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Special Alert

Mitochondrial Genetic Susceptibility to Anesthetics in Patients with Venezuelan Heritage

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On January 27th, the American Society of Anesthesiologists (ASA) and Society of Pediatric Anesthesia (SPA) released their 2nd Consensus Statement regarding a group of unexpected deaths or severe neurological outcomes in patients of Venezuelan lineage—predominantly children— who had undergone uncomplicated general anesthetics for routine surgical procedures. These incidents are believed to be due to the administration of sevoflurane in patents with a mitochondrial mutation.[1] The Chilean Society of Anesthesiology and the Chilean Ministry of Health have reported these cases in a Letter to the Editor[2] and one non-peer-reviewed article has been published.[3]

Background

In July of 2025, the Chilean Society of Anesthesiology reported on six clinical cases of pediatric patients between 2021 and 2025 who, after their respective elective surgical interventions without incidents, presented severe neurological compromise or did not wake up. In addition, the Spanish Society of Anesthesiology, Resuscitation and Pain Therapy recognized an international

cohort of patients with similar conditions—including some adults—in Chile, Guyana, the United States, Germany and Spain. Some sources estimate the total to be approximately 36 cases worldwide. Almost all the affected patients received sevoflurane, but the duration and concentrations were unknown. Neuroimaging findings across these cases frequently involved **bilateral basal ganglion lesions** with additional involvement of the cerebellum, substantia nigra and other deep gray matter structures—thus suggesting hypoxic–ischemic encephalopathy.

Detailed family histories of the patients who had been recently affected revealed that *all* were of **Venezuelan heritage**. In addition, several had family members with a history of adverse outcomes after an otherwise uneventful general anesthetic.

Genetic testing performed on a subset of these patients identified multiple mitochondrial mutations, including one that is believed to be responsible for these deaths and adverse events: a point mutation of the NADH dehydrogenase 4 (ND4) gene (mtND4 m.11232T>C), which is a **subunit of complex I** of the mitochondrial electron transport chain. Complex I is a **known target** of volatile anesthetics—and is also known to be **inhibited by propofol**. Prior work has shown that impaired complex I activity correlates with hypersensitivity to volatile anesthetics in both animals and humans. ND4 is a protein subunit of complex I that is maternally inherited through mitochondrial DNA.

In this population, patients expressing the mutant gene do *not* appear to exhibit significant signs of mitochondrial dysfunction **until anesthetic exposure**.

Inhibition of complex I by volatile anesthetics can decrease ATP production, thereby suppressing central nervous system activity. As of late 2025, there have been no *formally reported* or documented cases in Venezuela—but we expect more information to be published soon. At the Venezuelan Congress of Anesthesiology in November of 2025, authors of a related research study presented the keynote speech. They discussed a series of eight patients with similar outcomes, five of whom were operated on in Venezuela from 2003 to 2025.[4]

The authors went on to describe the mitochondrial DNA variant thought to be responsible for these patients' neurological outcomes; and presented laboratory studies. In this *in vitro* study, exposure to sevoflurane in cells with the mutation caused a 90% drop in oxygen consumption—leading to immediate energy collapse. Although propofol can also affect mitochondrial bioenergetics, it does so through pathways that do *not* interact destructively with this specific structural defect. In the same laboratory study where sevoflurane was lethal to mutant cells, propofol behaved benignly. At clinical concentrations (< 0.06 mM), propofol did not cause a significant decrease in oxygen consumption nor showed differences between healthy cells and those carrying the mutation.

Mitochondrial DNA inheritance is maternal, although there is modulation of mitochondrial DNA by nuclear DNA. This could explain why there may be people with the mutation who might not manifest susceptibility, even when exposed to the trigger.

