



PERSPECTIVE

Anesthesia-Related Neurologic Risk in Patients of Venezuelan Descent: Implications for Ophthalmology

THOMAS DIEHL, TA CHEN PETER CHANG, GUNEY BADEMCI, ALECIA L.S. STEIN, AND NEIL H. MASTERS

• **PURPOSE:** To alert ophthalmologists to an emerging pattern of catastrophic neurologic injury following general anesthesia in patients of maternal Venezuelan descent, to describe the proposed genetic mechanism, and to provide practical guidance for ophthalmologists regarding this high-risk population.

• **DESIGN:** Perspective

• **SUBJECTS:** Patients of maternal Venezuelan descent who experienced neurologic complications following elective surgical procedures under general anesthesia, including 1 pediatric patient undergoing strabismus surgery who had prior exposure to general anesthesia. Approximately 40 cases have been identified as of April 2026, spanning multiple countries, including the United States, Chile, Germany, Spain, and Guyana.

• **METHODS:** Narrative review of emerging case reports, genetic analyses, and evolving clinical guidance for ophthalmologists pertaining to anesthesia-related neurologic injury in patients carrying the m.11232T>C variant of the mitochondrial gene *MT-ND4*. Recommendations were synthesized and applied to the ophthalmologic clinical context.

• **CONCLUSIONS:** Emerging evidence in the past year has established a consistent clinical pattern and a biologically plausible mechanism for these cases of severe neurologic injury following general anesthesia in otherwise healthy patients of Venezuelan descent. By incorporating targeted screening, ensuring early anesthesiology consultation, and adapting perioperative management, ophthalmologists are in a unique position to help prevent devastating outcomes. (Am J Ophthalmol 2026;289: 129–133. © 2026 Elsevier Inc. All rights are reserved, includ-

ing those for text and data mining, AI training, and similar technologies.)

IN 2025, VARIOUS SOUTH AMERICAN ANESTHESIA medical societies released advisories detailing reports of devastating neurologic complications and brain death in previously healthy patients, primarily children of maternal Venezuelan descent, following elective procedures under general anesthesia.^{1,2} Between July 2025 and April 2026, nearly 40 cases have been identified globally in countries such as Chile, Guyana, the United States, Germany, and Spain in children and young adults originating primarily from the Carabobo state of Venezuela.³ These reports have emerged globally due to the large volume of the Venezuelan diaspora resulting from the Venezuelan political instability of the past 2 decades and the resulting public health crisis.⁴ We submit this notice to the broader ophthalmology community, as this is a global issue that ophthalmologists must carefully consider when managing patients who require general anesthesia. This is of particular concern for ophthalmologists who care for children, as several pediatric ophthalmic conditions (eg, childhood glaucoma, retinoblastoma, and congenital corneal diseases) may require repeated anesthetic exposures.

EMERGING CLINICAL PICTURE

The first published case series originating from the Chilean Ministry of Health comprised 6 children (median age 5 years) and 1 young adult (36 years) who underwent a range of outpatient surgical procedures, such as adenotonsillectomy or inguinal hernia repair. Following the procedures, most patients experienced delayed emergence from anesthesia, followed by neurologic sequelae including altered consciousness, abnormal limb movements, cranial nerve deficits, and dysfunction of the corticospinal tract. In most cases, neurologic symptoms were detected immediately on emergence, though their onset was delayed by up to 10 days in some patients. All patients received the volatile

Accepted for publication May 9, 2026.

From the University of Miami Miller School of Medicine, Miami, Florida, USA (T.D.); Department of Ophthalmology, Bascom Palmer Eye Institute (T.C.P.C.); Department of Human Genetics, Hussman Institute of Human Genetics (G.B.); Department of Anesthesiology (A.L.S.S., N.H.M.), University of Miami Miller School of Medicine, Miami, Florida, USA.

Inquiries to Neil H. Masters, University of Miami Miller School of Medicine, Miami, Florida 33136, USA; e-mail: nhmasters@med.miami.edu

anesthetic gas sevoflurane and fentanyl, but many also received the intravenous anesthetic agent propofol. Subsequent neuroimaging revealed bilateral basal ganglion lesions with additional findings involving the cerebellum and deep gray matter structures, suggestive of hypoxic-ischemic encephalopathy.⁵ Of the 7 patients, 4 progressed to global cerebral edema and eventual brain death. Although most cases have occurred in children, another recently published case involving a 20-year-old woman confirms that the risk is not strictly limited to the pediatric population.⁶

In response to heightened sensitivity, additional cases have come to light worldwide, including one involving a 6-year-old boy undergoing strabismus surgery who had previously tolerated general anesthesia in his native Venezuela without complications.⁷ Despite an uneventful procedure, he never regained consciousness after anesthesia, and neuroimaging revealed evidence of increased intracranial pressure and diffuse hypodensity of the cerebellum and bilateral basal ganglia. Although there is currently only a single reported case during ophthalmic surgery, this topic is evolving at a rapid pace.

