

Anesthesia and Sedation Risks in Children Labeled with Autistic Spectrum Disorder

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Children who are labeled Autistic Spectrum Disorder have a range of medical problems across many organ systems. For children with this complex disorder, procedures such as endoscopies, colonoscopies and ear tube placement are all common medical procedures that require anesthesia.

What complications are sometimes seen in ASD children, following anesthesia and sedation?

For many children with ASD anesthesia and sedation presents no complications. However, for some children with ASD, anesthesia comes with significant adverse reactions:

1. Great difficulty coming out of the anesthesia. Exceeding a normal time frame for “recovery”.
2. Developmental regressions- loss of developmental skills after anesthesia including expressive and receptive language, gross motor skills, fine motor skills, cognitive skills and overall neurological deterioration (skill loss may be permanent in some children)
3. Excessive fatigue and reduced energy levels following anesthesia or sedation (for days, weeks, on-going)
4. Even death, in the most extreme cases

For some ASD children, the effects of anesthesia are catastrophic, losing years of language and developmental gains after anesthesia and sedation in a massive developmental regression. The purpose of this document is to highlight the medical issues surrounding anesthesia and sedation in ASD children so parents are better informed prior to their child having a procedure that requires either.

What are the risk factors for anesthesia complications?

A few of the risk factors for adverse reactions from anesthesia are:

1. a history of seizures
2. preoperative respiratory problems
3. poor clinical condition of the patient prior to the procedure
4. undiagnosed mitochondrial disease (disorder of energy production)

A lot of recent research has emerged recently suggesting that many ASD children may actually have an underlying mitochondrial myopathy known as mitochondrial oxidative phosphorylation (called, OXPHOS). “Recently, Oliveira and colleagues published a population-based survey of school age children with ASD. They found that 7% of those

who were fully tested met criteria for definite mitochondrial respiratory chain disorders and were also clinically indistinguishable from other children with ASD.” In 2008, at the American Academy of Neurology’s 60th Annual Meeting, the following data was presented. “A retrospective analysis of 41 children with ASD who were being evaluated for suspected mitochondrial disease showed that 32 (78%) had defects in skeletal muscle oxidative phosphorylation (OXPHOS) enzyme function and 29 of 39 (74%) harbored abnormalities in the OXPHOS proteins.” This emerging research suggests that mitochondrial disorders are extremely prevalent among ASD children which makes them “at risk” for anesthesia regression/issues, like other children who have confirmed of clinically diagnosed mitochondrial disease.

What this indicates is that many ASD children actually have underlying disorders of mitochondrial oxidative phosphorylation, due to mitochondrial disease, but remain essentially “undiagnosed”. Children that have a diagnosis of a definitive mitochondrial myopathy are aware of the risks involved in procedures requiring anesthesia and the following precautions are taken with these children when using anesthesia and sedation.

In November 2009, Dr. Richard Kelly, a well known geneticist from the Kennedy Krieger Institute, who is also knowledgeable about autism, has stated that the following labs should be completed prior to anesthesia (in children with known mitochondrial disease) to reduce the risk of complication during and after anesthesia and sedation. “Prior to the anesthesia, the patient should have a complete physical examination and laboratory testing pertinent to known and potential medical problems. Baseline laboratory testing at the time of admission or in the previous week for outpatient procedures should include:

1. comprehensive metabolic profile
2. magnesium
3. CBC with differential
4. creatine kinase
5. amylase
6. ammonia”

There is increasing evidence that a large number of ASD children have underlying mitochondrial myopathies, also known as respiratory chain disorders or disorders of energy production.

In an article posted on the United Mitochondrial Disease Foundation web site written by leading experts in the field of mitochondrial medicine, Bruce Cohen M.D., John Soffner, M.D., and Glenn DeBoer, M.D., titled *Anesthesia and Mitochondrial Cytopathies*, make the following recommendations for patients with mitochondrial disease.

“1. Strict attention should be made to respiratory function before, during and after surgery, especially in patients with abnormal preoperative respiratory signs and symptoms. Vigorous respiratory physiotherapy should be standard postoperative care in patients with pulmonary difficulties. Early use of ventilation, maintaining normal

oxygenation, Co2 elimination and vigorous respiratory physiotherapy should be standard preoperative care in any patient with pulmonary difficulties.

2. There should be a heightened level of suspicion for infection such as pneumonia, which should be promptly treated.
3. Lactated Ringer’s solution (also known as Ringer’s lactate) **should be avoided** as an intravenous fluid during the procedure, as it contains lactic acid (and these children generally have elevated blood lactate levels).
4. Normal blood glucose, body temperature, and acid-based balance should be maintained during surgery. Low blood glucose should be avoided. However, a high blood glucose may indicate an acute disturbance in pyruvate metabolism or oxidative phosphorylation. In this situation, lactic acid levels may be elevated.
5. Avoid depolarizing muscle relaxants (such as succinylcholine) although these have been safely used in many patients with mitochondrial diseases. Anesthesiology 1979: 51:343-345
6. Delay elective surgery if there is any evidence of infection.
7. Potent inhalational anesthetic agents appear to be safe in the majority of patients with mitochondrial disease. In patients at risk for MH (malignant hypothermia), such as those patients with myopathies that are often associated with their mitochondrial disease, the risks and alternative methods of anesthesia must be considered by the physician. Certainly if there has been a previous adverse reaction in the patient or family member, these agents should be avoided.

