English Statement

SOCIEDAD
VENEZOLANA
DE ANESTESIOLOGIA

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Information statement from the Venezuelan Society of Anesthesiology regarding susceptibility to general anesthetics in patients of Venezuelan origin

Social media and the news media shape the narrative used by a large part of the community. This flood of messages often generates considerable anxiety within the medical community and the general public. **Our intention with this statement is to reassure the public** and encourage a healthy dose of anticipation within the medical community, awaiting further scientific evidence to understand this rare and novel phenomenon that requires appropriate explanations.

What do we know about this problem?

In July 2025, the Chilean Society of Anesthesiology reported six clinical cases of pediatric patients who, following uneventful elective surgical procedures, presented with severe neurological impairment or failed to regain consciousness. Fifteen days later, the Spanish Society of Anesthesiology, Resuscitation, and Pain Therapy recognized an international cohort of patients with similar conditions: Chile (6), Guyana (1), USA (2), Germany (2), and Spain (3).

The American Association of Anesthesiologists and the Society of Pediatric Anesthesia issued a joint statement in January of this year expressing a clinical alert regarding cases of patients with severe neurological sequelae following routine anesthesia. In their official statement, the ASA and the SPA do not specify an exact numerical figure.They merely confirm qualitatively that, following the initial reports in South America,"Additional cases have been identified in Europe and the United States". Scientific societies emphasize that detailed clinical information is limited because much of it has been shared through personal communications and non-peer-reviewed publications, and access to complete records is restricted by health information protection laws. However, the Spanish Society of Anesthesiology reported four cases in the US, two of which were genetically confirmed.

And in Venezuela?

In a 2025 statement, the SVA reported that there were no cases formally. These cases are neither documented nor reported. Some specialists, in personal communications, are aware of patients with similar outcomes. And in a research paper presented as a keynote address at the Venezuelan Congress of Anesthesiology in November 2025, the authors presented a series of eight patients, five of whom underwent surgery in Venezuela. This work will soon be published in an indexed anesthesiology journal. This discrepancy between the figures recognized by the Venezuelan Society of Anesthesiology (SVA) in July 2025 and the events reported by the authors of the research paper highlights the complexity of underreporting and the importance of this work in making visible a clinical reality that has gone unnoticed or not officially reported.

Do we know the cause of this situation?

The research paper presented at the Congress describes a variant of mitochondrial DNA (mtND4 m.11232T>C). This generates instability in the protein involved in energy production, particularly in high-energy-consumption cells, such as neurons in the central nervous system, when exposed to inhaled anesthetics; in this study, sevoflurane was specifically examined. In vitro exposure to sevoflurane in cells with the mutation caused a drop of 90% 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 the mutant cells, propofol behaved benignly. At clinical concentrations (< 0.06 mM), propofol did not cause a significant decrease in oxygen consumption and showed no differences between healthy cells and those carrying the Venezuelan mutation.

Mitochondrial DNA is inherited maternally, although there is modulation of mitochondrial DNA by nuclear DNA, which may explain why some people with the mutation may not show susceptibility, even when faced with the trigger.

In the general world population (outside of the specific Venezuelan lineage), the variant is virtually unknown. The variant has not been reported in any of the 285,539 sequences analyzed in MITOMAP (the reference database for the human mitochondrial genome) nor in more than 250,000 controls from additional samples around the world. This confirms that it is not a common polymorphism, but a very specific, private mutation that is not circulating in the general European, Asian, or North American populations. Even within Venezuela, the variant does not appear to be ubiquitous, making it difficult to detect without a targeted search. The variant was not found in a review of 414 venezuelan individuals from the existing medical literature, nor in the 71 venezuelan controls specifically analyzed by the research team.

Of the eight patients presented in the main cohort of the study (which includes cases in Venezuela, the USA, Germany and Spain), in five (5) they were able to trace their direct maternal lineage to Carabobo State. It is estimated that the specific mitochondrial haplotype containing the mutation is **15 times more common in Carabobo** than in the rest of Venezuela. The epidemiological importance of this geographic location lies in the fact that if the variant were random or uniformly distributed, the mathematical probability of randomly finding 8 affected patients who share exactly this same mitochondrial haplotype would be from one in 3.1×10^{21} (a number with 21 zeros).

We must say that we are most likely dealing with an extremely rare condition. Sevoflurane is the most widely used inhalational anesthetic in the world due to its safety profile and rapid recovery. According to data submitted to the World Health Organization (WHO) for inclusion in the List of Essential Medicines: It is estimated that, from its introduction until January 2022, more than **1.194 billion patients**. Nearly 1.2 billion people worldwide have received sevoflurane anesthesia. This figure of over one billion successful uses contrasts with the rarity of serious adverse events, underscoring that the recently discovered mitochondrial toxicity is a phenomenon of **ultra-low frequency pharmacogenetics.**

Is it possible to detect this mutation before surgery?