GENETIC RISK FACTORS

There is increasing evidence that these complications are, in part, associated with the presence of the m.11232T>C variant in the mitochondrial gene *MT-ND4*, a mutation with a probable founder effect in the Carabobo state in Venezuela.⁸ Of the 14 initially reported cases, 10 underwent genetic testing, and all carried this variant, which is extremely rare elsewhere.⁹ As more cases are recognized, additional patients are testing positive. The *MT-ND4* gene encodes a subunit of complex I of the electron transport chain; importantly, this gene is maternally inherited.¹⁰ Because the *MT-ND4* gene is integral to complex I function, the m.11232T>C variant likely impairs oxidative phosphorylation in neurons.¹¹ This impairment is clinically significant because sevoflurane, an agent widely used for the induction and maintenance of general anesthesia in both children and adults, directly inhibits complex I.¹² In patients carrying this variant, sevoflurane's inhibition of complex I may compromise mitochondrial function, leading to suppression of mitochondrial oxygen consumption and plausibly explaining the neuroimaging findings of ischemic changes in many of these patients.^{5,10} The selective vulnerability of the basal ganglia and deep gray matter is consistent with the well-established pattern of injury observed in other mitochondrial complex I disorders, such as Leigh syndrome, wherein structures with the highest oxidative metabolic demand are preferentially injured under conditions of impaired mitochondrial respiration.

All reported cases as of April 2026 were exposed to sevoflurane. Although propofol was co-administered in many cases, 1 study published in *Anesthesiology* revealed

that a subset of patients with the *MT-ND4* variant had previously tolerated propofol-based total intravenous anesthesia without complications, suggesting that this phenomenon may be specific to halogenated volatile anesthetics (eg, sevoflurane, isoflurane, and desflurane) rather than all inhaled anesthetics, as nitrous oxide does not seem to share this risk.¹⁰ This same study's in vitro analysis also showed that cell lines with the variant demonstrated significant suppression of mitochondrial oxygen consumption when exposed to sevoflurane but not with propofol or other controls.¹⁰

Current guidance, therefore, suggests the use of intravenous anesthetic agents such as propofol or ketamine as a safer alternative to volatile agents, although the risk is still considered moderate given propofol's use in several affected cases.¹³ Furthermore, although several cases occurred during a patient's first exposure to anesthesia, many affected patients, such as the strabismus case discussed earlier, had previously tolerated general anesthesia with volatile agents. These observations suggest that prior tolerance of volatile agents neither excludes the presence of this variant nor eliminates the risk of these neurologic complications. Therefore, neither a negative family history of anesthetic complications nor a personal history of prior general anesthesia should be considered reassuring.

OPHTHALMOLOGY'S UNIQUE POSITION

This emerging clinical picture has important implications for ophthalmologists. Although ophthalmologists may be accustomed to reassuring patients based on prior anesthetic tolerance, greater caution is warranted in patients of maternal Venezuelan descent. Unlike emergency surgical settings, many ophthalmic procedures are elective in nature, providing a critical window for risk stratification and intervention. Historically, the literature on ophthalmic anesthesia has suggested that a single brief anesthetic exposure is unlikely to lead to long-term neurodevelopmental deficits in children or young adults.¹⁴ However, the growing recognition of this variant, particularly in the pediatric population, necessitates a reassessment of this assumption in this specific, high-risk subgroup. This reassessment aligns with a broader emphasis in the ophthalmology literature on personalizing anesthetic approaches to the individual patient.¹⁴

PRACTICAL GUIDANCE FOR OPHTHALMOLOGISTS

- **PREOPERATIVE:** Before scheduling surgery, ophthalmologists should screen patients with a brief question about ma-

TABLE. Perioperative Considerations for Ophthalmologists Managing Patients of Maternal Venezuelan Descent.

