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General Anesthetic Use in Fragile X Spectrum Disorders

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Abstract

The fragile X premutation is characterized by a repeat expansion mutation (between 55–200 CGG repeats) in the Fragile X Mental Retardation 1 (*FMR1)* gene, which leads to RNA toxicity at the cellular level. This may cause patients with the premutation to be particularly susceptible to environmental toxins, which could manifest clinically as new or worsening ataxia and memory loss. Multiple published case reports have also suggested general anesthetics as a potential toxin leading to negative side effects when used in patients with fragile X- associated disorders. However, at this time, there have been no formal research studies regarding cellular changes or long-term clinical manifestations after general anesthetic use in this population. This review aims to highlight previous case reports regarding sequelae related to general anesthetic use in fragile X-associated disorders. New case reports related to this phenomenon are also included.

Keywords

FXTAS; fragile X syndrome; *FMR1* mRNA; general anesthesia; postoperative cognitive dysfunction; POCD

Introduction

Fragile X spectrum disorders are due to an unstable cytosine-guanine-guanine (CGG) repeat expansion mutation in the Fragile X Mental Retardation 1 (*FMR1)* gene, which codes for the fragile X mental retardation protein (FMRP). Greater than 200 CGG repeats (full mutation)

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causes *FMR1* to become methylated and transcriptionally silenced leading to the absence of FMRP and the development of fragile X syndrome (FXS). Patients with FXS have developmental delays, behavioral problems and often an autism spectrum disorder (ASD).[1] These patients are easy to recognize due to their prominent ears, hyperextensible joints and behavior problems related to their intellectual disability. In contrast, the fragile X premutation (55 to 200 CGG repeats) typically does not cause unusual physical features nor intellectual disability. This is because normal levels of FMRP are usually produced since the gene is not turned off from methylation as it is in the full mutation. Instead, excessive transcription occurs, leading to high levels of *FMR1*-mRNA (typically 2 to 8 times normal levels).[2] Having a family member diagnosed with FXS is an indicator of possibly being a carrier of the premutation. Patients with the premutation can also be recognized by the medical problems associated with the premutation, including primary ovarian insufficiency (FXPOI: menopause before age 40), neuropathy, psychiatric problems including depression and anxiety, migraines, hypertension, propensity for autoimmune diseases such as hypothyroidism, fibromyalgia, chronic pain syndrome and the fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS is a neurodegenerative syndrome involving an intention tremor, cerebellar ataxia, cognitive decline and white matter hyperintensities in addition to atrophy on MRI.[3]

The high levels of *FMR1* mRNA in premutation carriers cause RNA toxicity at the cellular level primarily through sequestration of proteins that are essential for neuronal function.[3,4] Additional causes of toxicity in premutation carriers include: calcium dysregulation in neurons, as described by J. Liu et al. in induced pluripotent stem cell (iPSC)-derived *FMR1* premutation neurons[5] and by Robin et al. in animal models[6], mitochondrial dysfunction,[7] iron dysregulation and iron deposition in the brain,[8] chronic DNA damage repair signaling[9] and formation of FMRPolyG secondary to repeat associated non adenine-uracil-guanine (AUG) (RAN) translation.[10] FMRPolyG is an abnormal FMRP that can be neurotoxic due to a polyGlycine tail.

FXTAS as one of the presentations of premutation carriers has a typical onset at around 60 years of age.[11,12] The size of the CGG repeat expansion correlates positively with the number of CNS inclusions, and negatively with the age of onset and age of death from FXTAS.[13] Recent reports have also shown carriers of the gray-zone allele (45–54 repeats), [14,15] the unmethylated full mutation,[16] or carriers of mosaic alleles – a combination of a premutation allele and a full mutation allele[17] to be susceptible to developing FXTAS as well.

As previously mentioned, FXTAS manifests as a progressive intention tremor and gait ataxia, although patients may develop additional complications such as memory and executive function deficits.[18] Definitive criteria for the diagnosis of FXTAS include an underlying premutation allele, CNS white matter lesions in the middle cerebellar peduncle (MCP sign) and/or brain stem, and neuronal intranuclear inclusions found post-mortem.[9,19–21]

The premutation can be identified by ordering a fragile X DNA test which involves only a PCR study rather than DNA sequencing and is usually covered by insurance.

Approximately 40% of males and 16% of females with the premutation develop FXTAS.[22,23] Due to incomplete penetrance, it is hypothesized that additional genetic or epigenetic influences, environmental toxins, or protective factors likely play a role in its development.[12] Premutation neurons die earlier in culture compared to neurons without the premutation suggesting a general vulnerability of premutation cells.[24] Previous case reports have implicated environmental toxins,[25] medical comorbidities,[26] substance abuse,[27,28] and pharmacological treatments[29] as toxic insults that may exacerbate or accelerate FXTAS symptoms.

