# *Perioperative management of mitochondrial encephalopathy associated with a novel AIFM1 mutation in a high-risk pregnancy: A case report*

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## ABSTRACT

**Perioperative management of mitochondrial encephalopathy associated with a novel AIFM1 mutation in a high-risk pregnancy: A case report**

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Mitochondrial diseases represent a wide range of disorders caused by impairment of mitochondrial metabolism and energy production. We report a case of an uneventful perioperative management of a pregnant patient with early childhood-onset mitochondrial encephalopathy, attributed to a novel AIFM1 (Apoptosis-Inducing Factor, Mitochondrion-associated 1) mutation. After a multi-disciplinary team consultation, it was decided to be posted for elective caesarean delivery at $36^{+2}$ weeks of gestation, under titrated combined spinal-epidural anaesthesia and multimodal analgesia. Unique anaesthetic challenges were to ensure normoglycaemia, normothermia and adequate hydration while avoiding perioperative stress and acidosis.

## INTRODUCTION

Mitochondrial diseases are a group of disorders caused by dysfunctional mitochondria, the organelles that generate energy for the cell. Thus, mitochondrial dysfunction most commonly affects the central nervous system, the heart, the gastrointestinal tract, and the muscular system[1]. They may be caused by mutations (acquired or inherited), in mitochondrial DNA (mtDNA), or in nuclear genes that code for mitochondrial components)[2].

The "Apoptosis-Inducing Factor, Mitochondrion-associated 1" (AIFM1) gene is a flavoprotein involved in mitochondrial metabolism which is located on the chromosome X (Xq26.1)[3]. The array of mutations in AIFM1 is

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associated with syndromes with a broad range of clinical manifestations, from Leigh syndrome which is fatal in infancy, through to a slowly progressive peripheral neuropathy resembling Charcot-Marie-Tooth syndrome[4].

In this case report, we present the uneventful management of a parturient with AIFM1-related early childhood-onset mitochondrial encephalopathy, undergoing a caesarean delivery following a spontaneous pregnancy.

## CASE REPORT

A 34-year-old Greek parturient (G1, P0) with an X-linked AIFM1-related mitochondrial encephalopathy, was referred to our obstetric unit for early preconception counseling to eliminate any concerns of genetic transmission. She was scheduled for caesarean section at $36^{+2}$ weeks of gestation.

Although X-linked inheritance was a reason to doubt that this is the cause of her disease, analysis of her mtDNA revealed that she suffered from a mild form of AIFM1 deficiency caused by skewed lyonization in a heterozygote or from the combination of her AIFM1 mutation (c.134C>G; p.Pro45Arg) with a second, de novo or inherited nuclear genetic lesion that also affects mitochondrial function. Moreover, she had two siblings who died in early childhood from acute Reye-like crisis, while at the same age she suffered a prolonged unexplained comatose state for a week.

She had a body mass index (BMI) of 27 (height 167 cm and term weight 74 kg). Her regular medications included a multivitamin (B, C, E), coenzyme $Q_{10}$, riboflavin, and montelukast while her hypothyroidism was treated with levothyroxine. She also suffered from minor motor seizures, due to early childhood-onset encephalopathy, so she was on a daily dose of levetiracetam 4000mg.

After she had been fully informed about the related benefits and risks of the procedure, caesarean delivery was performed on maternal request, since mitochondrial disease is not an absolute contraindication in a primigravida. Choice of regional over general anesthesia was fully explained. She had not previously received anesthesia as an adult.

On pre-anaesthetic evaluation, pulse rate was 88 per minute, blood pressure was 115/80 mm Hg and preoperative $SpO_2$ was 99%. Neurologically, she had a mild hypotonia along with hesitant, often inarticulate speech. The electrocardiograph along with the echocardiography displayed no abnormalities. Lung function tests, arterial blood gases (ABGs) and other laboratory tests (complete blood count, electrolytes and glucose, renal and liver function tests, ammonia, creatine phosphokinase, coagulation parameters) were normal.

Preoperative care included two oral doses of 150mg of ranitidine (the night before and the day of surgery) and 6 hours of fasting, while a