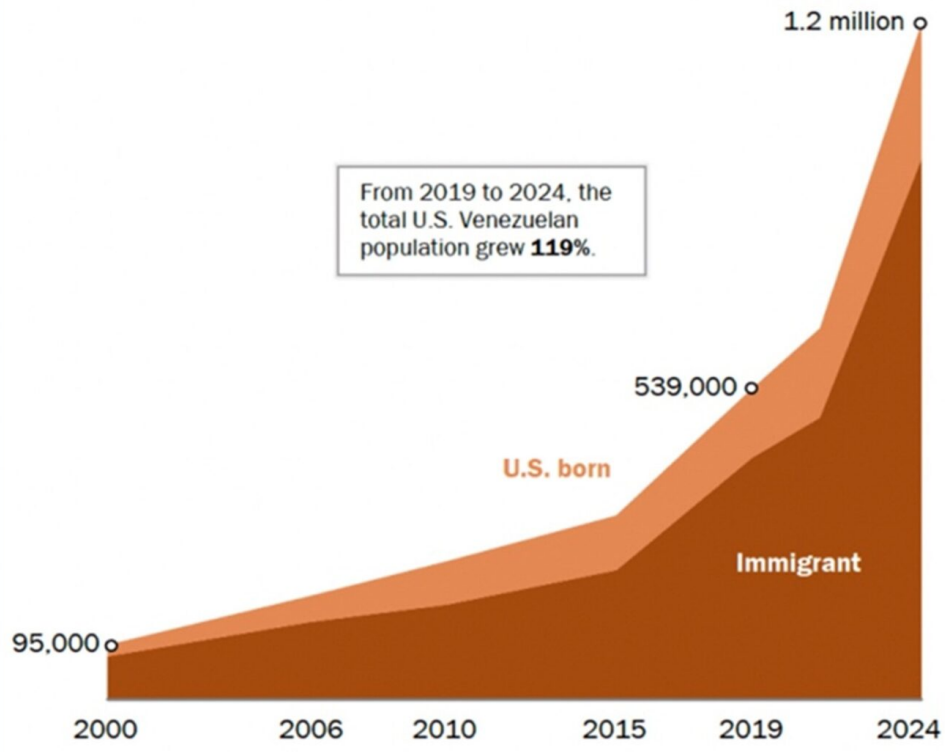
For at-risk patients, there is a laboratory test that can **diagnose this mutation** via a targeted testing looking only at the specific mitochondrial variant of interest: m.11232T>C in ND4, using either blood or a buccal swab.

The potential for underreported and underrecognized cases must be acknowledged and at this time, assumed. Fortunately, this is likely an extremely infrequent condition. Sevoflurane is the most widely used inhalational anesthetic in the world. According to data presented to the World Health Organization (WHO) for inclusion in the **List of Essential Medicines**, it is estimated that from its introduction until January 2022, almost **1.2 billion patients** have received anesthesia with sevoflurane globally. Even in Venezuela, the incidence of this mutation is thought to be very low, with people originating from the Carabobo State believed to have a 15-fold higher risk than the general Venezuelan population.

If complications occur in patients with the ND4 mutation, anesthesiologists should report the case to their institutions' patient safety organization and the Anesthesia Quality Institute's Anesthesia Incident Reporting System (AIRS): https://www.asahq.org/aqi/registries/airs