A number of reports, as well as anecdotal evidence, suggest general anesthetics may serve as a toxic insult to older premutation carriers, thereby worsening symptoms of tremor, ataxia, and/or cognitive decline.[3,12,30,31] While there is case evidence of these effects, there are no studies that have formally explored the consequences of general anesthesia in older premutation carriers to date. This paper will review case reports of premutation carriers who have experienced negative side effects following general anesthesia, review the toxicity of different types of general anesthesia and provide additional new reports encountered through medical practice.

Effects of Anesthesia in Elderly Population

There are numerous reports about neurocognitive side effects after surgery and use of general anesthetics in the elderly population. The most notable includes postoperative cognitive dysfunction (POCD), which was first described in the Lancet in 1955.[32] POCD is characterized by a reduction in the ability and speed of information processing, particularly in areas of learning, memory, concentration, executive function, and mental flexibility following a major operation.[33] These changes are often subtle and prolonged following surgery; however, most effects are not permanent and tend to decrease with time.[34] Nonetheless, some evidence suggests POCD is associated with higher mortality.[35,36] Currently, there is no rigid definition or accepted criteria for diagnosing POCD, making it difficult to compare studies and trials.[37]

Apart from advanced age, several other risk factors for the development of POCD have been identified. Reduced preoperative cognitive level, lower preoperative educational level, mild cognitive impairment (MCI), and previous cerebral vascular accidents[38] increase the risk of POCD. They are thought to limit “brain reserve” and recovery following general anesthesia and surgery. Additional patient-related risk factors include MRI evidence of white matter disease,[39] as well as the co-existence of a metabolic syndrome.[40,41] Non-patient related risk factors include inpatient surgery (versus outpatient surgery), more invasive surgery, and the need for a second operation.

Additional risk factors include postoperative pulmonary complications.[35,42–45]

The etiology of POCD is under debate. Some research suggests this may develop due to the surgical stress itself.[45–47] Inflammatory responses are presumed to play a role in the development of POCD.[37,48] These responses can also lead to a disruption of the blood-brain barrier as another presumed mechanism.[37,49,50]

Other studies suggest cellular changes secondary to general anesthetic use. For example, alterations in calcium homeostasis are considered to be one factor leading to neurotoxicity and apoptosis.[51] Other studies have shown reduced neuronal proliferation and differentiation that could potentially explain cognitive changes.[52] Synaptic plasticity may also be impaired and therefore play a part in cognitive decline.[37,53] Recently, biomarkers for neuronal injury have received more attention and are being investigated to identify patients at risk and to quantify cerebral damage.[37,47,50,54,55] It is important to note that in non-cardiac surgeries, hypotension and cerebral hypoperfusion have not been shown to be causative mechanisms of POCD.[42]

Whether the type of general anesthesia has an influence on the development or severity of POCD is being discussed. Some studies have concluded certain volatile anesthetics might cause more severe forms of cognitive impairment.[56,57] Of these, Isoflurane and Sevoflurane have been the most studied for the development of POCD.[48,51,58–63] Propofol, on the other hand, has been shown to have a more favorable side-effect profile, and may limit the development of POCD.[64–66] Other studies, however, have found contradicting evidence showing no increase in overall incidence of POCD with general anesthetics.[67,68] Ultimately, the results of POCD studies have to be taken with a degree of caution as the overall quality of these studies has been questioned.[37,69] With patient consent we here report two cases of premutation carriers with FXTAS who have experienced progression of their motor and/or cognitive problems after general anesthesia suggesting that this group of patients because of their molecular profile are at high risk for CNS dysfunction after anesthesia.

Case Reports

Case 1

Case 1 is a 70-year-old Caucasian male with FXTAS who underwent surgery for an asymptomatic ascending aortic aneurysm. Prior to surgery, he was living independently and able to attend to his activities of daily living. However, he was having tremor, intermittent ataxia, and had fallen a number of times. His premutation of 101 CGG repeats in *FMR1* was discovered in 2008 after his daughter was diagnosed with FXPOI. Prior to this discovery, his neurologist had diagnosed benign senile tremor, and cerebral MRIs showed nonspecific grey matter changes with dilated ventricles.

His past medical history was significant for gastroesophageal reflux for which he had multiple upper gastrointestinal endoscopies, a Nissen fundoplication, and for which he required famotidine.

He used albuterol as needed for asthma; his hypertension was controlled with labetalol.

