Attention-Deficit Hyperactivity and Anxiety Disorder in a Child with Repeated Exposure to General Anesthesia

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Abstract

Background: Repeated and prolonged exposure to general anesthesia in early childhood has increasingly been linked to adverse neurodevelopmental outcomes like Attention-Deficit Hyperactivity Disorder(ADHD) and Anxiety.

Case presentation: We report the case of an 8-year-old boy who presented with attention difficulties, executive dysfunction, and anxiety symptoms. His medical history was notable for fibular hemimelia, necessitating multiple prolonged surgeries under general anesthesia during critical periods of brain development. The patient was subsequently diagnosed with ADHD and comorbid anxiety, which responded well to methylphenidate and methylfolate.

Methods: A qualitative investigation of English language literature published after the year 2000 was performed in PubMed and Google Scholar. Keywords included ADHD, anxiety disorders, general anesthesia, and neurodevelopmental outcomes. The review encompassed various study designs, including case reports, large cohort studies, and meta-analyses.

Conclusion: This case uniquely demonstrates the concurrent emergence of ADHD and anxiety, potentially linked to repeated general anesthesia exposure. It highlights the importance of long-term neuropsychiatric monitoring in children undergoing early and recurrent surgeries, and the need for further research into the sequelae of pediatric anesthesia.

Keywords: ADHD; Anxiety; Case Report; General anesthesia; Neurodevelopment; Pediatric Surgery; Review of literature.

Introduction

General anesthesia(GA) is a medically induced state of unconsciousness that interacts with neurotransmitter systems and modulates neuronal communication between different brain regions.[1] Undergoing surgery with GA is an essential process for children who have severe medical problems. Although GA has been previously considered a safe approach for facilitating invasive procedures, long-standing concerns remain prevalent regarding its safety. [1] Given the heightened vulnerability of the brain during the critical periods of synaptogenesis, it is plausible to hypothesize that exposure to pharmacological agents during this time may affect brain functions.[2] However, it remains unclear whether GA increases the risk of neurocognitive and other psychiatric outcomes in children.[5]

In this context, we narrowed the focus to Attention-Deficit/Hyperactivity Disorder (ADHD) and anxiety disorders associated with early exposure to GA. ADHD is one of the most common neurodevelopmental disorders in children.[12-14] It is characterized by inattention, impulsivity, and hyperactivity, leading to critical impairment in childhood.[12-14] The global prevalence is estimated to range between 7.6% and 11.4% indicating that approximately one in ten children in the United States has been diagnosed with ADHD at some point.[12-14] Several studies have shown that individuals who are previously exposed to anaesthetic agents have a higher risk of inattention and aggressive behaviour.[6,7,9,10] This trend exhibits a positive correlation between the number and duration of the drug exposure.[7,8] A previous retrospective cohort study reported significantly higher scores in obsessive-compulsive symptoms and social phobia in children with multiple anesthesia exposures before the age of three compared to unexposed controls.[11]

Furthermore, repeated exposure to GA and surgery in early childhood has also been associated with anxiety-related behaviours.[10] Anxiety disorders are an umbrella term encompassing fear-related conditions such as generalized anxiety disorder, panic disorder, and specific phobias.[15] These disorders are common in the pediatric population and frequently co-occur, with comorbidity rates ranging from 25%- 50%.[15-17] Children diagnosed with both ADHD and an anxiety disorder tend to exhibit greater impairments in mood regulation and executive functioning, despite showing reduced levels of hyperactivity and impulsivity.[18] In contrast, the evidence linking GA to anxiety disorders remains limited. In this review, we focus on the relationship between early exposure to anesthesia and the development of both ADHD and anxiety disorders. We report the first case specifically highlighting the association between GA and the development of ADHD and anxiety disorders

Case Presentation

An 8-year-old boy presented to the clinic with significant learning difficulties and behavioral concerns. The child's difficulties included pronounced distractibility, restlessness, impulsive behavior, and pervasive anxiety, all of which had a detrimental impact on his academic performance and social interactions. There was no reported family history of any psychiatric illnesses.

