# Anesthetic Management of Two Patients With m.11232T>C (MT-ND4) Mitochondrial Variant Using Total Intravenous Anesthesia After Sevoflurane Toxicity: A Case Report

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Patients with the m. 11232 T> C MT-ND4 mitochondrial variant may develop catastrophic neurologic injury after sevoflurane exposure. We describe two patients who experienced delayed emergence, basal ganglia injury, dystonia, and cognitive decline after volatile anesthesia, yet later underwent four procedures uneventfully under propofol-based total intravenous anesthesia (TIVA) with remifentanil, dexmedetomidine, and careful metabolic management. These cases, together with recent in vitro data, support volatile-free TIVA as a safer anesthetic strategy for patients with this variant or strong suspicion of sevoflurane-associated toxicity syndrome. (A&A Practice. 2026;20:e02288.)

In 2025 and early 2026, clusters of severe neurologic complications and deaths were reported in previously healthy pediatric and young adult patients of Venezuelan ancestry after elective surgery under general anesthesia. Several national and international societies, including the Chilean Society of Anesthesiology, the Spanish Society of Anesthesia and Reanimation (SEDAR), the American Society of Anesthesiologists (ASA), and the Society for Pediatric Anesthesia (SPA), issued alerts about patients who developed delayed emergence, stupor, movement disorders, and basal ganglia necrosis after exposure to sevoflurane.[1–5]

Subsequent work by Sanz-Pons et al identified a shared mitochondrial DNA haplotype (F-Vh, haplogroup D1b) and several private variants in affected patients, including the m.11232T>C variant in the *MT-ND4* subunit of respiratory complex I and the m.15164T>C variant in *MT-CYB*.[6] The m. 11232 T> C mutation causes a leucine-to-proline substitution (L158P) in ND4, destabilizing the alpha-helix structure of complex I and rendering cells extremely sensitive to volatile anesthetics.[7] In vitro, exposure of cells harboring this variant to sevoflurane reduces oxygen consumption to approximately 10% of normal levels, leading to localized bioenergetic failure in high-metabolic regions such as the basal ganglia, whereas propofol does not produce the same degree of differential inhibition in this specific genetic subset.[6]

Unlike classic mitochondrial syndromes such as MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes), in which anesthetic agents exacerbate preexisting metabolic instability, sevoflurane-associated toxicity syndrome is triggered by volatile exposure in patients who may otherwise be clinically asymptomatic.[8,9] Given emerging evidence that sevoflurane is a specific precipitant in patients with a wide range of mitochondrial diseases, there is an urgent need to define safe anesthetic strategies for individuals carrying the mt.11232>C variant.[10] We present the anesthetic management of two pediatric patients with the m.11232T>C variant who suffered catastrophic neurologic events after sevoflurane anesthesia but subsequently underwent uneventful surgery using TIVA. Both patients were managed at institutions in Venezuela

This manuscript adheres to the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines. Written informed consent for publication of these case reports, including all clinical details, neuroimaging, and any accompanying material, was obtained from the parents/legal guardians of both patients, with assent obtained from the patients where developmentally appropriate. Copies of the signed consent forms are available for review by the Editor-in-Chief of this journal on request.

## CASE DESCRIPTION

### Patient 1

A previously healthy 14-year-old male underwent open reduction and internal fixation of a humeral fracture under sevoflurane anesthesia (end-tidal 2%–3%). The emergence from anesthesia was markedly delayed (approximately 6 hours), followed by stupor, vomiting, and progressive generalized dystonia. Magnetic resonance imaging (MRI) obtained 48 hours postoperatively showed restricted diffusion in the globus pallidus and cerebellum, consistent with basal ganglia and cerebellar injury.

