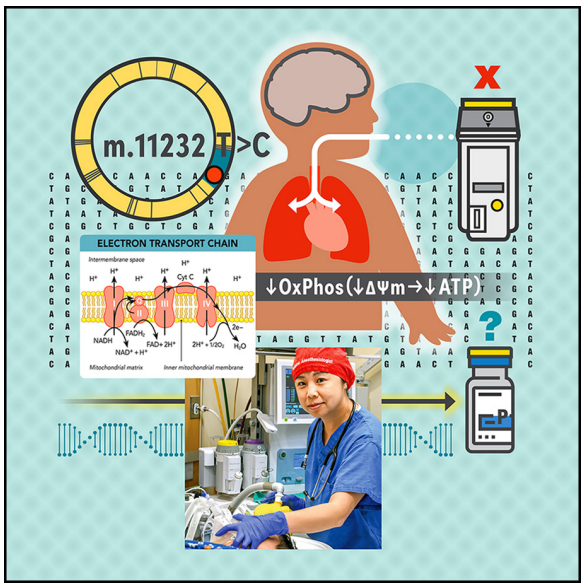
Ancient Mitochondrial Genetic Variant, Modern-day Pandora's Box

Richard J. Levy, M.D., Phil G. Morgan, M.D.

Recently, there have been numerous anecdotal reports of devastating outcomes in healthy patients after a relatively unremarkable general anesthetic exposure. In a Letter to the Editor in this issue of Anesthesiology, Yanez Hinojosa *et al.*[1] highlight a cohort of seven adults and children, comprising both sexes, that developed severe neurologic complications or death after general anesthesia. Neuroimaging identified lesions in the basal ganglia, cerebellum, substantia nigra, and other deep gray matter structures, raising suspicion for an underlying genetic etiology. Nothing in the preoperative history heightened concerns that this group of patients might be at increased risk from an anesthetic exposure. Exome sequencing in a subset of patients did not indicate any consistent changes in the group; however, sequencing of the mitochondrial genomes revealed a consistent variant in the *MT-ND4* gene: m.11232T>C (p.Leu158Pro) in a homoplasmic state. At the time of submission, m.11232T>C was classified as a variant of uncertain significance. This exact mutation (in a homoplasmic state) was also reported in a 2023 non–peer-reviewed case report of a relatively healthy 12-yr-old girl who was neurologically devastated after an uneventful 1-h general sevoflurane anesthetic (Candelo E, Arango A, Franco D, et al. Fatal outcome in a patient with an unknown mitochondrial disease after anesthetic exposure: A clinical literatura review from the anesthetic perspective. Preprint. Posted online March 3, 2023. Research Square. doi:10.21203/rs.3.rs-2539495/v1).



"… the authors' findings convincingly demonstrate that mitochondria with [specific] mutations are exquisitely sensitive to sevoflurane, providing the first insight into how sevoflurane may have led to the catastrophic outcomes."

The cohort of patients described by Yanez Hinojosa *et al.*[1] shared a few key features: each was born to a mother of Venezuelan origin, each was exposed to sevoflurane, and most (six of seven) received boluses of propofol and fentanyl. However, granular details of the anesthetic exposures were lacking. Therefore, it is impossible to know the duration, concentration, or dosage of each administered drug. Thus, conclusions about the inciting pharmacologic agent(s) cannot be drawn. The non–peer-reviewed case report from 2023 provided some further detail about anesthetic management; however, causation cannot be established from a single case. In addition, while devastating outcomes were not reported with other anesthetics, more detailed evaluations of subtler outcomes were not done. In particular, longer-term neurologic follow-up of these patients has not been undertaken. Thus, while it is tempting to arrive at the inference that sevoflurane was the sole culprit and that other anesthetics may not have caused injury and are safe, the data at present do not allow such a firm conclusion.

