

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 in which the patient developed neurologic symptoms.

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 and a possible mitochondrial disorder, exome sequencing

Table 1. Demographic and Clinical Characteristics of the Cases

Variable	Value	Median	Range
Total patients, No.	7	—	—
Sex (male), No. (%)	5 (71)	—	—
Patients with neurologic history, No. (%)	1 (14)*	—	—
Patients with comorbidities, No. (%)	2 (29)†	—	—
Age at first event, yr	—	5	1–36
Anesthesia exposures, No.	—	1	1–4
Duration of surgical procedure at primary event, min	—	47	20–165
Use of sevoflurane (MAC), No. (%)	7 (100%)	0.95	0.70–1.60
Use of propofol (mg/kg), No. (%)	6 (86%)	2.02	1.81–3.42
Use of fentanyl (µg/kg), No. (%)	7 (100%)	2.5	1.92–2.89
Symptoms onset, days	—	0	0–10
Time to death, days	—	9.5	1–22
Deaths, No. (%)	4 (57%)	—	—

*Attention-deficit/hyperactivity disorder. †Acute renal failure stage 1 to 2 due to rhabdomyolysis; asthma.

was performed in three cases, yielding no relevant findings. Subsequently, mitochondrial DNA sequencing revealed the variant MT-ND4:m.11232T>C (p.Leu158Pro) in a 100% homoplasmic state, classified as a variant of uncertain significance according to the American College of Medical Genetics and Genomics (Bethesda, Maryland) and the Association for Molecular Pathology (Rockville, Maryland) variant interpretation guidelines.^{2,3}

MT-ND4 encodes the NADH-ubiquinone oxidoreductase chain 4 subunit of complex I, which transfers electrons from NADH to coenzyme Q while pumping protons from the mitochondrial matrix to the intermembrane space, generating the proton motive force for adenosine triphosphate synthesis.⁴ Experimental evidence has shown that isoflurane and sevoflurane can impair mitochondrial respiration by inhibiting NADH-ubiquinone oxidoreductase, leading to NADH accumulation and decreased adenosine triphosphate production while also increasing reactive oxygen species flux,⁵ which may contribute to the observed cellular damage.⁶ In patients with mitochondrial disorders, particularly those with ND4 mutations, sevoflurane could potentially exacerbate mitochondrial dysfunction,^{5,7} potentially increasing perianesthesia metabolic stress and contributing to hypoxic-ischemic patterns.

The MT-ND4:m.11232T>C (p.Leu158Pro) variant has previously been linked to chronic progressive external ophthalmoplegia⁸ but, to the best of our knowledge, not to acute, potentially fatal perianesthesia encephalopathy. These genetic findings raise the possibility that the DNA variant could represent a pharmacogenetic condition relevant to preoperative assessment. However, a causal link between anesthesia exposure and the neurologic damage observed in carriers has not been demonstrated. A similar case described in Colombia suggests a potential but unconfirmed association.⁹

Given the available evidence and the absence of established clinical guidelines for these events, the Chilean

Ministry of Health issued a technical communication providing clinical recommendations. This guidance emphasized the importance of enhancing preanesthesia evaluations with a focus on early recognition of possible mitochondrial dysfunction and, when such suspicion arises, prioritizing anesthetic agents considered safer for mitochondrial function.¹⁰

In collaboration with scientific societies and multidisciplinary experts, the Chilean Ministry of Health has initiated coordinated actions for surveillance, risk assessment, and research. A detailed case series based on medical records is currently in preparation. For this purpose, offering genetic testing is under consideration. Future steps include epidemiologic and functional studies to investigate the etiology of this emerging condition and eventually implement preventive measures.

Competing Interests

The authors declare no competing interests.

Constanza I. Yanez Hinojosa, M.D., M.M.Sc.¹
 Samanta Anríquez Jiménez, Dr.P.H., M.D., M.Sc.²
 Cristian Felipe Lara Román, M.Sc.²
 Javiera Esperanza Fuentes Contreras, M.D.²
 Jorge Felipe Pacheco Jara, M.D., M.Sc.²

¹University of Chile, Santiago, Chile

²Ministry of Health, Santiago, Chile

*jorge.pacheco@minsal.cl

DOI: 10.1097/ALN.00000000000005935

References

1. Ministerio de Salud de Chile: Circular C203 N°4:Alerta de evento de seguridad probablemente relacionado a medicamentos utilizados en anestesia general. Santiago: Subsecretaría de Redes Asistenciales, División de

- Gestión de la Red Asistencial; 2025 (Ministry of Health of Chile. Circular C203 No. 4: Alert on a safety event probably related to medications used in general anesthesia. Santiago: Undersecretariat of Healthcare Networks, Division of Healthcare Network Management; 2025.)
2. Richards S, Aziz N, Bale S, et al.; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17:405–24. doi:10.1038/gim.2015.30
 3. McCormick EM, Lott MT, Dulik MC, et al.: Specifications of the ACMG/AMP standards and guidelines for mitochondrial DNA variant interpretation. *Hum Mutat* 2020; 41:2028–57. doi:10.1002/humu.24107
 4. Hirst J: Mitochondrial complex I. *Annu Rev Biochem* 2013; 82:551–75. doi:10.1146/annurev-biochem-070511-103700
 5. Rodriguez E, Peng B, Lane N: Anaesthetics disrupt complex I-linked respiration and reverse the ATP synthase. *Biochim Biophys Acta Bioenerg* 2025; 1866:149511. doi:10.1016/j.bbabi.2024.149511
 6. Sun M, Xie Z, Zhang J, Leng Y: Mechanistic insight into sevoflurane-associated developmental neurotoxicity. *Cell Biol Toxicol* 2022; 38:927–43. doi:10.1007/s10565-021-09677-y
 7. Hsieh VC, Niezgoda J, Sedensky MM, Hoppel CL, Morgan PG: Anesthetic hypersensitivity in a case-controlled series of patients with mitochondrial disease. *Anesth Analg* 2021; 133:924–32. doi:10.1213/ANE.0000000000005430
 8. Pulkes T, Liolitsa D, Nelson I, Hanna M: Classical mitochondrial phenotypes without mtDNA mutations: The possible role of nuclear genes. *Neurology* 2003; 61:1144–7. doi:10.1212/01.WNL.0000090465.27024.3D
 9. Candelo E, Arango A, Franco D, et al.: Fatal outcome in a patient with an unknown mitochondrial disease after anesthetic exposure: A clinical literature review from the anesthetic perspective. Available at: <https://www.researchsquare.com/article/rs-2539495/v1>. Accessed July 23, 2025.
 10. Ministerio de Salud de Chile: Circular B27 N°10: Sobre el manejo clínico frente a posibles eventos neurológicos postoperatorios. Santiago: Subsecretaría de Salud Pública; 2025 (Ministry of Health of Chile. Circular B27 No. 10: On clinical management in the presence of possible postoperative neurological events. Santiago: Undersecretariat of Public Health; 2025.)

(Accepted for publication January 8, 2026.)