He underwent uneventful elective repair of the aneurysm that required cardiopulmonary bypass under general anesthesia with isoflurane and fentanyl. His postoperative course was complicated by possible seizure activity on post-operative day one; although a 24-hour video EEG was negative. He was discharged to an inpatient rehabilitation facility on post-operative day six. While in the rehabilitation facility, he was more unsteady on his feet, and initially required a walker for ambulation, but eventually progressed to a cane. When he was

discharged home after 14 days, he was able to ambulate without assistance. Upon his return home, he reported more difficulty walking and using the stairs, and his falls became more frequent. His tremor and penmanship also deteriorated to a new, lower plateau. This deterioration necessitated moving to a single level residence with more frequent assistance by family members.

Case 2

Case 2 is a 74-year-old Caucasian male with FXTAS who underwent microlaminectomy for a herniated disc at L4–L5. Prior to surgery he lived with his wife and was able to attend to his activities of daily living. He had mild ataxia and a subtle gait disturbance. His premutation had 95 CGG repeats. His past medical history was significant for coronary artery disease, status-post coronary artery bypass surgery; atrial fibrillation, for which he was being treated with warfarin and digoxin; and hypertension controlled with metoprolol, hydrochlorothiazide, and amlodipine. The microlaminectomy was performed under general anesthesia with desflurane and fentanyl. The surgery proceeded uneventfully. He remained in the hospital overnight and was discharged the next day. Upon discharge, he returned home with his wife and there were not any immediately reported changes in ataxia and gait. However, over the course of the next month the patient experienced a significant deterioration in balance that culminated in a fall requiring a visit to the emergency room. He was treated for minor skin abrasions and a CT of his head was devoid of any intracranial bleed. However, neurological examination revealed a significant deficit in gait, and increased ataxia so that he was discharged to an inpatient rehabilitation facility. It was clear at this point that his functional ability had deteriorated such that he would require more assistance with ambulation including regular use of a cane.

While the reason for the decline in these patients after their respective surgery and anesthesia is not clear, it seems reasonable to investigate the potential causes such as inhalational anesthesia or the inflammatory process that occurs as a consequence of surgery.

Summary of Additional Case Reports in Literature

We reviewed seven case reports for patients with the fragile X premutation that have a documented history of general anesthesia before or after the onset of neurological symptoms in adulthood (see table, supplemental digital content 1). Two gray- zone carriers were included in the review. The gray-zone (GZ; 45–54 CGG repeats in the *FMR1* gene) is rarely associated with FXTAS; and several studies have found a high frequency of GZ in movement disordered populations.[14] One patient with an unmethylated full mutation was also included due to his development of FXTAS symptoms after surgery.[17] These patients have increased transcriptional levels of *FMR1* mRNA consistent with the pathophysiology of premutation disorders.

Four patients reported worsening symptoms such as neuropathy, ataxia, and fine motor problems within three months of general anesthesia,[19,31] and six of the highlighted patients experienced worsening of symptoms within one year from their procedure. Three patients were identified to have multiple surgeries in their lifetime, and all three patients experienced neurocognitive declines after a subsequent surgery and before age 70. The worsening

symptoms in most of these case reports suggests general anesthesia may be a neurotoxin that accelerates FXTAS symptoms or decreases the age of onset of FXTAS, similar to the timelines of FXTAS symptoms triggered by environmental toxins,[25] methadone[28] or alcohol/ opioid use[27] described in other case reports. Each older patient who underwent general anesthesia experienced progressive deterioration without evidence of symptom improvement.

It should be noted that the stress from the surgical procedure itself could be a confounding factor that serves as a catalyst in the development of FXTAS symptoms.[46,47,60] Moreover, three of the reviewed cases underwent chemotherapy and/or radiation therapy prior to or after their surgical treatment, which likely added to the propensity of FXTAS symptoms. Finally, one patient underwent neurosurgery, which in itself could have caused the balance issue and neurological problems described.

In regards to the cases presented here, it is unclear if the patients' trajectory of cognitive decline actually worsened or whether this was perceived as such due to observational bias and an attempt to find causality. Nevertheless, these case reports cannot be dismissed and need to be carefully examined. It is also hard to elucidate if the underlying disease process necessitating surgery, the inflammatory response due to surgical stress, the specifics of the surgery (e.g. cardiopulmonary bypass) or the anesthetics led to the decline in cognitive skills.

