Risk of Anesthesia Regression in Children with Autism Spectrum Disorder and Mitochondrial Dysfunction

By Gail Szakacs, MD and Alyssa Davi

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Children with autism spectrum disorder (ASD) have a range of medical problems involving many organ systems. A subset of children with ASD hasve abnormal mitochondrial energy production and function that contributes to their physical, cognitive, and behavioral impairments. The presence of mitochondrial dysfunction increases the risk for potential damage to the brain, which is dependent on oxidative metabolism. This risk is more pronounced during procedures that require anesthesia. Because ASD children often undergo medical procedures (like endoscopies, adenoidectomies, tonsillectomies, and ear tube placement) requiring anesthesia, regression with anesthesia is of particular concern for the subset of children with ASD and mitochondrial dysfunction.

This article introduces aspects of emerging research, highlights potential risk factors, and suggests tools to help prevent adverse events from anesthesia in ASD children with mitochondrial dysfunction. The information in this article is meant to increase awareness about an evolving concern for a very vulnerable population and should be applied to an individual patient under the guidance of the doctors involved in the child's care.

WHAT DOES SOME OF THE RESEARCH SAY ABOUT MITOCHONDRIAL DISEASE IN ASD AND INCREASED ANESTHETIC SENSITIVITY WITH MITOCHONDRIAL DISEASE?

Emerging research suggests that a percentage of ASD children actually have underlying mitochondrial disease, specifically defects in mitochondrial oxidative phosphorylation (OXPHOS). Oliveira and colleagues published a population-based survey of school-age children with ASD in which they found that "7% of

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those who were fully tested met criteria for definite mitochondrial respiratory chain disorders and were also clinically indistinguishable from other children with ASD." Weissman, et al. published a comprehensive chart review of 25 ASD patients with a mitochondrial disorder in which they showed a non-chance occurrence of these two disorders.

Other research about specific mitochondrial abnormalities and increased anesthetic sensitivity may provide insight into how to better identify those at higher risk for anesthetic complications in the future. The background of this research is explained here, in addition to the actual research, to highlight its importance.

Mitochondria are the main source of cellular energy metabolism, and the central nervous and muscular systems have a very high energy demand. As the targets of anesthesia, these systems are particularly vulnerable in the presence of mitochondrial dysfunction. The mitochondrial oxidative phosphorylation pathway consists of five protein complexes (I-V), and complex I is the entry point for this pathway in normal mitochondria. Therefore, problems in complex I may more significantly and negatively affect overall functional capacity in the central nervous and other systems. Subcomplex I lambda is part of complex I.

Along with other researchers, Marni J. Falk, MD (assistant professor of pediatrics, Division of Human Genetics at The Children's Hospital of Philadelphia), has studied certain aspects of complex I mitochondrial dysfunction. They conclude "subcomplex I lambda subunits along the electron transport pathway specifically control whole animal anesthetic sensitivity." Dr. Falk conducted this research in conjunction with two well-known researchers in the field of anesthesiology and genetics, Dr. Philip G. Morgan and Dr. Margaret M. Sedensky, who have been studying the mechanism of anesthesia since the 1990s. The importance of this emerging research is that the extent of subcomplex I lambda impairment seems to correlate with animals' response to anesthesia. The extent to which a child has a reduction in complex I enzyme function (within sub-unit lambda), therefore, *may* help predict how that child responds to anesthesia. Perhaps the adverse results of some ASD children who undergo procedures requiring anesthesia could reflect undiagnosed mitochondrial dysfunction within subcomplex I lambda in those children.

WHAT ARE SOME OF THE RISK FACTORS FOR ANESTHESIA COMPLICATIONS?

Since ASD children commonly have one or more of the following underlying medical problems, they are often at increased risk for complications from procedures requiring anesthesia.

1. History of seizures
2. Preoperative respiratory problems
3. Poor clinical condition prior to the procedure
4. Undiagnosed mitochondrial disease
5. MTHFR (methylenetetrahydrofolate reductase) gene polymorphism
6. Increased homocysteine levels
7. General B-vitamin complex deficiency or B12 deficiency (indicated by increased methylmalonic acid) as the cause of increased homocysteine levels

WHAT COMPLICATIONS CAN BE SEEN IN ASD CHILDREN WITH MITOCHONDRIAL DYSFUNCTION FOLLOWING ANESTHESIA?

Anesthesia and sedation do not present a problem for most children with ASD. However, ASD children with mitochondrial disturbances are at increased risk for the following potential complications:

1. Excessive timeframe or difficulty in coming out of the anesthesia.
2. Developmental regressions, which could include loss of expressive and/or receptive language, gross motor skills, fine motor skills, cognitive function, and overall neurologic deterioration. In some children, skill loss may be permanent.
3. Excessive fatigue and reduced energy levels: temporary (for days or weeks) or persistent.
4. Possible death.