U.S. Venezuelans reached nearly 1.2 million in 2024

U.S. Hispanic population of Venezuelan origin, by nativity

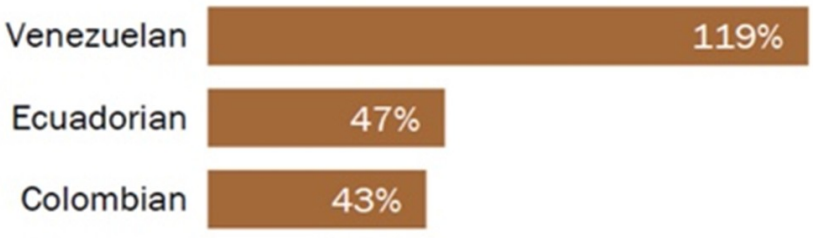


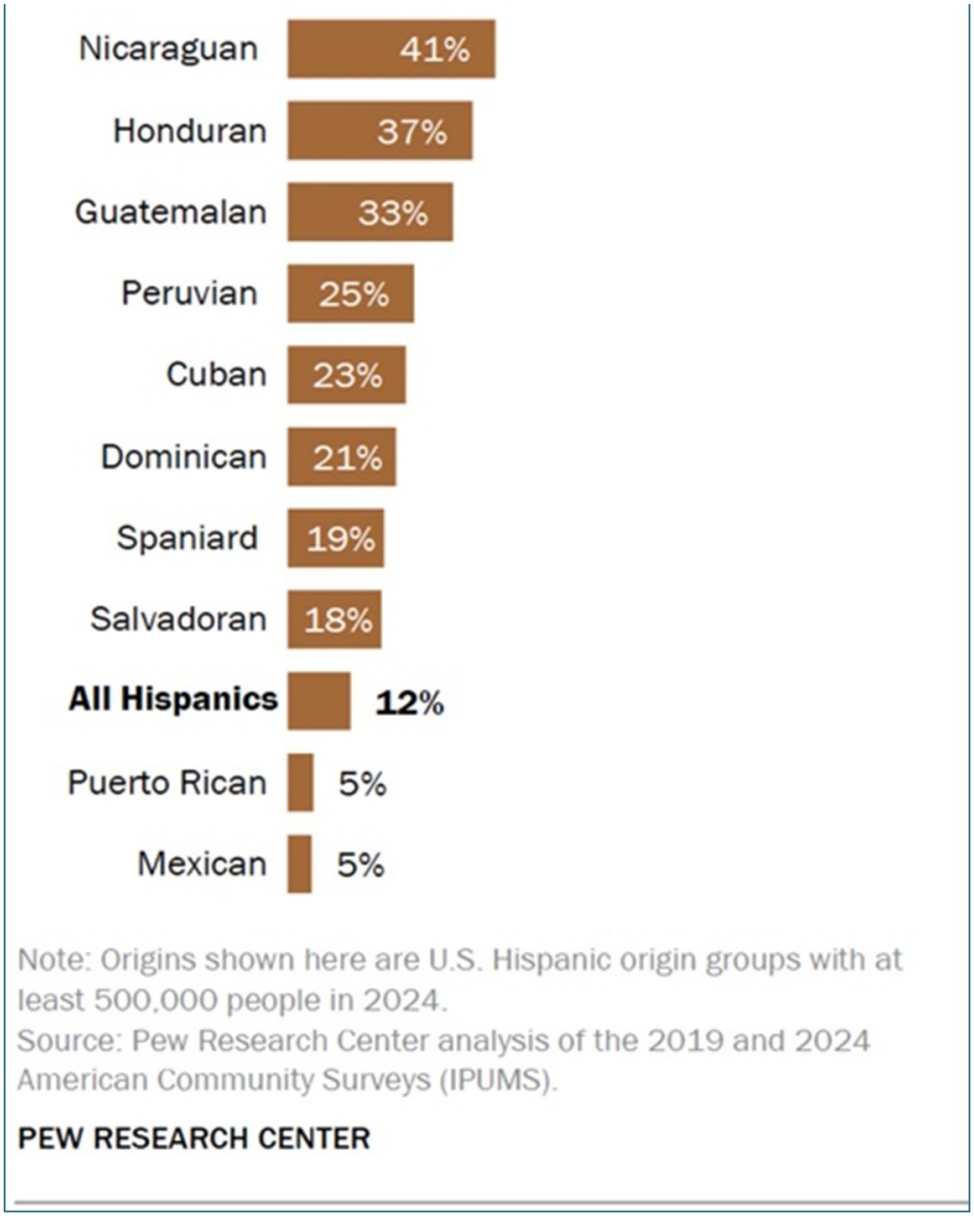
Source: Pew Research Center analysis of the American Community Survey for 2024, 2021, 2019, 2015, 2010 and 2006 (IPUMS) and 2000 decennial census 1% sample (IPUMS).

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U.S. Venezuelan population has grown much faster than other Hispanic groups

% increase in U.S. Hispanic populations from 2019 to 2024, by origin group





Clinical

While understanding the **genetic background** is essential, the *greater* challenge lies in translating that knowledge into informed clinical **decision-making**.

