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WORLD FEDERATION OF SOCIETIES OF
ANAESTHESIOLOGISTS

World Federation of Societies of Anaesthesiologists (WFSA) Statement on Adverse Neurological Outcomes in Paediatric and Young Adult Patients Undergoing General Anaesthesia

This statement was developed under the leadership of the WFSA Paediatric Anaesthesia Committee in collaboration with international experts, partner organizations, and contributors from across the global anesthesia community.

The WFSA wishes to advise its members of an emerging phenomenon which may be implicated in adverse neurological outcomes in patients undergoing general anaesthesia.

Since July 2025, statements from the Societies of Anaesthesiologists of Chile¹, Colombia², Venezuela³, Spain⁴ and the United States of America⁵ have described anecdotal case reports of paediatric patients with Venezuelan ancestry having severe neurological compromise or not waking after general anaesthesia.

Yanez Hinojosa et al⁶ have described seven cases, six children and one adult, all having a Venezuelan mother, who experienced severe neurological complications or death after general anaesthesia. This is relevant as mitochondrial DNA inheritance is maternal. It was hypothesized that problems with the mitochondrial respiratory chain may be responsible.

Sanz-Pons et al⁷ conducted clinical and genetic studies on seven patients who experienced severe acute neurologic deterioration following general anaesthesia. The maternal lineage of five of the patients could be traced back to the state of Carabobo in Venezuela. Several mitochondrial genetic variants were identified, with the authors focusing on two specific ones - m.15164T>C in MT-CYB, which encodes the cytochrome b subunit within complex III of the electron transport chain, and m.11232T>C in MT-ND4, which encodes the ND4 subunit of complex I.

Volatile anaesthetics are known to inhibit mitochondrial complex I, decreasing ATP production and suppressing central nervous system activity. When abnormal mitochondria are exposed to volatile anaesthetics, it can create instability within the mitochondria leading to destruction of intracellular energy production. Clinically, this can result in multi-organ dysfunction including failure to wake after a general anaesthetic. Sanz-Pons et al found in their *in vitro* studies, that when cells with the m.11232T>C genetic variant were exposed to sevoflurane, there was “a pronounced



suppression of mitochondrial oxygen consumption, with prominent effects on complex I-dependent respiratory pathways”.

While the anaesthesia community waits for further peer-reviewed published evidence, the WFSA suggests anaesthesiologists use the following screening measures to identify patients who may be at increased risk of a general anaesthetic:

1. Patients with a Venezuelan maternal line
2. Patients with a history of anaesthetic problems within their maternal line, which may indicate mitochondrial dysfunction, such as:
 - a. Unexpected or unexplained delayed awakening after a general anaesthetic
 - b. Unexpected weakness after general anaesthetic such as respiratory depression
 - c. Unexpected neurological problems after general anaesthesia such as ataxia
 - d. Unexplained sudden death after a general anaesthetic
3. Patients of any ancestry who have a maternal family history of the complications described in criterion 2 above. Given migration patterns and the possibility that the m.11232T>C variant may not be limited to Venezuelan lineage, clinicians should maintain a high index of suspicion when a relevant maternal anaesthetic history is present, regardless of stated ancestry.

For patients who meet the above criteria, the recommendations for anaesthesia are:

- **Multidisciplinary team consultation** including but not limited to, anaesthesiologists, metabolic and/or neurology physicians, genetics specialists and surgeons, with the patient and their family to consider:
 - the urgency of procedure
 - counselling
 - appropriate pre-operative testing noting that:
 - genetic testing for the m.11232T>C mitochondrial DNA genetic variant may be available in some countries
 - the inability to perform genetic testing on patients identified as at risk should not exclude them from receiving anaesthesia/surgical care
 - anaesthetic technique
 - surgical technique
- **Consider the best location and resources available** for providing anaesthesia care for these patients, including equipment and pharmacological resources as well as anaesthesia expertise. This may require transferring patients to another centre, if their clinical status allows.
- **Avoid use of volatile anaesthetics**
- **Strict Avoidance and Equipment Decontamination:** In patients with suspected risk, absolute avoidance of sevoflurane is recommended. Aligning with the



precautionary principles used in malignant hyperthermia, institutions should mandate the use of uncontaminated, clean anesthesia circuits (utilizing flushing protocols and charcoal filters) to prevent exposure to residual volatile anesthetics. This is a low-burden, high-benefit intervention that may save lives.

- **Preference for regional anaesthesia**

- Whenever appropriate, neuraxial anaesthesia or peripheral nerve blocks should be utilized to minimize systemic drug exposure.

