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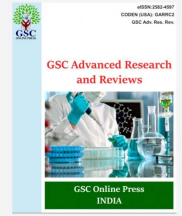


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## Pediatric neurodegenerative disorders and anesthesia considerations

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### Abstract

Pediatric neurodegenerative disorders encompass a wide range of conditions that result from progressive damage to cells and nervous system connections that are essential for mobility, coordination, strength, sensation, and cognition. Neurodegenerative diseases affect millions of people worldwide. Neurological disorders are disorders that involve the brain, spinal cord or nerve and muscle. Children with neurological disorders may have disorders such as epilepsy, developmental delay, cerebral palsy, meningitis, genetic/metabolic diseases or diseases of muscle or nerve such as muscular dystrophy or peripheral neuropathy. These illnesses are frequently severe and potentially have long lasting consequences for the affected children. The pathologies most frequently responsible for psycho-physical disorders can be summarized into three groups: collaboration difficulties (autism spectrum disorders, intellectual impairment, phobia); motor dysfunction (cerebral palsy, epilepsy, other brain pathologies, neuromuscular disorders), and craniofacial anomalies (Down syndrome, other genetic syndromes). Due to their clinical history, and the lack of collaboration, in pediatric non-cooperative patients with Special Needs (SN), the anesthesiological risk may result difficult to assess, despite the fact that they meet the criteria of the outpatient management applied for the patient without disabilities. The perioperative management of pediatric patients with psycho-physical disorders with related relational and cognitive problems must be carefully planned, in order to make the entire hospitalization process as comfortable and as less traumatic as possible. General anesthesia is the most suitable type of anesthesia in pediatric patients with Special Needs (SN), although anesthetic complications are more frequent in these patients, mainly due to comorbidities, taken drugs and anatomical peculiarities. Some studies observed no correlation between multiple anesthesia exposures and neurodevelopmental deficits, while others reported that even a single exposure could increase the risk of deficits. An increased risk of developmental or behavioral disorders as the consequence of surgeries requiring general anesthesia was observed. Based on current studies, it is necessary to endeavor to limit the duration and numbers of anesthesia and the dose of anesthetic agents. The evaluation must include history and physical examination pertaining to the conditions requiring special anaesthetic considerations. Early diagnosis and intervention are crucial in managing these neurological disorders in pediatric patients to improve overall quality of life and long-term outcomes.

**Keywords:** Neurological; Disorder; Pediatric; Anesthesia; Seizures; Complications

### 1. Introduction

Pediatric functional neurological disorder (FND) is a common condition that can affect multiple types of movement or sensation. It is caused by abnormalities in how the brain responds to sensory information. The brain “misfires” and sends signals to the body by mistake. These abnormalities are present at birth and do not come from or cause injury to the structure of the brain. This makes the recovery of FND better, on average, than many brain-based disorders. FND is sometimes confused with other conditions. Doctors used to call it “conversion disorder” or “psychogenic,” but these terms are not up to date with the latest science. You may also hear people refer to “functional movement disorder” or “non-epileptic seizures.” These are subtypes of FND. Importantly, people with FND are not “faking it.” They are not

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consciously controlling their symptoms or using the symptoms to get attention. Neurological disorders commonly seen in pediatric patients include attention deficit hyperactivity disorder (ADHD), developmental delays, epilepsy, migraines, and neuromuscular diseases. These conditions are commonly found in pediatric patients due to various factors such as genetic predisposition, environmental influences, and abnormalities in brain development. ADHD is characterized by inattention, hyperactivity, and impulsivity, and is often diagnosed in childhood. Developmental delays encompass a wide range of conditions that affect a child's physical, cognitive, communication, and social skills. Epilepsy is a neurological disorder characterized by recurrent seizures and is one of the most common neurological conditions in children. Migraines, while often associated with adults, can also occur in pediatric patients and are characterized by severe headaches, often accompanied by nausea, vomiting, and sensitivity to light and sound. Neuromuscular diseases, such as muscular dystrophy, can also manifest in childhood and affect the muscles and their control over movements. There are four types of FND. Each type is named for the effect it has on the body, but all are thought to come from the same brain changes. A person can have more than one type of FND at a time, and the forms they have can change over time. Functional movement disorders are one of the most common types of FND. It affects how a child moves or walks. It can be episodic (come and go) or be constant. Functional seizures (non-epileptic seizures) are another common type. It causes a child to have jerky, shaky episodes. Functional seizures are sometimes mistaken for epilepsy, but they have different causes. Epilepsy is caused by uncontrolled electrical signals in the brain, and functional seizures are caused by the brain handling information incorrectly. Functional disorders of consciousness involve blackouts (periods of unresponsiveness) or episodes of confusion. Functional sensory disorders may result in tingling, numbness or other unusual sensations in parts of the body. These sensations follow patterns that are different than when they have a brain or nerve injury. Symptoms of pediatric functional neurological disorders (FND): weakness, tremor, falls, events that look like seizures, abnormal walking, changes to vision or hearing. Epilepsy is one of the most prevalent neurological disorders in children, characterized by recurrent seizures. Seizures can vary in severity and frequency, affecting a child's daily activities and quality of life. Causes of epilepsy in children may include genetic factors, brain injury, or developmental disorders. Treatment often involves medications to control seizures, lifestyle modifications, and sometimes surgical interventions. A set of conditions known as cerebral palsy impact motor abilities, tone of muscles, and movement. Damage to the developing brain, which frequently happens prior to birth or throughout infancy, is the cause of it. Children with cerebral palsy may experience difficulties with walking, coordination, and fine motor skills. Treatment aims to improve mobility and function through physical therapy, occupational therapy, and sometimes surgical interventions. Autism Spectrum Disorder (ASD) is a kind of developmental disability that impacts behavior, social interaction, and communication. While the exact cause of ASD is unknown, it is believed to involve a combination of genetic and environmental factors. Children with ASD may exhibit repetitive behaviors, difficulties with verbal and non-verbal communication, and challenges in social situations. Early intervention with behavioral therapy, speech therapy, and educational support can help improve outcomes for children with ASD. Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disease marked by hyperactivity, impulsivity, and trouble focusing. It can significantly impact a child's academic performance, social relationships, and overall functioning. While the exact cause of ADHD is not fully understood, it is thought to involve a combination of genetic, environmental, and neurological factors. Treatment often involves a combination of behavioral therapy, medication, and support services. Developmental delay refers to a child's failure to reach developmental milestones within the expected time frame. It can encompass delays in areas such as language, motor skills, cognitive abilities, and social development. Developmental delay can result from various factors, including genetic conditions, prenatal exposure to toxins, or environmental factors. Early intervention with therapies such as speech therapy, occupational therapy, and educational support can help address developmental delays and promote optimal development [1-7].