At age 17, he underwent anesthesia with sevoflurane again for the repair of a clavicle fracture. Intraoperatively,

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**Table 1. Sevoflurane-Associated Toxicity**

| Patient | Age/year | Surgical procedure | Adverse event after sevoflurane anesthesia | Documented neurologic sequelae |
|---|---|---|---|---|
| 1 | 14 y | Open reduction and internal fixation of a humeral fracture | Delayed emergence (~6 h), stupor, vomiting | MRI: globus pallidus and cerebellar injury; progressive generalized dystonia |
| 1 | 17 y | Clavicle fracture | Coma for 10 d. Later aggravated dystonia | MRI: global cerebral and cerebellar atrophy |
| 2 | 8 y | Cochlear implant surgery | Very late awakening, progressive generalized dystonia, rigor, and ataxia. | Cranial CT performed on the 5th postoperative day showed evolving ischemic lesions involving both basal ganglia |

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

he developed refractory hypotension requiring vasopressor support and was admitted to the intensive care unit (ICU), resulting in a 10-day comatose state. His postoperative course was complicated by severe dystonia. This patient corresponds to case number 2 in the series described by Sanz-Pons et al.[6]

Based on the clinical suspicion of sevoflurane-related mitochondrial toxicity, subsequent surgeries were performed with TIVA and strict avoidance of volatile anesthetics:

At age 20, the patient underwent removal of the clavicle osteosynthesis material. Anesthesia was induced and maintained with TIVA using propofol and remifentanil administered via target-controlled infusion (TCI). The propofol effect-site target concentration was 3 mcg/mL (Schnider model), and remifentanil was titrated to an effect-site concentration of 4 ng/mL (Minto model). Rocuronium was administered in intermittent boluses. Standard monitors were used, with a fraction of inspired oxygen ($FiO_2$) of 0.5, and the airway was managed with an i-gel laryngeal mask (size 5). Anesthesia time was 50 minutes. Hemodynamics remained stable, and emergence was rapid, without any new neurologic deficits or changes in his baseline dystonia.

At age 26, he underwent an orbital floor repair that lasted 70 minutes. TIVA was again delivered with propofol via TCI (Schnider model), maintaining an effect-site concentration between 3 and 3.5 mcg/mL. Because remifentanil was unavailable at the time of this procedure due to local medication shortages, alternative multimodal adjuncts were used. Adjuncts included magnesium sulfate (2.5 g at induction, then 10 mg/kg/h) and lidocaine (100 mg bolus at induction, then 1.5 mg/kg/h) to achieve opioid-sparing anesthesia and multimodal analgesia, with NMDA receptor modulation. Rocuronium boluses were used as needed, $FiO_2$ was 0.5, and the airway was secured with a 6.0-mm cuffed endotracheal tube. Anesthesia lasted 70 minutes. Hemodynamic stability was maintained, and the postoperative course was uneventful, with no change in his chronic neurologic status.

## Patient 2

Patient 2 was a 14-year-old man with a history of microcephaly and sensorineural hearing loss. At age 8, he underwent cochlear implant surgery under sevoflurane anesthesia at another institution. The postoperative course was complicated by acute neurologic collapse with delayed awakening, stupor, and new-onset dystonia. MRI demonstrated ischemic lesions in the basal ganglia, and he was left with permanent dystonia. No intraoperative neuromonitoring was available at the time of this index event. This patient corresponds to case number 7 in the series by Sanz-Pons et al.[6]

At age 14 (2024), he required a left hip derotational osteotomy with locking compression plate fixation. In light of his previous catastrophic reaction to sevoflurane and the identification of the m.11232T>C mitochondrial variant, a sevoflurane-free technique was planned using TIVA for neuroprotection. Anesthesia was induced and maintained with propofol TCI (Eleveld model) and dexmedetomidine, administered at a maintenance dose spanning 0.3 to 0.7 mcg/kg/h as an adjuvant. Volatile agents were strictly avoided. Standard ASA monitors were applied, $FiO_2$ was maintained at 0.5, and care was taken to avoid hypothermia, hypotension, hypoglycemia, and prolonged fasting. Intraoperative neuromonitoring could not be used during the index procedure because the facility lacked the requisite equipment. Anesthesia lasted 220 minutes. The patient remained hemodynamically stable, emerged without delay, and returned to his preoperative neurologic baseline without any new deficits (Tables 1 and 2; an overview of both cases is provided in the Figure.)