Many clinicians have incorporated targeted questions into their preoperative evaluations to identify patients with potential familial ties to Venezuela. Particular attention is directed toward maternal family history and any previously reported adverse anesthetic outcomes. When such a history is elicited, the

question becomes how best to operationalize this information in perioperative planning.

Practice patterns across New York State remain variable.

- In predominantly office-based and ambulatory surgery center settings, cases involving at-risk individuals are frequently postponed and rescheduled for *hospital-based* facilities that offer greater resources.
- When the procedure is elective, patients are often referred for genetic screening prior to surgery. However, this strategy is not feasible in urgent or time-sensitive cases—necessitating an empiric management approach.

Many anesthesiologists elect to manage these patients in the same way as one would a patient potentially susceptible to Malignant Hyperthermia, thus avoiding inhaled volatile anesthetic agents.

Informal discussions with providers across the state who have encountered this issue reveal **differing approaches** to the conduct of general anesthesia.

- Some clinicians limit propofol infusions to shorter procedures, typically those anticipated to last less than two hours.
- Others report comfort with propofol-based total intravenous anesthesia (TIVA) irrespective of surgical duration—citing its favorable pharmacologic profile in this context.

Midazolam, dexmedetomidine, ketamine and opiates can be added as adjusts to maintain anesthesia and have not been implicated. But greater variability emerges when regional anesthesia is contraindicated or insufficient for the planned procedure.

The routine use of processed electroencephalographic (EEG) monitoring to assess depth of anesthesia—or detect burst suppression—has not been widely described in current practice patterns.

Patients at risk should be monitored for extended period to assess return to their neurocognitive baseline. Extended post-operative observation and monitoring of acid-base status should be considered if clinical complications are

suspected.

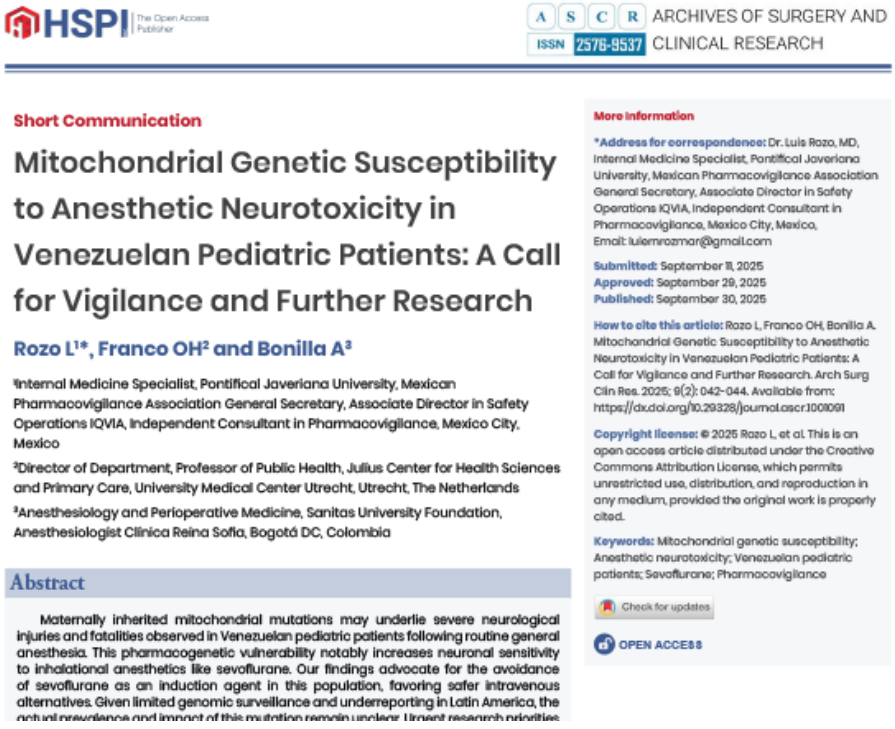
Conclusion

This issue remains actively under investigation—and at present, there is far more unknown than known. Until more robust scientific data with specific laboratory testing becomes available, anesthesiologists should approach this concern with vigilance. Heightened awareness is appropriate, particularly when caring for patients with maternal Venezuelan ancestry or with a strong family history suggestive of anesthetic complications. A thorough preoperative evaluation, clear communication with patients and families and individualized anesthetic planning are essential. Based on current clinical case reports and expert consensus, sevoflurane and other volatile anesthetics should be avoided—and the management of the case should be treated with precautions like malignant hyperthermia.