We must conduct a targeted medical history. This is the highest-performing preoperative screening tool. Since the child's physical phenotype is irrelevant (children may be blond, brunette, or of mixed race due to the mixing of nuclear DNA), we must trace the origin of the mitochondria.

The question isn't just the child's nationality, but where are their mother and maternal grandmother from? Mitochondrial DNA is inherited exclusively through the maternal line. If the maternal line comes from the State of Carabobo, the pre-test risk increases exponentially (it is estimated to be 15 times more frequent in this area due to the founder effect).

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The traditional medical history of "anesthesia allergies?" is insufficient. We must actively inquire about the clinical expression of mitochondrial dysfunction in the maternal family, which is often subtle or misinterpreted.

The Sign of "Late Awakening": Ask specifically: Did any of your maternal relatives take a long time to wake up, become very weak, or go to intensive care 'as a precaution' after surgery?. This delayed awakening is often the clinical manifestation of a mitochondrial energy crisis in patients who survived the exposure.

Sudden Death or Unexplained Events: Inquire about the deaths of maternal cousins or uncles in childhood following minor procedures.
Although affected children are usually healthy (silent phenotype), look for a history of chronic fatigue, ptosis (drooping eyelids), severe migraines, or exercise intolerance in the mother or siblings, which may suggest an underlying mitochondrial disease.

Currently, there is no rapid point-of-care test that provides immediate results in the operating room. However, specific laboratory methods exist to identify the variant.m.11232T>C in the gene MT-ND4. According to current evidence:

1. Confirmatory Genetic Tests

There are two main methods for identifying the mutation, which can be performed using samples of blood or, less invasively, through a buccal swab (saliva sample).

- PCR-RFLP (Restriction Fragment Length Polymorphisms): This option can be performed in many standard molecular biology laboratories. It is a test specifically designed to detect this point mutation. Its limitation is that it cannot process hundreds of samples simultaneously as quickly as massive parallel sequencing, but it is very effective for individual diagnosis.
- Sequencing (Sanger or NGS):It is the definitive method. It allows reading the complete mitochondrial genetic code or gene ND4. Specifically, massive sequencing allows for the study of many patients daily, although it requires laboratories with more advanced technological equipment.

2. Metabolic Biomarkers (Indirect Screening):

If there is no time for genetic testing (for example, during emergency surgery), we can look for indirect signs of mitochondrial dysfunction, although these are not diagnostic of the specific mutation:

- Serum Lactate:Baseline lactate levels > 3 mmol/L or a Lactate/Pyruvate ratio > 20 may suggest an underlying mitochondrial disorder.
- Limitation:Many patients with this specific mutation have normal lactate levels at rest and only decompensate under anesthetic stress, so a normal lactate does not rule out the risk.

Can we perform intraoperative screening for this problem?

If you decide to proceed with general anesthesia in a suspected patient (due to urgency or lack of evidence), the anesthetic depth monitor (BIS or SedLine) becomes a real-time diagnostic tool. Patients with Complex I defects (such as this mutation) show an abrupt drop in the bispectral index (BIS < 60) with very low concentrations of sevoflurane (0.5%–1%) during induction.

What are we doing at the Venezuelan Society of Anesthesiology?

The Venezuelan Society of Anesthesiology (SVA) faces a unique epidemiological challenge: defining the true magnitude of a genetic "founder effect" that has transformed a routine practice into a life-threatening risk for a specific subgroup.
To study the prevalence of the variant m.11232T>CTo mitigate risk without stigmatizing the general population or paralyzing operating rooms, the SVA must propose a phased strategy based on four fundamental pillars, relying on its alliance with the Institute for Advanced Studies (IDEA) and the Ministry of Science and Technology:

1. "Zero Ground" Study (Targeted Genetic Screening)

Sequencing the entire Venezuelan population is neither viable nor cost-effective. The SVA should propose a stratified sampling focused on the state of Carabobo.

- Justification:Current evidence suggests that the risk haplotype is 15 times more frequent in Carabobo than in the rest of the country, indicating a founding effect in this region.
- Proposed Methodology:Implement tests of PCR-RFLP(Restriction Fragment Length Polymorphisms) instead of initial full sequencing. This technique is inexpensive, fast, and can specifically detect the m.11232T>C mutation in saliva (buccal swab) or blood samples.
- Target Population:Neonates or pediatric patients scheduled for elective surgery in the main hospitals of Valencia and surrounding areas, comparing them with a control group from another region (e.g. Caracas or Zulia).