**Table 2. Anesthesia Management With TIVA**

| Patient | Age/year | Surgical procedure | TIVA technique and adjuncts | TCI model/targets | Duration (min) |
|---|---|---|---|---|---|
| 1 | 20/2012 | Removal of clavicle osteosynthetic material | Propofol + remifentanil + Rocuronium | Propofol Schnider 3 µg/mL; Remifentanil Minto 4 ng/mL | 50 |
| 1 | 26/2018 | Orbital floor repair | Propofol TIVA + Magnesium sulfate 2.5 g + 10 mg/kg/h; Lidocaine 100 mg + 1.5 mg/kg/h; Rocuronium boluses | Propofol Schnider 3–3.5 µg/mL | 70 |
| 2 | 14/2024 | Hip derotational osteotomy with LCP plate | Propofol + dexmedetomidine | Propofol Eleveld (effect-site, targets (NR) | 220 |

Abbreviations: NR, not reported; TCI, target-controlled infusion; TIVA, total intravenous anesthesia.


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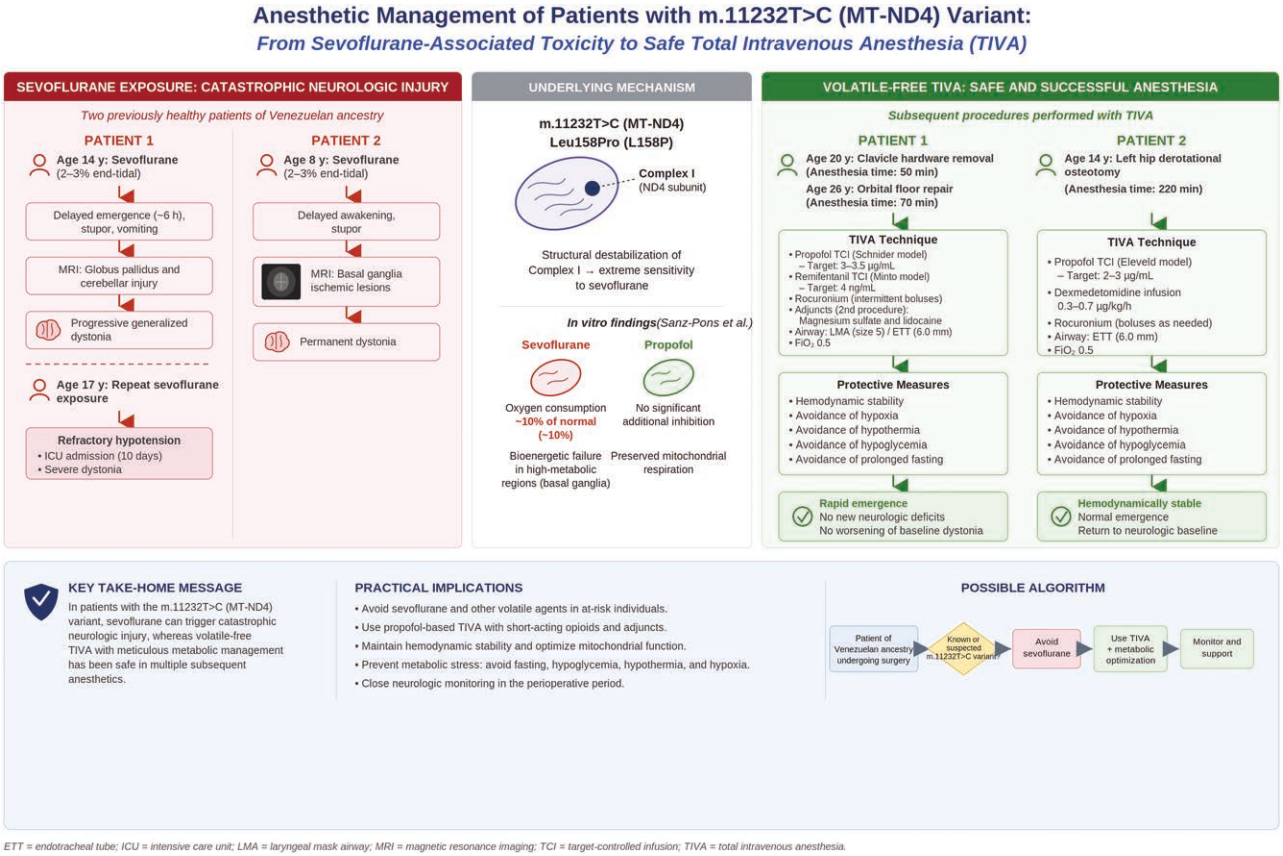