Ongoing case reporting and future research on genomic sequencing, metabolic profile and mitochondrial enzyme analysis along with systematic data collection will be essential in understanding this phenomenon more broadly. Until more evidence becomes available, anesthesiologists should continue to rely on sound clinical judgement, meticulous physiological management and a patient-centered approach to perioperative care.

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Short Communication

Mitochondrial Genetic Susceptibility to Anesthetic Neurotoxicity in Venezuelan Pediatric Patients: A Call for Vigilance and Further Research

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Abstract

Maternally inherited mitochondrial mutations may underlie severe neurological injuries and fatalities observed in Venezuelan pediatric patients following routine general anesthesia. This pharmacogenetic vulnerability notably increases neuronal sensitivity to inhalational anesthetics like sevoflurane. Our findings advocate for the avoidance of sevoflurane as an induction agent in this population, favoring safer intravenous alternatives. Given limited genomic surveillance and underreporting in Latin America, the actual prevalence and impact of this mutation remain unclear. Urgent research priorities

More information

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Keywords: Mitochondrial genetic susceptibility; Anesthetic neurotoxicity; Venezuelan pediatric patients; Sevoflurane; Pharmacovigilance

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include comprehensive genomic sequencing, metabolic profiling, and pharmacokinetic studies to clarify the mutation's role and guide anesthetic management. Immediate clinical measures should incorporate enhanced perioperative vigilance and family history assessment. To mitigate this emerging risk, strengthened transnational pharmacovigilance cooperation and capacity building in genomic diagnostics are essential. This work underscores the need for heightened awareness, diagnostic preparedness, and preventative strategies to protect genetically predisposed pediatric patients from anesthesia-related neurotoxicity.

Introduction

Several Venezuelan children, who were previously healthy, experienced severe brain injuries or died after undergoing routine surgeries with general anesthesia. These tragic events occurred despite the surgeries and anesthetic procedures appearing normal. After examining the cases, the authors believe the children may carry an inherited change in their mitochondrial DNA—a type of genetic material passed down from mothers—which affects how their cells produce energy. This inherited condition can make their brains extremely sensitive to certain anesthetic gases, particularly sevoflurane. Similar cases have been reported in Spain, suggesting that certain genetic traits may be more common in specific populations. The authors recommend avoiding this anesthetic in Venezuelan children until more is known and instead using safer alternatives. They also suggest that families be carefully evaluated for any history of related problems. Further research is urgently needed to identify the genetic cause, improve testing, and guide safer anesthesia practices. Because many countries in Latin America lack strong systems for tracking such medical problems, the full extent of the risk may not yet be known. This study calls for better international cooperation, genetic testing tools, and early reporting to prevent future harm.

Scientific comment

The reported cases of severe postoperative neurological injury and death in previously healthy Venezuelan pediatric patients following uneventful anesthesia suggest a maternally

LETTER TO THE EDITOR

Potential Mitochondrial Pharmacogenetic Susceptibility to Severe Neurologic Events after General Anesthesia: Report from the Chilean Ministry of Health

To the Editor:

On July 15, 2025, the Chilean Society of Anesthesiology (Santiago, Chile) reported on its institutional Web site five cases of previously healthy children who developed severe neurologic injury after elective surgery under general anesthesia performed in Chile between 2021 and 2025, four of whom subsequently died. All affected children were born to mothers of Venezuelan descent.