Table 1: Malignant Hyprethermia (MH) Precautions

Factor	Treatment
History	Acknowledge the potential for problems in patients with muscle disease, those with a past history or a family history of MH
Muscle Relaxants	Avoid depolarizing drugs such as succinylcholine; and use non-depolarizing agents such as pancuronium instead
Anesthetic Agents	-Avoid the potent inhalational agents such as halothane and enthrone -Use agents such as nitrous oxide, barbiturates, benzodiazepines, and narcotics
Preparations for MH	Have adequate amounts of Dantrolene available and use it as soon as the first signs of MH occur

8. Anesthesia with combinations of barbiturates, narcotics, benzodiazepines, and nitrous oxide also pose a theoretical risk for patients with disorders of oxidative phosphorylation. (Table 2) This risk should be considered only as a potential risk unless a patient has

experienced a bad reaction to any of the medications. The apparent paradox between the two methods of general anesthesia must be addressed with each patient, and the anesthesiologist must determine what is the safest route.

9. Animal studies indicate that propofol, a new intravenous anesthetic, impairs mitochondrial function to a greater degree than other anesthetics. However, this drug has been used safely as an anesthetic in many patients with mitochondrial cytopathies. 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.”

Doctors Cohen, Shoffner and DeBoer make the following conclusion: “ An increased awareness is needed whenever a person with a mitochondrial cytopathy is contemplating or undergoing a surgical procedure. By virtue of the illness itself, there are greater risks involved with every medical intervention. 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. With additional research, more will be learned about these problems.”

The following table created by Dr. Cohen, Dr. Shoffner and Dr. DeBoer illustrates the adverse effects of general anesthesia on mitochondrial function.

Table 2- Effects of Anesthetic Agents on Mitochondrial Function

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 N ₂ O)	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

Therefore, the logical connection is that some of the precautions taken in mitochondrial patients should be considered with ASD children when anesthesia is selected because some children with ASD share problems with energy production just like children with diagnosed mitochondrial myopathies. Both groups may have elevated blood lactate, glucose metabolism issues, trunk muscle weakness, and respiratory problems.

Marni J. Falk, M.D., Assistant Professor of Pediatrics, Division of Human Genetics at The Children's Hospital of Philadelphia recently spoke on the Gen Cast Network in October 2009 in a pod cast and she reported that she and her research team have identified the exact “sub-unit” Lamda within the respiratory chain (Lamda is one of the three known sub-units within complex 1) that is responsible for anesthesia control. She conducted this research in conjunction with two well known anesthesiologists from University of Washington, Dr. Douglas Morgan and Dr. Margaret Sedensky who have been studying the mechanism of anesthesia since the 1990's. The importance of this emerging research is that the extent of Complex I subunit Lamda impairment seems to correlate with the patients response to anesthesia. To what extent a child has a reduction in Complex1 enzyme function (within sub-unit Lamda) appears to translate to a patient's surgery and anesthesia response. What this research group has discovered is that a typical functional dose of anesthesia may be too high a dose if sub-complex I Lamda isn't working correctly in a patient and they further hypothesis that this may be what is responsible for hypersensitivity to anesthesia in some patients resulting in subsequent poor anesthesia response. This is important research as it will help provide more information about the inner workings of mitochondria and what is actually happening when a child has an adverse reaction to anesthesia and sedation.

Why do some ASD children experience terrible and irreversible adverse reactions to anesthesia while others do not? Could it be that some ASD children actually have reduced mitochondrial function within sub unit Lamda within Complex I?

What other research exists regarding the risks of anesthesia selection?

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. “On the strength of the current findings, we believe that 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.”

In 2004, Kalikiri, et al. published an article outlining the implications of elevated homocysteine and methylmalonic acid levels when nitrous oxide is administered. “Blood homocysteine assays by High Performance Liquid Chromatography (HPLC) should be considered before using nitrous oxide as anesthesia in patients with a personal or family history of cardiovascular disease, but in whom the well-established risk factors for cardiovascular disease such as smoking, high blood cholesterol, high blood pressure, diabetes, physical inactivity and obesity do not exist. If these patients show elevated homocysteine levels, further work up for the etiology of elevated homocysteine levels should be done before using nitrous oxide as anesthesia.”

“In patients with B vitamin complex (B6, B12 and Folate) deficiency as the cause of elevated homocysteine levels, a one-week course of oral B vitamins can prevent the postoperative increase in homocysteine from nitrous oxide.”