**Figure.** Anesthetic management of two patients with the m.11232T>C (MT-ND4) mitochondrial variant, showing the transition from sevoflurane-associated toxicity to safe volatile-free TIVA. Both previously healthy patients of Venezuelan ancestry developed catastrophic neurologic injury after sevoflurane—delayed emergence, stupor, dystonia, and basal ganglia and cerebellar injury on MRI. The variant causes a leucine-to-proline substitution (L158P) in the ND4 subunit of respiratory complex I, conferring extreme sevoflurane sensitivity; in vitro, sevoflurane reduced oxygen consumption to approximately 10% of normal, whereas propofol preserved mitochondrial respiration (Sanz-Pons et al). Subsequent procedures were performed uneventfully with volatile-free TIVA—propofol TCI with remifentanil, dexmedetomidine, and multimodal adjuncts under meticulous metabolic and hemodynamic management—with rapid emergence and return to neurologic baseline. The lower panel summarizes the key message, practical implications, and a proposed perioperative algorithm. ETT indicates endotracheal tube; ICU, intensive care unit; LMA, laryngeal mask airway; MRI, magnetic resonance imaging; TCI, target-controlled infusion; TIVA, total intravenous anesthesia.

## DISCUSSION

### Pathophysiologic Rationale

The m.11232T>C variant in *MT-ND4* results in an L158P substitution in the ND4 subunit of respiratory complex I, destabilizing the alpha-helical structure and impairing electron transport. In vitro experiments by Sanz-Pons et al demonstrated that, in cells harboring this variant, exposure to sevoflurane markedly suppresses oxygen consumption to approximately 10% of baseline, whereas cells without the mutation show minimal changes.[6] At present, empirical data regarding whether other halogenated agents exert comparable inhibitory effects on respiratory complex I remain unavailable, as the investigation by Sanz-Pons et al focused exclusively on sevoflurane and propofol.[6] This investigative priority likely reflects the global ubiquity of sevoflurane in modern anesthetic practice. Conversely, propofol does not produce the same variant-specific suppression of oxidative phosphorylation, suggesting a unique interaction between sevoflurane and the altered complex I in this genetic background.[6]

The current global distribution of this mitochondrial mutation remains undetermined; however, it is plausible that the variant occurs in other populations worldwide. Existing evidence suggests that the ancestral origin of this variant is localized to north-central Venezuela, specifically within Carabobo state. This geographic link is underscored by the emergence of clinical clusters following the widespread adoption of sevoflurane in 2000 and later.[11]

This pathophysiology contrasts with classic mitochondrial syndromes such as MELAS, in which anesthetic agents can exacerbate global metabolic fragility but are not necessarily uniquely toxic.[9] In sevoflurane-associated toxicity syndrome, the volatile agent acts as the primary trigger of catastrophic neurologic injury in patients who may have been clinically silent until their first anesthetic exposure. Metabolically active structures, such as the basal ganglia and cerebellum, are particularly vulnerable, consistent with the MRI findings in both patients and the in vitro metabolic data.[12]

### Role of TIVA and Propofol

Historically, clinicians have been cautious about using propofol in patients with mitochondrial disease due to concerns


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about propofol-related infusion syndrome (PRIS) and its inhibitory effects on complex I. However, PRIS is associated with prolonged, high-dose infusions in critically ill patients, and emerging data suggest that short-duration TIVA, particularly when combined with multimodal analgesia and careful metabolic management, can be safely administered to diverse populations of individuals with mitochondrial pathologies who are undergoing scheduled elective surgical interventions.[13–15]