The current issue of Anesthesiology also contains a timely, related, and very important evaluation of a likely

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genetic cause for the response of these patients to sevoflurane.[2] Sanz-Pons *et al*.[2] reasoned that the temporal and geographic separation between these cases indicated a likely genetic basis for the devastating effects of sevoflurane exposure. They sequenced both the nuclear exome of three patients and mitochondrial DNA (mtDNA) of seven affected patients of Venezuelan origin in a search for genetic changes that correlated with the occurrence of the severe patient outcomes. They did not find any consistent changes in the nuclear genome; however, each affected patient belonged to the D1b mitochondrial haplogroup and harbored several notable additional genetic variants. This same haplogroup with the additional private variants was found in healthy mothers of three probands. The variants in the mtDNA were consistent with the pattern of maternal inheritance (all mtDNA is inherited from our mothers), and the majority of patients had maternal ancestry that could be traced back to Venezuela (most commonly to the state of Carabobo). The authors then honed in on two specific mitochondrial mutations thought to be functionally significant: m.15164T>C in *MT-CYB* (encodes the cytochrome *b* subunit within complex III of the electron transport chain) and m.11232T>C in *MT-ND4* (encodes the ND4 subunit of complex I). A single amino acid change in the mitochondrial complex I subunit, ND4, is predicted to induce a change in the enzyme that would significantly alter its structure. Given that complex I is known to be uniquely sensitive to volatile anesthetics inhibition and that patients with complex I defects have been shown to be very hypersensitive to sevoflurane,[3,4] the authors focused on the change in ND4 as possibly causative.

Sanz-Pons *et al*.[2] then undertook a beautiful set of experiments to evaluate the sensitivity to sevoflurane of mitochondria from these patients. They used both fibroblast cells from the mother of one of the patients, as well as cybrid cell culture (cells with D1b haplotype mitochondria containing the 41 genetic variations of interest transferred into cells lacking mtDNA). They studied the degree of inhibition of oxidative phosphorylation by anesthetics in these cells. In each case, they found complex I–dependent mitochondrial respiration in cells harboring the mtDNA variants of interest to be exquisitely sensitive to sevoflurane. There was near complete (approximately 90%) inhibition of complex I–dependent respiration at sevoflurane concentrations commonly used in clinical pediatric practice. In comparison, complex II/III–dependent function was unaffected, narrowing the primary effect to complex I. The authors concluded that their results supported the model that the ND4 mutation (m.11232T>C) is likely causative. However, the list of cybrid control cell lines was not exhaustive. While their approach included a cybrid containing the CYB mutation (which did not alter sevoflurane sensitivity), it lacked important inclusion of a cybrid line harboring only the ND4 mutation. Therefore, it is unknown whether it is the combination of mutations (such as ND4 + CYB) that leads to a functional consequence or the ND4 mutation by itself. Such a question will need to be assessed in future work. Despite this limitation, it should be stressed that the authors' findings convincingly demonstrate that mitochondria with the D1b haplogroup and the private additional ND4 and CYB mutations are exquisitely sensitive to sevoflurane, providing the first insight into how sevoflurane may have led to the catastrophic outcomes. In parallel experiments, they found no significant increase in sensitivity to propofol in either the fibroblasts or the cybrids. However, it should be noted that the authors tested pure propofol (chemical formulation) and did not assess the clinical formulation (intralipid solvent) currently used in clinical practice. In addition, they tested only sensitivity and not any measure of the longer-term mitochondrial toxicities that may be caused by propofol,[5] so their findings do not fully eliminate potential problems with propofol. Taken at face value, the data provide a suggestion that D1b haplogroup mitochondria, containing additional ND4 and CYB changes, may not be any more sensitive to propofol than mitochondria lacking the DNA variants in question. Future work will need to focus on the safety of propofol in this genotype.

Nearly two decades ago, one other patient was reported to harbor the ND4 mutation described here.[6] However, the mutation was not present in the homoplastic state, there was no reported Venezuelan heritage, and that patient was symptomatic with chronic progressive external ophthalmoplegia with disease onset that occurred at an age greater than any patient described in these reports. This raises the possibility that the patients described by Yanez Hinojosa *et al*.[1] and Sanz-Pons *et al*.[2] were simply too young to be symptomatic.