Pramood C. Kalikiri, M.D. and Reena Sachan Garjraj Singh Sachan M.D continued on to report, “Patients with suspected B12 deficiency (megaloblastic anemia and neurological dysfunction) should undergo serum B12 and methylmalonic acid assays before using nitrous oxide as anesthesia to prevent postoperative morbidity and mortality due to myocardial ischemia and neurological deterioration resulting from elevated plasma homocysteine and methylmalonic acid levels respectively. If B12 deficiency is diagnosed, the patient should receive a one-week course of B vitamins before using nitrous oxide to prevent postoperative complications such as myocardial ischemia and neurological dysfunction.”

It is important to know the associated risks before anesthesia and or sedation is selected and the procedure takes place. The following testing should be considered by your physician prior to giving anesthesia to a child labeled ASD, based on the above research.

1. Testing for MTHFR mutations/deficiency.
2. Check homocysteine level.
3. Check serum B12 status.
4. Check methylmalonic acid assays (especially if the child is suspected to be B12 deficient)
5. Do fasting glucose levels to make sure there are not problems with glucose metabolism.
6. Check a child’s lactate levels (on a morning fast, without a tourniquet, in a free flowing venipuncture).

What are other healthcare providers saying about anesthesia in ASD children?

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 (where they work with Dr. Anju Usman) discussed the risk of anesthesia in ASD children and proposed the following:

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

1. Ask not to use Nitrous Oxide (as many ASD kids have B12 deficiency)
2. Consider placement of an IV **without sedation** (midazolam (Versed) or other)
3. Inform the anesthesiologist of all medications and supplements your child is taking at the time of the procedure
5. Make the anesthesiologist aware of IgE allergies
6. Make the anesthesiologist aware that your child has difficulty detoxing
7. Discuss any other drugs that might also be given during the procedure

After the anesthetic, implement the following liver detoxification protocol:

1. Activated charcoal

2. DMG, TMG, methyl B12, methylfolate
3. Epsom Salt baths
4. Silymarin (milk thistle)
5. Bentonite Clay
6. Antioxidants- vitamin A, C, E
7. Magnesium
8. Reduced Glutathione

Many ASD children actually have undiagnosed MTHFR deficiency making nitrous oxide a poor choice. And some ASD children have an undiagnosed mitochondrial disorder which impairs energy production and makes anesthesia selection, procedures and precautions even more critical.

With anesthesia there are always some associated risks and even being cautious, there is no guarantee that the procedure will not have complications. Becoming better informed and advocating for the careful selection of anesthesia and sedation in you child with your chosen anesthesiologist, will reduce the likelihood of problems for your child.

What precautions should be taken prior to the procedure?

1. Giving a B vitamin complex (B6, B12 and Folate) one week prior to the procedure should be discussed with your physician.
2. Make sure your child is well hydrated (with water) prior to the procedure
3. Minimize the length of the fast required. Request that your child be the first procedure of the day. See Dr. Kelly's article for further information on fasting prior to the procedure and discuss this with your physician and anesthesiologist.

How should the parent of an ASD child best advocate for their child prior to a procedure requiring anesthesia and sedation?

1. Know what type of anesthesia and sedation your child is getting prior to the procedure
2. Get some lab work done in advance on your child
3. Communicate your concerns to the doctor and anesthesiologist clearly **and in writing** prior to the procedure.
4. Share this document with your doctor and anesthesiologist prior to the procedure.

Make sure your child's doctors fully understand the complex issues surrounding children with ASD, undiagnosed mitochondrial disease and anesthesia and sedation selection in this patient population. This is important because there is very little knowledge in the general medical community about the link between mitochondrial disease, ASD and anesthesia/sedation risks.

Dr. Kelly discusses several poignant issues every anesthesiologist should consider prior to anesthesia selection in his article titled, Information for Anesthesiologists and Surgeons for Operative and Preoperative Care of Patients with Mitochondrial Disease.

Research Articles:

Kelly, R. (2009) Information for Anesthesiologists and Surgeons for Operative and Preoperative Care of Patients with Mitochondrial Disease. Kennedy Krieger Institute **(need a link to document)**

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Falk MJ. (2010) Mitochondrial Gene Defects and Disorders –Interview with Marni J. Falk, M.D., Assistant Professor of Pediatrics, Division of Human Genetics, The Children's Hospital of Philadelphia, the audio web cast is available on the Mitochondrial Medicine Society website (www.mitosoc.org) approx. 22 minutes long
<http://www.genengnews.com/genecasts.aspx?id=286>

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<http://www.autismone.com/content/how-get-your-mainstream-physician-see-beyond-autism-sonja-hintz-rn-and-sym-rankin-crna-apn>

Additional websites of interest on this topic:

The Mitochondrial Medicine Society
<http://www.mitosoc.org/blogs/diagnosis>

The United Mitochondrial Disease Foundation (UMDF)
<http://www.umdf.org/site/c.otJVJ7MMIqE/b.5472191/k.BDB0/Home.htm>

MitoAction
<http://www.mitoaction.org/>