CANADIAN ANESTHESIOLOGISTS' SOCIETY

ADVISORY STATEMENT

Emerging Reports of Severe Neurologic Complications Following General Anesthesia in Patients with Maternal Venezuelan Ancestry

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Background and Content

The Canadian Anesthesiologists' Society (CAS) would like to inform members about emerging international reports that describe rare but serious neurological complications—such as prolonged delayed emergence, basal ganglia necrosis, and death—in otherwise healthy pediatric and young adult patients of maternal Venezuelan ancestry following routine general anesthesia.

Around 30 known or suspected cases have been documented worldwide in regions including South America, Europe, and North America. Some of these patients have been identified as carriers of MT-ND4 m.11232T>C (p.Leu158Pro), a rare mitochondrial DNA variant that affects NADH-ubiquinone oxidoreductase chain 4 in Complex I of the electron transport chain[4].

Although peer-reviewed evidence remain limited and causality has not been definitively established, the consistency of ancestry, the unknown prevalence of the variant of concern in affected individuals, and a history of unexpected adverse neurological outcomes following exposure to volatile anesthetics — particularly sevoflurane — has prompted precautionary communications from the the Venezuelan Society of Anesthesiology (SVA), American Society of Anesthesiologists (ASA), the Society for Pediatric Anesthesia (SPA), and, among others[1-5].

Clinical Reports Featured

- Previously healthy pediatric or young adult patients
- Uneventful intraoperative course
- Exposure to inhaled volatile anesthetics

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- Marked delayed emergence (hours)
- Neurological sequelae, including delayed emergence, altered mental status, headaches, vomiting, localized or generalized weakness, hemiparesis, ataxia and gait disturbances, speech disturbances, dysphagia, new onset postoperative seizures, hemiplegia, quadriplegia, generalized dystonia, spasticity, cerebral edema and brain death
- ·Neuroimaging frequently demonstrates basal ganglia and cerebellar injuries
- ·Lactic acidosis disproportionate to procedural duration

Genetic and Testing Considerations

The MT-ND4 m.11232T>C variant is maternally inherited, and a significant number are from Carabobo or other surrounding states in center-west Venezuela, suggesting a founder effect from a common maternal ancestor. Given the scarcity of evidence, MT-ND4 m.11232T>C is still classified as a variant of uncertain significance (VUS), it may not be reported by some laboratories unless specifically requested to test for the variant of concern or to report all detected variants, including VUSs.

Not all individuals harbouring MT-ND4 m.11232T>C have experienced adverse outcomes after exposure to general anesthesia. The precise pathophysiologic mechanism and magnitude of risk remain under investigation. Therefore, a negative family history of complications after inhaled anesthetics does not rule out carrying the variant of concern.

Current Evidence Status

Published clinical evidence is limited, and the number of confirmed cases, based mainly in personal communications, is small relative to the global use of volatile anesthetics. Therefore, no formal evidence-based guidelines can yet be issued, as the optimal anesthetic management for patients with suspected or confirmed risk has not been established.

Considering the severity of reported outcomes, we propose a precautionary approach for risk screening and management of patients with suspected risk while further evidence emerges.

Considerations for Clinical Practice (Precautionary)

- Routinely inquire about personal or family history of delayed emergence and unexpected neurological complications including postoperative seizures, dystonia, or death, especially in patients of admixed American (Latino) ancestry.
- Sensitively inquire about maternal ancestry, particularly Venezuelan ancestry, specifically the state of Carabobo, within broader family history discussion.

- In non-urgent cases with suspected risk (e.g., adverse postoperative neurological outcome, maternal Venezuelan ancestry), consider referral for genetic consultation and targeted mtDNA testing. Alert laboratories [VI1] [MA2] to specifically test for and report the variant of concern MT-ND4 m.11232T>C.
- Avoid inhaled halogenated anesthetics (e.g., sevoflurane) in patients with suspected or confirmed genetic risk until more safety evidence becomes available.
- Consider total intravenous anesthesia (TIVA) or regional techniques where appropriate.
- Use EEG-guided depth-of-anesthesia management. Consider decreasing the anesthetic dose if EEG index values fall below the manufacturer's recommended lower limit; avoid burst suppression (e.g, set low alarms for BIS < 40, PSi < 25, SR>0)
- Monitor closely for delayed emergence. Involve neurology/genetics early if unexpected adverse neurological outcomes occur.
- Report suspected cases to institutional patient safety programs and national quality and safety bodies when appropriate.

Communication and Sensitivity

Discussions regarding ancestry should be conducted with cultural sensitivity and framed within the broader context of medical history. Care should be taken to avoid stigmatization while ensuring appropriate risk identification.

Ongoing Review

CAS will continue to monitor emerging scientific evidence and international guidance. Updates will be provided as peer-reviewed data and consensus recommendations become available. This advisory aims to promote awareness and prudent clinical vigilance in an evolving area of pharmacogenetic research.

References

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