16]. An 11-year-old patient received propofol 2 mg/kg and fentanyl 2 mcg/kg for induction anesthesia along with sevoflurane 6-8% and nitrous oxide 55% for maintenance anesthesia. The patient had a stable post-operative course with no complications. One of the largest case series published discussed 122 children with mitochondrial dysfunction that underwent minor surgical procedures and 119 of them had normal anesthesia-related outcomes.

Propofol can uncouple oxidative phosphorylation, inhibit electron flow along electron transport chain, antagonize beta receptor binding, and act directly on calcium channel proteins diminishing contractility [6]. However, there have been several case reports published that describe successful use of propofol in patients with mitochondrial dysfunction [17,18].

Patients receiving propofol in the existing literature received infusions for 30-60 minutes, but not longer. Acidemia and electrolyte disturbances are two complications that may occur with prolonged propofol infusions. Our patient received a one-time dose of propofol 120 mg intra-operative without any complications.

Volatile anesthetics should be used cautiously as mitochondrial patients may potentially be hypersensitive to these agents. Additionally, they have been shown to inhibit complex I activity. Drissen et al. and Footitt et al. both reported successful cases of anesthesia management with sevoflurane and isoflurane [17,18]. Halothane, thiopental, and nitrous oxide may exacerbate complex I inhibition affecting mitochondrial function, and therefore should be avoided. Isoflurane and sevoflurane are different because they do not exacerbate complex I inhibition to the extent other general anesthetics do [19]. The patient received isoflurane for anesthesia and did not demonstrate any hypersensitivity reactions or complications.

Local anesthetics such as lidocaine, ropivacaine, and bupivacaine can potentially inhibit mitochondrial bioenergetics and disrupt oxidative phosphorylation. However, there have been no published reports discussing adverse effects with this medication. Our patient received a one-time dose of lidocaine 40 mg intravenously and tolerated it well.

Non-depolarizing muscle relaxants have been reported to increase the sensitivity to paralytic effects and prolonged responses. Patients with mitochondrial disease have been shown to be at risk for developing malignant hyperthermia and thus, providers should remain vigilant about their use. Therefore, non-depolarizing muscle relaxants including rocuronium, vecuronium, and cisatracurium, are preferred. Succinylcholine is likely thought to be safe. In this case report, our patient received cisatracurium for muscle relaxation and remained hemodynamically stable with no indications of malignant hyperthermia.

In patients with MELAS, the liver may not be able to completely metabolize excessive endogenous production of lactate. Therefore, avoidance of Lactated Ringers is also imperative in the OR as this greatly increases the patient's risk of developing lactic acidosis. Metabolic stressors such as hypothermia and hypotension can also lead to decompensation in patients with mitochondrial disease so monitoring hemodynamics throughout surgery has particular importance.

With regards to immunosuppression management post-transplant, little evidence is available. One report of two patients undergoing heart transplant showed no issues with the use of tacrolimus, mycophenolate, and prednisone for immunosuppression [20]. There is a proposed theoretic benefit to calcineurin based therapy with patients with MELAS as it has potential protective effects that can decrease both ischemic and oxidant damage at the cellular level [21].

At the time of this publication, the patient is approximately 6 months post-transplant and is doing well, as described above. He maintains his current regimen of triple immunosuppression. He has been restarted on his mitochondrial targeted regimen of coenzyme Q10, arginine, and riboflavin.

Centers that consider transplanting patients with mitochondrial disorders should have a multi-disciplinary team including genetics consultation, if possible, and a medication management plan in place prior to active listing and transplantation. In conclusion, this case report describes the successful transplantation of a patient with MELAS and successful management post-transplant with maintenance immunosuppression.

#### **Conflict of Interest**

None declared.

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