- **Use of Total Intravenous Anesthesia (TIVA)**

- While TIVA is generally preferred over volatile agents for patients with mitochondrial complex I disorders, caution is warranted with propofol. Propofol also affects mitochondrial function⁸. Sanz-Pons et al found that when cells with the m.11232T>C mitochondrial DNA genetic variant were exposed to propofol, there was a dose-related decrease in cellular oxygen consumption, however it was comparable with the control cells. When using TIVA, it is recommended to use multimodal anaesthesia to either avoid use of propofol or dose it at the minimum effective concentration. This may include but is not limited to use of:

- dexmedetomidine infusions
- short or ultra-short acting opioids e.g. remifentanyl
- ketamine
- benzodiazepines

- **Neurological monitoring**

- The use of processed electroencephalography (e.g., BIS, Sedline, Entropy) is strongly recommended to monitor brain activity, prevent burst suppression and ensure adequate depth of anesthesia while using the minimum amount of anaesthetic agent. Patients with mitochondrial disorders may show a rapid decrease in processed electroencephalography readings upon exposure to volatile anaesthetics.

- **Post-operative Monitoring**

- All at-risk patients should have an explicit post-operative monitoring plan. Neurological deterioration may be delayed in onset. Where intensive care or high-dependency care is available, admission should be considered following general anaesthesia. Extended recovery room observation with a minimum of hourly neurological assessment for at least four hours post-anaesthesia is recommended, with clear escalation criteria documented prior to the procedure. Patients and families should be encouraged to contact the anaesthesia team should any new neurologic findings occur in the first few weeks after the anaesthetic.



- **Incident surveillance**

- Should a patient experience unexpected neurological deficit or failure to wake post-anesthesia, practitioners should report the event to an anaesthesia incident reporting system e.g., Anesthesia Incident Reporting System (AIRS) (<https://www.asahq.org/aqi/registries/airs>).

- **Considerations for Resource-Constrained Settings**

The WFSA recognizes that many of its members practice in settings where access to advanced monitoring, specialist consultation, and a full pharmacological formulary may be limited. The following guidance is offered for these contexts.

- **When processed electroencephalography neurological monitoring is unavailable**

- Avoid volatile anaesthetic agents entirely in at-risk patients, as this remains the single most important risk-mitigation measure regardless of monitoring availability
- When using TIVA, titrate to clinical signs of anaesthetic depth (e.g., haemodynamic response, movement, lacrimation) and use the minimum effective doses of all agents

- **When availability of TIVA drugs is limited**

- TIVA remains the preferred technique. Where commonly used TIVA agents (e.g., propofol, remifentanyl, dexmedetomidine) are unavailable:
 - **Ketamine** should be considered the primary agent. It is widely available globally, has a well-established safety profile and does not share the same mitochondrial complex I inhibition mechanism as volatile agents. It can be used as the sole anaesthetic agent or as the backbone of a multimodal regimen
 - **Benzodiazepines** (e.g., midazolam) combined with ketamine may provide adequate anaesthesia and anxiolysis in many procedural contexts
 - **Dexmedetomidine**, where available, is a valuable adjunct to ketamine-based anaesthesia. It provides sedation and analgesia without respiratory depression, reduces ketamine-related emergence phenomena such as dysphoria and agitation, and offers opioid-sparing properties — making it a particularly useful addition in resource-limited settings where managing post-anaesthetic complications may be more challenging.
 - Local and regional anaesthesia techniques should be maximized to reduce the required dose of any systemic agent



- **When genetic testing is unavailable**

- Genetic testing for the m.11232T>C mitochondrial DNA variant will not be accessible in many countries. This must not delay or deny surgical or anaesthetic care for patients who require it. Patients identified as at risk through clinical screening criteria should be managed according to these precautionary recommendations regardless of whether genetic confirmation is possible.

- **When transfer to a higher-level centre is not feasible**

- Transfer to a higher-level centre is recommended when clinically appropriate, particularly for elective procedures. However, when transfer is not possible - due to patient clinical status, geography, or resource constraints - the following approach is recommended:
 - For urgent or emergency procedures where deferral is not safe, proceed using the safest available technique, prioritising regional anaesthesia and ketamine-based TIVA, with avoidance of volatile agents
 - Ensure the most experienced available anaesthesia provider manage the case
 - Plan for extended post-operative monitoring (see below)

- **Post-operative monitoring in resource-constrained settings**

- Where intensive care or high-dependency care is available, admission should be considered for at-risk patients following general anaesthesia. In lower-resource settings, extended recovery room observation with a minimum of hourly neurological assessment for at least four hours post-anaesthesia is recommended, with clear escalation criteria documented prior to the procedure.

It is important to note that this statement is a precautionary screening and safety strategy, while the anaesthesia community waits for further published, peer reviewed evidence on this issue. The American Society of Anesthesiologists have created a webpage (<https://www.asahq.org/advocating-for-you/genetic-anesthesia-neurologic-mortality-risks>) with resources for the anaesthesia community which will be updated as further developments occur.

The vision of the WFSA is “Universal access to safe anaesthesia” and it is imperative that all people, regardless of their background receive equitable, timely peri-operative care.



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