dextrose-containing maintenance infusion was initiated to avoid hypoglycaemia. Monitoring included ECG, BP, $SpO_2$ and body temperature. Co-loading with 500ml of normal saline was performed and a right radial artery line was placed for repeated ABGs measurement. Actions to prevent hypothermia were taken (temperature's room adjusted to 26°C, warmed intravenous fluids, forced-air warming blanket). Under aseptic conditions, a combined spinal-epidural technique (CSE) was performed in the left lateral position. A paramedian approach was followed from the right lateral side, due to scoliosis. An epidural Tuohy needle (Portex©; 18G, 80 mm in length) was introduced at the $L_2$-$L_3$ interspace, while loss of resistance to air was encountered at 60 mm. The subarachnoid space was located using a pencil point spinal needle (27G) following the needle-through-needle technique. After aspirating clear cerebrospinal fluid, 2 ml of 0.75% of ropivacaine with 15μg of fentanyl were administered intrathecally. No pain or paraesthesia was noted. Finally, the epidural catheter was easily inserted and secured at skin, leaving 5 cm in the epidural space. The patient was subsequently placed in a wedged, supine position. A T8 sensory block to pinprick was achieved after five minutes, and this was extended to a T4 block height using two incremental doses of 3 ml lidocaine 2%, administered through the epidural catheter at five minute intervals. Oxygen supplementation was administered via Venturi mask, while $SpO_2$ remained in the range of 98-100%. All cardiovascular parameters remained stable during block development and surgery, without the need of any vasopressors. Arterial blood gases, serum lactate and blood glucose levels were monitored. Her body temperature was maintained between 35.8 and 36.8°C. A healthy boy of 1990 g was delivered with normal Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. Umbilical cord blood gases were normal. Adequate uterine contraction was achieved with oxytocin infusion after delivery of the placenta. Blood loss was approximately 500ml, while urine output was 200ml. The patient received a total of 1500ml of sodium chloride 0.9% and 300ml of dextrose solution during surgery. After the operation, she was transferred to the High Dependency Unit (HDU) for further management. In the afternoon of the first postoperative day and despite regular intravenous administration of ondasentron and adequate rehydration, four episodes of vomiting were reported. The next day, a mild hyponatraemia was successfully treated with additional intravenous administration of 500ml of sodium chloride 0.9%, while she was encouraged to oral intake of an electrolyte replacement solution. Postoperative analgesia was achieved with 2 epidural doses of 3mg of morphine at 12-hour intervals as well as supplemental epidural doses of 6 ml ropivacaine 0.2% at 6-hour intervals, for a total

of 3 days, until the epidural catheter was removed. Paracetamol 1000mg orally 3 times per day and ibuprofen 400mg twice a day were administered. After the caesarean section, she recovered well and on the 7th postsurgical day she was discharged home.

## DISCUSSION

The perioperative management of a parturient with mitochondrial encephalopathy raises important issues to be discussed[5]. Indeed, there are several published cases of anaesthetic approach of pregnancies with mitochondrial diseases of variable clinical patterns[6-7], but this a novel AIFM1 disorder that its anaesthetic implications has not been published before. Only one patient with the same mutation is reported in the ClinVar database of the National Center for Biotechnology Information (NCBI)[8].

Due to the variability in phenotype in mitochondrial disorders, the degree of neurologic, cardiac, muscular and metabolic dysfunction should be assessed and the anaesthetic technique should be clearly individualized[9-10]. After a multidisciplinary team approach, the appropriate time of delivery as well as the choice of anaesthesia must be decided. An elective caesarean delivery may be the preferred method of delivery, since uterine smooth muscle contraction during labor increases stress and therefore lactate production[5]. Additionally, pregnancy-induced increase in metabolic demand and oxygen consumption may exacerbate derangements in acid-base status, so a careful monitoring is imperative[5].

Main perioperative considerations include avoiding prolonged fasting, preventing hypoglycaemia, postoperative nausea and vomiting, hypothermia and shivering, acidosis and hypovolaemia[9]. Electrolyte disturbances are common and although may occur in any stage of the disease, a case of severe hyponatraemia due to surgical stress has been published[11]. Glucose measurement during surgery is also considered necessary because hyperglycaemia may worsen lactic acidosis while hypoglycaemia increases lactate production. Low body temperatures impair mitochondrial function, therefore increase stress so a close monitoring of patient's body temperature is required. Furthermore, lactate-containing intravenous fluids should not be administered due to lack of normal lactate metabolism[9].

Neuraxial anesthesia is generally preferred to avoid multidrug administration, especially neuromuscular blocking agents12. In our case, a titrated neuraxial technique was planned because a controlled sensory block could minimize the stress of a possible respiratory depression and effective postoperative analgesia could be provided through the administration of epidural opioids. Among amide local anaesthetics, ropivacaine and lidocaine are preferred over

bupivacaine because they interfere less with carnitine metabolism.

If general anaesthesia was eventually employed, meticulous attention is required in patients with hypotonia and generalized myopathy, more prone to upper airway obstruction, aspiration, hypoventilation and acidosis[13]. As far as maintenance anaesthetics (intravenous or inhaled) is concerned, a careful titration is mandatory (clinically or based on Bispectral Index), given that some mitochondrial diseases exhibit exquisite sensitivity to some of them. While volatile agents suppress oxidative phosphorylation, their rapid elimination allows re-establishment of mitochondrial function after their discontinuation. Due to multiple mitochondrial effect sites of propofol, it is advised against propofol infusion techniques, while other drugs such as opioids or dexmetomidine are considered to be safe[14-15]. Apart from succinylcholine which is contraindicated in patients with myopathies, nondepolarizing neuromuscular blocking agents should be avoided due to induced exaggerated sensitivity. Effective postoperative analgesia is important to provide early ambulation. Non steroidal anti-inflammatory drugs have also been used, while it is advised against repeated doses of acetaminophen, because of the potential of increased metabolic liver demand. Wound infiltration with local anaesthetics or TAP block are safe and should also be considered[16].

In conclusion, uneventful management of a similar high-risk pregnancy requires consideration of drugs that affect mitochondrial function and ideally an opioid-sparing technique such as a titrated CSE.

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**Author Disclosures:**

Authors Kalopita K, Antsaklis P, Saiti A, Valsamidis D have no conflicts of interest or financial ties to disclose.

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