Possible Mechanisms of Anesthesia Toxicity

The effects of general anesthesia have been investigated in other disease models, which may provide insight into the mechanisms of FXTAS progression. A systematic review in 2016 concluded that the volatile anesthetics, Isoflurane and Sevoflurane, may accelerate the development of cognitive dysfunction in the general population.[63] In Alzheimer's disease (AD) studies, these anesthetics have been shown to increase beta amyloid production leading to protein aggregation and plaque deposition in both tissue and mouse models.[48,51,58–62] This is considered to be due to anesthetic-induced calcium dysregulation leading to increased pro-apoptotic caspase activity and altered proteolysis.[51] However, despite this relationship between calcium dysregulation and plaque formation, the number of plaque deposits in AD has not been shown to correlate with the degree of cognitive deficit.[70] Alternatively, it is speculated that increased calcium loads may lead to a general state of neuronal cytotoxicity, as evident from *in vitro* studies of Presenilin-1 (*PSEN1*) gene mutations.[71] *PSEN1* normally regulates calcium release from the endoplasmic reticulum, and mutations in this gene are associated with familial AD. In the presence of some general anesthetics, *PSEN1* mutations allow excessive calcium release from the endoplasmic reticulum compared to wild-type levels, which correlated with increased marker levels of mitochondrial dysfunction and cell membrane damage.[71] Since calcium dysregulation - elevated intracellular Ca2+ levels and early dysregulation of Ca2+ homeostasis - occurs in premutation neurons,[5,72,6] it is possible that anesthetic agents exacerbate this dysregulation in premutation neurons.

Tau protein aggregation is another core pathophysiological feature of AD. Tau protein normally acts as an accessory protein for microtubule assembly, but is hyperphosphorylated in AD leading to aggregation. General anesthetics have been shown to increase tau protein phosphorylation *in vitro* in mouse models,[73–75] with some studies reporting this effect lasting hours[75] to weeks[73] following anesthesia. Altered Tau protein activity is believed to be a cause of POCD. Whittington et al. (2011) showed propofol inhibited phosphatase activity providing further evidence that altered Tau protein activity may be a catalyst for pathophysiological changes at the cellular level.[75] Finally, the timing of surgery and anesthesia may be a contributing factor as patients with exposure to general anesthesia before age 50 showed an earlier onset of AD, whereas patients with exposure after age 50 did not show such a relationship.[76] Interestingly, studies in mouse models have shown anesthetics may enhance or inhibit the effects of certain phosphatase activity depending on the age of the mouse.[77,78] Some studies have suggested that propofol might be able to improve cognitive function in patients with AD due to its agonistic effect on GABA receptors and attenuation of mitochondrial dysfunction that is secondary to amyloid beta accumulation.[66] Since mitochondrial dysfunction is a significant problem in FXTAS,[7,79,80] propofol may be the safest anesthetic agent to use in this population. Future studies should investigate the additive effects of calcium dysregulation with certain anesthetic agents and whether a synergistic effect is seen with the calcium abnormalities in premutation neurons. There is currently a knock- in mouse model for the premutation that models the neuropathology and cognitive deficits reported in fragile X premutation carriers. This animal has been used for studies of FXTAS and calcium dysregulation.[6,81] In addition, premutation neurons can be studied on microelectrode arrays to assess inter-neuronal communication and electrolyte changes[6] with and without anesthetic agents.

Randomized controlled clinical trials comparing patients suffering from FXTAS with a matched cohort could clarify if patients with FXTAS are indeed more susceptible to neurotoxic effects of general anesthesia and if their trajectory of decline does accelerate. Further clinical studies comparing different anesthetic agents (e.g volatiles versus propofol, addition of Dexmedetomidine) are also warranted to identify the safest choice in the adult premutation population. It would also be interesting to investigate if patients with the premutation have a different anesthetic requirement to achieve adequate depth of anesthesia.

Conclusion

This case series highlights two trends, which, combined, are distinct causes for concern in the premutation population: 1) many cases exhibited a lack of symptom reversibility despite a single exposure to general anesthesia, and 2) multiple exposures to general anesthesia may severely accelerate decline in cognition. While the underlying pathophysiology remains unclear, research in AD provides some insight into possible mechanisms contributing to the development of FXTAS such as anesthesia-induced calcium dysregulation and altered Tau protein activity. Further research is necessary to fully comprehend the effects of general anesthesia in patients with the fragile X premutation.

We have recommended that general anesthesia should be avoided in older premutation carriers if possible,[82] but this is obviously not always an option. The case reports highlighted

in this review suggest that some general anesthetics may contribute to the development or progression of FXTAS in premutation carriers. Carriers experience mitochondrial dysfunction and calcium dysregulation even before the onset of FXTAS, and these may be important factors in creating vulnerability of the premutation neurons to the effects of general anesthesia. This review has highlighted the toxicity of various forms of anesthesia. If general anesthesia is necessary, then the least toxic forms should be utilized. The evidence acquired from research mentioned in this article suggests that propofol might be the most reasonable and safest choice. This could be paired with a depth of anesthesia monitor to avoid unnecessary depths of anesthesia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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