His medical history was notable for multiple prolonged surgical procedures under GA during infancy and early childhood periods, critical for brain development. Following these exposures, his parents reported progressive problems with concentration, increasing restlessness, and heightened anxiety.

On examination, physical and neurological findings were unremarkable. Cognitive assessment confirmed severe learning disability with marked impairments in executive functioning and attention regulation. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria, he met the diagnostic requirements for ADHD characterized by persistent patterns of inattention, hyperactivity, and impulsivity, and for anxiety disorder, evidenced by excessive worry.

The patient was started on L-methylfolate (15 mg daily) and methylphenidate hydrochloride (5 mg daily). A follow-up after two weeks was planned, with close monitoring to evaluate treatment efficacy and adjust management as needed.

Methodology:

Inclusion Criteria:

Studies published from the year 2000 onward reflect contemporary clinical and experimental findings. Peer-reviewed articles including original research, systematic reviews, meta-analyses, and case reports relevant to the neurodevelopmental impact of GA exposure, particularly focusing on ADHD and anxiety disorders.

Studies involving pediatric populations (neonates to adolescents) with documented exposure to GA. Preclinical (animal model) studies elucidating mechanisms of anesthesia-induced neurotoxicity and neurodevelopmental alterations.

Articles investigating the pathophysiology, clinical presentation, risk factors, and long-term outcomes related to anesthesia exposure and neuropsychiatric conditions.

Exclusion Criteria:

Studies exclusively involving adult populations without direct implications for pediatric neurodevelopment. Articles focusing solely on anesthetic techniques or perioperative complications unrelated to neurodevelopmental or psychiatric outcomes.

Non-English language publications.

Case Documentation:

The clinical case was documented through detailed patient history-taking, structured psychiatric assessments based on DSM-5 criteria, and review of medical records. Symptomatology was assessed during initial presentation and follow-up visits to monitor progression and treatment response.

Discussion and Review of Literature

Exposure to GA during early childhood may interfere with critical neurodevelopmental processes, potentially contributing to a range of cognitive and behavioral alterations.[20]

ADHD is thought to arise from multifactorial etiologies, involving interactions between genetic predisposition, neurobiological mechanisms, and environmental influences.[27] A leading hypothesis attributes the pathophysiology of ADHD to dysregulation within the dopaminergic and noradrenergic neurotransmitter systems.[27] Individuals with ADHD have been found to exhibit reduced dopamine transporter availability and altered dopamine receptor function, which are associated with deficits in motivation and attentional control.[27] Evidence of delayed cortical maturation, particularly within the frontal lobes, has been observed in children with ADHD, reinforcing the hypothesis of a neurodevelopmental basis for the disorder.[28] The proposed mechanism by which general anesthetics may contribute to ADHD development is by disrupting neural circuitry, glutamatergic imbalance, reduced Brain Derived Neurotrophic Factor (BDNF), and impaired synaptogenesis.[3]

Anxiety disorders are characterized by dysregulation of neural circuits involved in fear processing and emotional regulation, particularly the amygdala, prefrontal cortex, and hippocampus. Hyperactivity of the amygdala, coupled with diminished inhibitory control from the prefrontal cortex, is believed to underlie heightened fear responses and impaired emotional regulation.[4] Neurotransmitters such as Gamma-aminobutyric acid (GABA), serotonin, and norepinephrine are also involved in the pathophysiology.[4] Agents such as sevoflurane have been shown to induce widespread neuroapoptosis and disrupt synaptogenesis, thereby impairing the formation of neural circuits in brain regions critical for emotional processing.[2] The mechanisms through which GA may contribute to the development of anxiety remain under investigation, while emerging evidence suggests otherwise.[2]

Multiple preclinical studies have highlighted potential neurotoxic effects of commonly used anesthetic agents during early stages of brain development. Animal studies in both rodents and nonhuman primates have demonstrated that anesthetic agents such as sevoflurane, isoflurane, and propofol can trigger widespread neuronal and oligodendrocyte apoptosis, frequently accompanied by neuroinflammation and subsequent long-term cognitive or behavioral impairments.[19] Another study suggested that the concurrent disruption of N-methyl-D-aspartate (NMDA) and Gamma-aminobutyric acid (GABA) receptor activity may underlie these neurotoxic effects.[20] However, interventions such as delayed environmental enrichment have demonstrated potential in mitigating anesthesia-induced memory impairments, underscoring the remarkable plasticity of the developing brain.[21] A study in Rhesus macaques, repeated exposure to sevoflurane during infancy was associated with normal fear and hostility responses but heightened self-directed, anxiety-related behaviors (e.g, scratching, self-grooming) under mild social stress.[26] While these findings are compelling, their direct applicability to humans remains uncertain.