2. Creation of the "National Late Awakening Registry"

Clinical prevalence is often just the tip of the iceberg. Many patients with Complex I dysfunction do not die, but they exhibit hypersensitivity to halogenated compounds.

- Proposal:The SVA should establish a mandatory (non-punitive) reporting protocol for any pediatric patient who presents unexplained delay in waking up or abrupt drop in the bispectral index (BIS < 40) with low doses of sevoflurane (< 1 MAC).
- Scientific Value:These patients ("intermediate phenotypes") are ideal candidates for confirmatory genetic testing, which would allow the identification of carrier families before a fatal event occurs.

3. Retrospective Audit of "Cold Cases" (Neuroimaging)

There are likely previous undiagnosed cases, mislabeled as cerebral palsy, hypoxic encephalopathy, or "idiosyncratic reactions."

- Proposal: Request a review of databases from the last 10-15 years from the Neurology and Radiology services of the reference pediatric hospitals (e.g., Hospital J.M. de los Ríos, Ciudad Hospitalaria Dr. Enrique Tejera).
- Search Criteria: Patients who were admitted healthy and were left with postoperative neurological damage with the distinctive radiological pattern: bilateral necrosis of the basal ganglia (striatum)and cerebellar lesions, without evidence of intraoperative systemic hypoxia. This would help estimate the true penetrance of the disease in the past.
- If they are alive, they could be subjected to genetic screening to detect the variant.

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4. Standardization of Genealogical Anamnesis (Clinical Screening)

While awaiting the genetic data, the SVA should propose the immediate modification of the national pre-anesthetic evaluation form to include a section on "Mitochondrial Risk".

- Key Questionnaire: Not only ask for personal background information, but also trace the maternal lineage (geographic origin of the mother and maternal grandmother) and family history of fatigue, ptosis or sudden infant death in the maternal line.
- Action: If the patient has maternal lineage from Carabobo along with suggestive family history, he should be classified as "Theoretical Mitochondrial Risk" and managed under TIVA protocol (Propofol/Remifentanil/Dexmedetomidine) without exposure to inhalational anesthetics, regardless of the lack of genetic confirmation.

T**he Venezuelan Society of Anesthesiology (SVA)** not only is vigilant, but it has also activated a high-level scientific and professional oversight structure to address this patient safety crisis.

The SVA has deployed a team of professionals who operate under the principles of scientific rigor and epidemiological prudence, structured as follows:

1. Activation of the Board of Directors and Scientific Committees. The SVA Board of Directors has assumed an active leadership role, issuing interim "Technical Safety Reports" to pediatric anesthesia units to guide clinical practice in the face of diagnostic uncertainty. Its institutional stance rejects speculation and rumors, focusing instead on the genomic and clinical evidence to define safe handling protocols.
2. **National Strategic Alliances**: The Venezuelan Society of Anesthesiology (SVA) is not working in isolation. It has established direct working groups with the governing bodies of science and health in Venezuela to guarantee a serious investigation.

- Governmental and Academic Collaboration:High-level meetings have been held with the Ministry of Popular Power for Science and Technology (Mincyt), the Ministry of Health, and bioethics experts.
- Genetic Research:The society works in conjunction with leading institutions such as the Venezuelan Institute for Scientific Research (IVIC) and the Institute for Advanced Studies (IDEA).The goal is to move beyond anecdotal data and initiate mitochondrial DNA sequencing studies in the local population to determine the true prevalence of the mutation.m.11232T>C.

3. Connection with Global and Regional Experts: The SVA team has functioned as an international academic bridge to bring the most up-to-date information to the Venezuelan community:

- Expert Network:They have convened world authorities on the subject, including Dr. Eduardo Ruiz-Pesini(principal investigator of the genetic study in Spain), Dra. Irene Paradisi (human geneticist at IVIC) and Dr. Philip Morgan (US expert in mitochondrial anesthetic sensitivity), organizing symposia to discuss the pathophysiology of the problem directly with researchers.
- **Latin American Coordination**: We have actively participated in joint committees with the Chilean Society of Anesthesiology (SACH), the Colombian Society of Anesthesiology and Resuscitation (S.C.A.R.E.) and the Latin American Confederation of Anesthesiology Societies (CLASA), seeking a regional consensus that protects patients without stigmatizing their nationality.

In summary, the **SVA has a multidisciplinary and vigilant team** which prioritizes science-based anesthetic safety, acting as the governing body to filter, analyze and disseminate any critical new information on this mitochondrial pathology to the country's anesthesiologists.

With regards,

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