In the specific context of the m. 11232 T> C variant, the in vitro data support a differential risk profile: sevoflurane shows pronounced variant-specific toxicity, whereas propofol does not. Our clinical experience aligns with this mechanistic rationale. Both patients suffered catastrophic neurologic events after sevoflurane yet subsequently tolerated multiple surgeries with propofol-based TIVA delivered via TCI, without new neurologic deterioration or metabolic decompensation. Current evidence suggests that the reported anesthetic hypersensitivity is most clearly linked to sevoflurane exposure; however, whether similar mitochondrial toxicity occurs with other volatile agents, such as isoflurane or desflurane, remains unknown, as the available experimental data have primarily examined sevoflurane and propofol. Epidemiologic and genetic studies indicate that the m.11232TC variant shows strong ancestral clustering in north-central Venezuela, particularly in Carabobo State, although global screening has not been systematic. To date, no confirmed reports have demonstrated this variant or the same post-anesthetic neurologic phenotype in populations outside the Venezuelan maternal lineage, so caution remains warranted when extrapolating to other groups.

Through meticulous effect-site titration and the incorporation of multimodal adjuncts—including dexmedetomidine, magnesium sulfate, and lidocaine—to achieve opioid-sparing analgesia, nociception reduction, and NMDA receptor modulation, we established a metabolic and hemodynamic "safe harbor." This comprehensive strategy, coupled with the rigorous avoidance of physiologic perturbations such as hypotension, hypoxia, hypoglycemia, and hyperthermia, served to minimize the perioperative mitochondrial stress in these vulnerable patients.

## Clinical Implications

Since 2025, the ASA, SPA, and other societies have issued joint communications warning anesthesiologists about severe neurologic complications and death after sevoflurane anesthesia in patients of Venezuelan ancestry, many with MRI evidence of basal ganglia necrosis. Clinicians should maintain a high index of suspicion for this mitochondrial variant in patients who present with

1. Unexplained delayed awakening or stupor after previous anesthesia.
2. New-onset dystonia, ataxia, or other movement disorders in the postoperative period.
3. A family history of similar perioperative neurologic events.
4. Ancestry linked to Venezuelan maternal lineages, which underscores how these mitochondrial conditions are passed through the matrilineal line.

In these cases, avoidance of volatile anesthetics, particularly sevoflurane, appears prudent until genetic testing and expert consultation are obtained. TIVA with propofol-based TCI, combined with agents such as remifentanil and dexmedetomidine, and supported by meticulous perioperative metabolic management, may provide a safer alternative. Although our experience is limited to two patients and four TIVA anesthetics, the congruence between the clinical course and mechanistic data supports the use of TIVA as a rational strategy for this vulnerable subgroup.

The collective clinical evidence indicates that the m.11232T>C *MT-ND4* variant may predispose patients to profound sevoflurane-associated neurotoxicity. In individuals presenting with a history of unexplained postoperative stupor or maternal lineages of Venezuelan ancestry, it is prudent to eschew volatile agents in favor of propofol-based TIVA, meticulously titrated and supported by rigorous metabolic support. Complementary risk-mitigation protocols should include

1. Continuous intraoperative electroencephalographic monitoring to assess cerebral function.
2. The thorough decontamination of anesthetic breathing circuits to eliminate residual halogenated vapors.

Proactive identification of this genetic susceptibility is essential to avert catastrophic neurologic sequelae and enhance the safety profile for this at-risk population.

As investigations into this syndrome remain in their preliminary stages, extensive research is required to delineate the regional and global distribution of this mitochondrial mutation. Furthermore, international efforts should prioritize developing accessible genetic screening modalities for use in resource-constrained environments.

Although preoperative genetic screening of pediatric patients would be advisable, such resources may be scarce in low-resource clinical settings. Consequently, we advocate implementing volatile-free TIVA strategies in pediatric cases of Venezuelan ancestry, particularly when there is a family history of delayed emergence. We contend that propofol-based TIVA, supplemented with multimodal adjuncts, provides a robust and safe anesthetic platform even in the absence of definitive genetic confirmation.Alternative intravenous agents, such as ketamine, were not utilized in these cases. Ketamine represents a viable option as it does not appear to impair mitochondrial respiratory complex I. Furthermore, the potential role of regional anesthesia in adolescents and young adults warrants consideration as a component of a volatile-free, multimodal strategy to mitigate perioperative risk.

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