In human studies, the evidence remains mixed, though it generally suggests a dose-dependent relationship between GA exposure and the development of ADHD. In a population-based cohort study, Sprung et al. (2012) reported that children with multiple exposures to GA before the age of two had nearly double the risk of developing ADHD, while a single exposure was not significantly associated with increased risk.[8]

A 2024 meta-analysis further supported these findings, concluding that children exposed to GA had an increased likelihood of developing ADHD, with risk amplified in those with repeated exposures. The analysis also indicated that longer anesthesia duration, particularly between 61 and 120 minutes, was associated with a greater risk, although no additional increase was observed beyond 120 minutes.[7]

In a large population-based cohort study from Taiwan, Sun et al. (2024) reported that among 15,072 children aged 0-3 years, the incidence of ADHD was markedly higher in those exposed to GA (122.45 per 10,000 person-years) compared to unexposed children (64.15 per 10,000 person-years). Greater number and longer duration of exposures, male sex, and central nervous system surgery emerged as significant risk factors.[22] The authors concluded that early GA exposure may represent a modifiable risk factor for neurodevelopmental disorders such as ADHD.[22] In another cohort study involving 185,002 children, exposure to anesthesia before the age of five was associated with an elevated risk of developing ADHD, with the risk being greater among those with multiple exposures compared to a single exposure. The association was particularly pronounced in non-White children, indicating potential racial disparities that warrant further investigation.[24]

In contrast, a study of 105 sibling pairs, one sibling underwent surgery with GA at a mean age of 17.3 months, while the other remained unexposed. All exposed children received inhaled anesthetics for a median duration of 80 minutes. At follow-up around age 10, no statistically significant differences were observed between exposed and unexposed siblings in IQ (full-scale, verbal, or performance) or in other neurocognitive and behavioral domains, including memory, attention, executive function, and language. These findings suggest that a single early exposure to anesthesia may not be associated with long-term neurodevelopmental impairment.[23]

While ADHD has been studied more extensively, fewer studies have examined the association between anesthesia and emotional disorders such as anxiety. Bakri et al. (2015) reported that young children who underwent repeated GA exhibited a significantly increased risk of anxiety-related problems, as measured by both the Child Behavior Checklist (CBCL) for ages 1½–5 years and the DSM-oriented scales.[10] Another study observed that children with high pre-sedation anxiety, as well as those of non-White ethnicity, had an elevated risk of negative behavioral changes within 1–2 weeks following procedural sedation with ketamine in the emergency department. These findings highlight a strong association between pre-procedural anxiety and adverse post-anesthesia behavioral outcomes in pediatric populations.[25] Human studies remain limited by confounding factors and inconsistent long-term psychological follow-up.

Conclusion

Our case suggests a possible link between repeated early childhood exposure to GA and the later onset of ADHD and anxiety. The findings from sibling cohort studies indicate this relationship may not be consistent across populations. Further prospective, multicenter research could help clarify dose-response effects and moderating factors such as baseline anxiety or comorbidities. Clinicians might consider incorporating periodic behavioral screening into postoperative follow-up for children with early or repeated anesthesia exposure to support earlier detection and intervention.

List of abbreviations

Attention Deficit Hyperactivity Disorder (ADHD); Brain Derived Neurotrophic Factor (BDNF); Child Behavior Checklist (CBCL); Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR); gamma-aminobutyric acid(GABA); General Anesthesia (GA); N-methyl-D-aspartate (NMDA).

Declarations

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Conflict of interest

None

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