Multiple previous reports of patients with mitochondrial disease undergoing anesthesia have reported about patients that were symptomatic from their mutations. In fact, most of them were undergoing a muscle biopsy to rule in or rule out mitochondrial disease. In the two articles discussed here,[1,2] all patients presenting for anesthesia were asymptomatic, and therefore, unlike previous reports of mitochondrial patients,[3,4] the anesthesiologists here had absolutely no reason to expect a bad outcome from sevoflurane exposure. This is one of the truly enigmatic, and troubling, characteristics of their presentation. The reason for this is not clear at this point, although it is possible that the lack of a phenotype might be explained by the multiple variations in the mitochondrial genome. In particular, the MT-CYB mutation could affect complex I function at baseline, perhaps even improving it. Another explanation is that ND4 might very well be a functional target of sevoflurane and that the mutant gene product inhibits complex I (profoundly) only when sevoflurane binds to it. Further work is required to better understand the mechanisms and may provide greater insight into how anesthetics induce unconsciousness.

In the supplemental digital content, Sanz-Pons *et al*.[2] present additional points that are extremely important. First, they show that the inhibition of complex I, at least from relatively low concentrations of sevoflurane, is fully reversible (supplemental fig. S5). In that sense, this untoward effect is *not* like that seen with malignant hyperthermia, in which a response is irreversibly triggered without

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additional treatment. This obviates the need to employ the usual precautions associated with malignant hyperthermia patients (charcoal, flushing systems, and others). Second, the mtDNA mutation can be identified by a simple sequencing technique, but that is not yet a routine clinical option. Sequencing the entire mitochondrial genome is a clinical service that is available at centers within the United States and that would identify the mutation but typically takes weeks to a month for results. Thus, definitively identifying at-risk patients in the preoperative period is challenging and logistically problematic.

Putting all of this together, one has a picture of a unique scenario: an otherwise healthy child, presenting for a simple, straightforward anesthetic that may carry the real risk of exhibiting a profound, life-threatening sensitivity to our most commonly used anesthetic. The sensitivity is such that our usual intraoperative observations of the patient may not be enough to warn us of the impending or ongoing damage. How are we to protect our patients from the harm we might cause in this situation? One recommendation is to induce a patient very slowly if sevoflurane is to be used, with a processed electroencephalography (EEG) monitor (as described in the two studies of children with mitochondrial symptoms previously). Not one of them had a single bad outcome after their sevoflurane anesthetic. Beyond that point, we remain somewhat in the dark at present due to lack of information. We do not know whether *every* at-risk child will have a bad outcome *every* time they are exposed. We do not know whether there are at-risk patients with partial presence (heteroplasmy) of the causative mutation. We do not know the incidence/prevalence of the causative mtDNA mutations or variations. We do not know whether other medications may be problematic. We do not know whether there is a safe cocktail of anesthetics. What we do know at this time is that the *MT-ND4*:m.11232T>C mutation in homoplasmic state is a real risk factor for anesthesia-induced neurologic injury or death: the so-called m.11232T>C–linked volatile anesthetic hypersensitivity. What we think we know is that sevoflurane is one such anesthetic agent that can induce such a catastrophic outcome.

As a result of the many things we do not yet know, we can only recommend a few things. First, be aware of the existence of this mtDNA variant, screen for it, and look for it. In a politically/socially sensitive and humane manner, inquire whether any patient might carry this genetic maternal lineage and whether there is a family history of a bad outcome after an anesthetic exposure. There is no phenotype for the causative genotype as we know it. If there is even a suggestion of risk, consider using processed EEG monitors to evaluate depth of anesthesia and probably avoid sevoflurane. Finally, frequently check the recommendations put out by the various organizations (American Society of Anesthesiologists [Schaumburg, Illinois], Society for Pediatric Anesthesia [Richmond, Virginia], and Chilean Society of Anesthesia [Santiago, Chile]) that are working closely together to follow the evolution of our understanding of the constraints of this mitochondrial phenotype. First, do no harm.

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Competing Interests

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