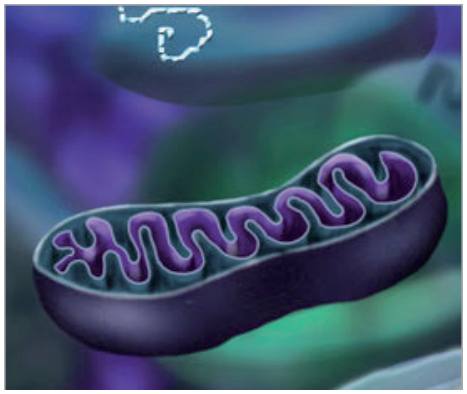
The following table is from a 1998 article, "Anesthesia and Mitochondrial Cytopathies," by Bruce H. Cohen, et al. It illustrates the mechanism for the effects of certain anesthetic agents on mitochondrial function and may at least partially explain the occurrence of adverse events noted above.

Medication	Biochemical and Clinical Effects on Mitochondrial Function
Barbiturates	Inhibits complex I activity at high levels
Benzodiazepines	Inhibits adenosine nucleotide translocase
Propofol and/or lipid carrier	Inhibits mitochondrial function
Halothane	Increased risk for heart rhythm disturbances
Nitrous oxide (chemical formula is N2O)	Neurotoxic, possibly by increasing nitric oxide production, which inhibits cis-acotinase and iron-containing electron transport enzymes; affecting energy production
Non-depolarizing agents	Increased sensitivity to the paralytic effects and prolonged responses reported
Local anesthetics	Bupivacaine uncouples oxidation and phosphorylation

HOW TO BEGIN THE EVALUATION OF THOSE AT INCREASED RISK FOR ANESTHESIA COMPLICATIONS

In addition to a comprehensive physical exam, experts in the mitochondrial disease field recommend considering the following testing prior to any procedures requiring anesthesia:

1. Comprehensive metabolic profile
2. Magnesium
3. CBC with differential
4. Creatine kinase
5. Amylase
6. Ammonia
7. MTHFR
8. Homocysteine
9. Methylmalonic acid (for B12 status)
10. Fasting glucose
11. Lactate level (on a morning fast, without a tourniquet, in a free flowing venipuncture)



In 2003, *The New England Journal of Medicine* published a report by Selzer, et al. on the risks of nitrous oxide in individuals with MTHFR and concluded, "patients with a diagnosis of severe MTHFR deficiency should not receive nitrous oxide as anesthesia. In the case of emergency procedures, patients whose clinical presentation fits that of severe MTHFR deficiency, even if the disorder has not been diagnosed, should also not receive nitrous oxide. In the case of elective procedures, patients whose clinical presentation fits that of severe MTHFR deficiency should be evaluated, and the diagnosis should be ruled out before anesthesia with nitrous oxide is contemplated."

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WHAT MEASURES CAN BE CONSIDERED BEFORE, DURING, AND AFTER PROCEDURES REQUIRING ANESTHESIA IN PATIENTS AT RISK?

With anesthesia, there are always some associated risks, and even when being cautious, there is no guarantee that the procedure will be free of complications. Becoming more informed and advocating with the anesthesiologist for the careful selection of anesthesia in a child will reduce the likelihood of problems.

Prior to the procedure, discuss the following with the anesthesiologist:

1. History of mitochondrial dysfunction
2. In a presentation at the Autism One Conference in May 2009, Sonja Hintz, RN, BSN, and Sym Rankin CRNA, APN, from True Health Medical Center in Naperville, Illinois, discussed the risk of anesthesia in ASD children and proposed the following:

a. Avoid nitrous oxide

i. Overall negative effect on methylation cycle, which is important for detoxification, neurotransmitters, myelin sheath formation, and DNA synthesis. In deactivating methionine synthase (B12 dependent enzyme that uses 5-methyltetrahydrofolate as a methyl donor and 5-methyltetrahydrofolate is formed from folic acid with the MTHFR B2-dependent enzyme), nitrous oxide causes homocysteine and overall oxidative stress to increase. Since cofactors and enzymes are needed for these biochemical pathways, a patient can be at particular risk for pathway disruption and clinical regression from nitrous oxide in the presence of B12 and MTHFR deficiency.

b. Consider IV placement without sedation (midazolam/Versed® or other).

c. All medications and supplements your child is taking at the time of the procedure.

d. IgE allergies.

e. Difficulty detoxifying.

f. Discuss any other drugs that might also be given during the procedure.