In response to these events, the Chilean Ministry of Health (Santiago, Chile) activated a surveillance measure instructing healthcare providers to report any patient—regardless of age or origin—who, since 2021, had died from a neurologic cause or developed neurologic damage after general anesthesia, whether inhaled or intravenous, for any surgical or medical procedure.[1]

Within 1 week of activating the surveillance system, two additional cases were identified, including one adult. In line with its mandate to safeguard public health, the Chilean Ministry of Health collected and reviewed the clinical records of all reported cases for analysis. Additional data from birth, death, and hospitalization registries were checked from administrative databases to enhance the case analyses. To the best of our knowledge, this letter provides the first documented description of these events

The initial case series includes seven patients—six children and one adult— with a median age of 5 yr (range, 1 to 36 yr), five of whom were male, all having a Venezuelan mother, who developed severe neurologic complications or death after surgical or diagnostic procedures performed under general anesthesia. Cases were considered unrelated based on absence of shared identifiers in national civil registries; however, distant maternal relatedness cannot be ruled out. The primary event was considered the surgery

Table 1 summarizes the data of the primary event for these patients.

The surgical procedures included one case of dermoepidermal graft, one flexor tendon repair, one video-assisted thoracoscopy surgery, one adenotonsillectomy, one comprehensive dental restoration, and two cases of inguinal hernia repair. All patients received sevoflurane (median dose, 0.95 minimum alveolar concentration [MAC]; range, 0.70 to 1.60 MAC). Six patients (86%) received propofol (median, 2.02 mg/kg; range, 1.81 to 3.42 mg/kg), and all (100%) received fentanyl (median, 2.5 μg/kg; range, 1.92 to 2.89 μg/kg).

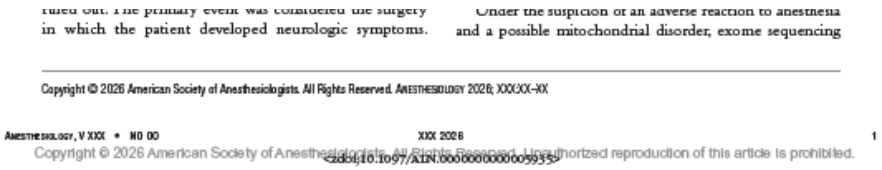
After the procedure, most patients experienced delayed emergence from anesthesia and a range of neurologic manifestations, including altered states of consciousness ranging from drowsiness to coma, abnormal limb movements, deep tendon abnormal reflexes, cranial nerve deficit, dysfunction of the corticospinal tract, and extrapyramidal syndrome. Neurologic symptoms developed after the first anesthetic exposure in six patients and after the second exposure in one patient. The latency to symptom onset ranged from 0 to 10 days, with most cases manifesting immediately upon emergence from anesthesia.

Four patients progressed to a severe clinical course, with intracranial hypertension secondary to cerebral edema, ultimately resulting in death, with a median time interval to death of 9.5 days (range, 1 to 22 days). Three cases were classified as hypoxic–ischemic encephalopathy and one as cerebral edema. Three patients developed severe cognitive and motor neurologic sequelae. Neuroimaging findings across cases frequently involved bilateral basal ganglion lesions with additional involvement of the cerebellum, substantia nigra, and other deep gray matter structures, suggesting hypoxic–ischemic encephalopathy.

In one case, malignant hyperthermia was suspected. However, both exome sequencing and targeted testing for the three common malignant hyperthermia genes (ryanodine receptor 1 [*RYR1*], calcium voltage-gated channel subunit alpha1 S [*CACNA1S*], and SH3 and cysteine rich domain 3 [*STAC3*]) yielded negative results. In another case, cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion syndrome was identified, illustrating a possible overlap of clinical manifestations.

In addition, clinical audits were conducted by local health provider committees for four cases. In general, audits have ruled out equipment malfunction, drug failure, and deviations from intraoperative clinical protocols or anesthesia procedures. None of these cases had a suspected or confirmed diagnosis of mitochondrial disease before the event, and suspicion became a diagnosis of exclusion.

Under the suspicion of an adverse reaction to anesthesia


failed out. The primary event was considered the surgery in which the patient developed neurologic symptoms. Under the suspicion of an adverse reaction to anesthesia and a possible mitochondrial disorder, exome sequencing

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