Phase	Recommendations
Preoperative	• Screen all patients with a brief maternal ancestry question • Inquire about personal and family history of adverse anesthesia events (eg, delayed emergence and prolonged sedation) • If history is positive, consult anesthesiology before scheduling surgery and consider referral for genetic testing • If genetic testing is not feasible, prioritize anticipatory perioperative planning
Intraoperative	• Consider avoiding all volatile anesthetic agents in patients with maternal Venezuelan ancestry • Use TIVA with continuous depth-of-anesthesia monitoring • Favor regional anesthesia techniques and local anesthesia with sedation whenever clinically appropriate
Postoperative	• Monitor for delayed emergence, altered mental status, or new neurologic deficits • Report cases through the Anesthesia Quality Institute registry

TIVA = total intravenous anesthesia.

ternal ancestry and a family history inquiry about events under anesthesia, such as delayed awakenings.¹⁵ Any patient with maternal Venezuelan lineage or a personal or family history of events under anesthesia should ideally receive an anesthesiology consultation before surgery is scheduled. When screening result is positive, genetic testing should be considered, particularly for elective cases. Laboratories must be specifically instructed to report whether the m.11232T>C variant of *MT-ND4* is present or absent, as it has historically been flagged as a variant of uncertain significance or of nonpathologic significance.¹⁵ Patients carrying the variant would benefit from genetic consultation or referral, and cascade screening in the maternal lineage should be considered for all carriers. When anesthesiology consultation or genetic testing is impractical or unavailable, those with positive screening results should be managed with the assumption that the variant is present, and sevoflurane should be avoided.

• **INTRAOPERATIVE:** Current guidance recommends avoiding all volatile anesthetics in patients with maternal Venezuelan lineage unless the presence of the *MT-ND4* variant is ruled out via genetic testing.^{9,15} The recommended approach is total intravenous anesthesia, avoidance of extreme anesthesia depths, and the use of depth-of-anesthesia monitoring via processed electroencephalogram devices.¹⁵ Regional anesthesia techniques are also important to consider. Ophthalmology already offers several options, such as peribulbar, retrobulbar, and sub-Tenon blocks, which can safely reduce or eliminate volatile agent requirements in cooperative patients.¹⁴ For specific pediatric cases, local anesthesia with sedation may be an option worth discussing with pediatric anesthesia colleagues. Guidance also speaks to the surgical setting for patients identified as being at highest risk; these patients should not undergo surgery in an outpatient ambulatory setting but rather in a hospital surgical setting where appropriate monitoring can take place.

• **POSTOPERATIVE:** Postoperatively, monitor patients for any delay in emergence, altered mental status, or new neurologic findings. Treat any of these findings in a patient of maternal Venezuelan descent as an adverse event and prompt for a neurologic evaluation. Report cases through the Anesthesia Quality Institute and any relevant institutional or national ophthalmology adverse event registries. The [Table](#) provides a concise summary of these perioperative recommendations, organized by perioperative phase, for quick reference at the point of care.

CULTURAL SENSITIVITY IN SCREENING

When screening patients for maternal Venezuelan ancestry, it is important to keep in mind that many patients may be reluctant to disclose their country of origin for fear that it may affect their treatment or immigration status. This may be of particular concern for patients who are not native English speakers. It should be established early on that this question pertains solely to the safety of the patient rather than to something broader. We have found success by asking directly about maternal Venezuelan ancestry and framing the question by explaining that there is a very specific mutation in the population that can pose risks for anesthesia.

CONCLUDING REMARKS

Significant uncertainties remain regarding this rare genetic variant and the potentially associated severe postanesthetic neurologic sequelae. The true prevalence among Venezuelan-descended populations in the United States and worldwide is unknown; however, the *MT-ND4* variant is very rare, and the anesthetic exposure threshold for

sevoflurane-induced injury remains uncertain, though it seems to be dose- and time-dependent. The influence of heteroplasmy level on risk and the safety profile of other anesthetics in this population remains unclear and should be prioritized in future research. Additionally, considering the emerging nature of this concern, ophthalmology-specific data regarding this variant essentially do not exist. Nevertheless, evidence in the past year has established a consistent clinical pattern and a biologically plausible mechanism linking this mitochondrial variant to catastrophic neurologic injury following general anesthesia with sevoflurane in otherwise healthy patients of Venezuelan descent. Ophthalmologists are uniquely positioned to mitigate this risk. By incorporating targeted screening and genetic testing, ensuring early anesthesiologist consultation,

and adapting perioperative management, they can help to reduce the risk of devastating postanesthetic outcomes.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Thomas Diehl: Writing – review & editing, Writing – original draft. **Ta Chen Peter Chang:** Writing – review & editing, Writing – original draft. **Guney Bademci:** Writing – review & editing, Writing – original draft. **Alecia L.S. Stein:** Writing – review & editing, Writing – original draft. **Neil H. Masters:** Writing – review & editing, Writing – original draft.

Funding/Support: This study received no funding.

Financial Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors attest that they meet the current ICMJE criteria for authorship.

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