Other precautions to consider include the following:

1. Make sure the child is well hydrated prior to the procedure.
2. Minimize the length of the fast required. Request that your child be the first procedure of the day. See Dr. Kelly's article ("Information for Anesthesiologists and Surgeons for Operative and Perioperative Care of Patients with Mitochondrial Disease") for further information on fasting prior to the procedure.
3. The following is a synopsis of some recommendations made by Bruce H. Cohen, et al. in their 1998 article, "Anesthesia and Mitochondrial Cytopathies."

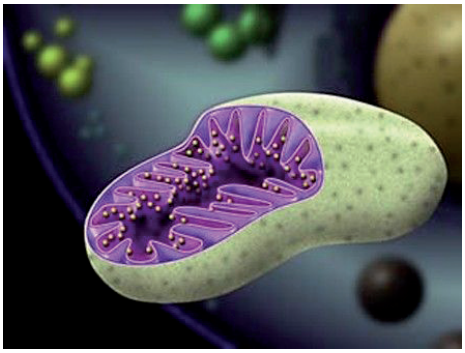
a. Respiratory function deserves special attention before, during, and after the procedure, especially in patients with respiratory difficulties. Maintaining normal oxygenation and implementing respiratory physiotherapy should be part of the care of these patients.

b. Be aware of infectious risk, and implement treatment if necessary.

c. Avoid Lactated Ringer's solution (also known as Ringer's Lactate) as an intravenous fluid since it contains lactic acid, and patients with mitochondrial dysfunction generally have elevated blood lactate levels.

d. Maintain normal blood glucose, body temperature, and acid-base balance.

e. Although depolarizing muscle relaxants (such as succinylcholine) have been safely used in many patients with mitochondrial diseases,



the use of these agents can present a risk to such patients and needs to be discussed with the anesthesiologist.

f. Postpone elective surgery if there is evidence of infection.

g. Take special precautions if at risk for malignant hyperthermia (see Dr. Cohen's article for more information on this condition).

h. Patients with mitochondrial dysfunction may be at increased risk when barbiturates, narcotics, benzodiazepines, or nitrous oxide are used for anesthesia, especially if there is a history of bad reactions to any of these in the past.

i. Although propofol has been used safely for anesthesia in patients with mitochondrial cytopathies, there is some concern with prolonged use of the drug. "Animal studies indicate that propofol… impairs mitochondrial function to a greater degree than other anesthetics. There have been observations that prolonged continuous use (days) at high dosages to treat frequent seizures cause a syndrome similar to mitochondrial failure, and therefore prolonged use in a patient with mitochondrial cytopathies may not be safe."

CONCLUDING COMMENTS:

Much more needs to be learned through ongoing research about the subset of ASD children with mitochondrial dysfunction, the risk for them during procedures requiring anesthesia, and the best ways to prevent complications with necessary procedures.

As more is learned, consider the following in advocating for children with ASD and mitochondrial disturbances prior to procedures requiring anesthesia to help promote the best possible outcomes.

1. Know what type of anesthesia and sedation is planned for the procedure.
2. Get some lab work done in advance (see above).
3. Communicate concerns to the involved doctors clearly and in writing prior to the procedure.
4. Consider the prevention measures highlighted in this article and discuss these with the clinicians involved in the care of the child for the upcoming procedure.
5. Consider supportive measures before and after the procedure (work with physicians to develop individualized plans based on a child's medical problems and needs):

a. Detoxification support (antioxidants, Epsom salt baths, etc.)

b. Mitochondrial and methylation support (methyl-B12, DMG, TMG, certain forms of folate, etc.)

As noted in "Anesthesia and Mitochondrial Cytopathies" (Cohen, et al.), "the safest anesthetic is not known, and the choice of anesthetic must be individualized to the patient's particular needs. Although anesthetic agents may play a contributing factor in causing an adverse event associated with surgery, the illness, the stress of that illness, the surgical procedure and concurrent infections may play a larger role in causing neurological deterioration."

As research in this area continues to emerge, when faced with the need for a procedure requiring anesthesia in a child with ASD and mitochondrial dysfunction, consider further evaluation and discussion with the child's physicians about factors that may put him/her at increased risk for complications and regression.

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Additional information and websites of interest:

Several issues that anesthesiologists should consider prior to anesthesia selection are discussed in an article titled "Information for Anesthesiologists and Surgeons for Operative and Preoperative Care of Patients with Mitochondrial Disease." The article can be found on the www.epidemicanswers.org website.

The Mitochondrial Medicine Society www.mitosoc.org

The United Mitochondrial Disease Foundation (UMDF) www.umdf.org

MitoAction www.mitoaction.org