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## 2. Neurological Disorders and drug interactions

Neurological disorders in children occur when something is abnormal in the brain, the nervous system or the muscle cells. These disorders can vary from epilepsy to migraine headaches to tic or movement disorders and more. International scientific literature defines pediatric patients with "special needs" (SN) as children suffering from psychophysical disorders with related relational and cognitive problems. The perioperative management of these pediatric patients must be carefully planned, in order to make the entire hospitalization process as comfortable and as least traumatic as possible. The standard perioperative path is inapplicable, mainly due to the surgical and anesthetic criticalities. These patients have a much-increased perioperative risk due to their anatomical features, underlying disease and the coexistence of complex comorbidities. Down Syndrome (DS) represents 9% of all interventions in patients with SN and 1.25% of all anesthetic procedures. Patients with DS have peculiar anatomical features such as a low set of ears, small teeth, flat nose (flat nasal bridge), stature delay, abnormal fingerprints and hypotonia. They also present microbrachycephaly, short neck, macroglossia and protruding tongue, hypertrophic tonsils and adenoids, narrow subglottic area and prolapsed epiglottis. Frequently, these patients are obese and obesity can add further anesthetic problems: omega epiglottis and tracheomalacia. Patients with DS are at risk of atlantoaxial instability (AAI). This condition is also referred to as an atlantoaxial subluxation and it has been reported to occur in 6.8% to 27% of the

DS population. Cri du Chat Syndrome is a very rare congenital genetic syndrome with peculiar clinical characteristics such as microcephaly, enlarged nose root, epicanthus, hypertelorism, low-set ears, micrognathia and typical acute crying which gives the name of the syndrome. The acute crying pitch depends on laryngeal anatomical abnormalities, including laryngomalacia with vocal cord paralysis, small and/or narrow larynx with diamond-shaped vocal cords, and epiglottitis, which may be elongated, curved and fluctuating, or short and flaccid, hypoplastic and hypotonic. Autism Spectrum Disorders (ASD) cause impairment in social interaction, communication and isolation problems, behavioral disturbances, disorders of the sensory sphere, as well as significantly altered motor skills. The problems of communication and social interaction are linked to a limited vocabulary, language deficits (deficit of acquisition, echolalia, occasional mutism), the inability to understand figurative language and the meaning of conversations. Some patients exhibit behavioral disturbances, such as self-mutilation, aggression, psychotic disturbances, resistance to change, gesture repetition, mechanical memory, excessive emotional reactions, and motor awkwardness, stereotyped patterns of movement, language or manipulation of objects, excessive adherence to a daily routine made up of motor or verbal rituals. Infantile cerebral palsy (CP) includes several clinical manifestations, from monoplegia with normal cognitive function to spastic quadriplegia with mental retardation. The causes are multiple and are responsible for damage to the central nervous system that can occur in the prenatal, perinatal or postnatal period. The Spastic Form, associated with intellectual disability and epilepsy, presents an altered control of the buccal muscles, tongue and pharynx resulting in various degrees of difficulty in feeding (nasogastric feeding or gastrostomy are often necessary). The dyskinetic form can be associated with dystonia, athetosis and chorea; epilepsy often concomitates, while the IQ is usually normal. Balance disorders, cerebellar tremors, language difficulties, epilepsy and cognitive deficits are associated with the ataxic form. Epileptic patients usually take long-term anti-epileptic therapy; monotherapy antiepileptic drugs are often effective in seizure control and a significant number of these patients require polypharmacological anti-comital therapy. It can be associated with the treatment of concomitant pathologies. Epileptic patients are exposed to an increased risk of clinically significant drug interactions, especially with traditional anti-epileptic drugs. With regards to the interactions examined between new generation anti-epileptic drugs and drugs used for the treatment of related non-epilepsy disorders, pharmacokinetic interactions have always referred to hepatic enzyme induction or inhibition. Furthermore, pharmacological dosages of anesthetic drugs, such as hypno-inducers was highlighted. The required dose of Propofol is significantly lower and the recovery time was longer. Oral benzodiazepines (midazolam) may be beneficial for small children as they provide sedation without respiratory depression and should be administered under supervision. An intravenous (IV) induction with propofol and neuromuscular block to facilitate endotracheal intubation is ideal in children. Children at risk for aspiration should undergo rapid-sequence anaesthetic induction. Anaesthesia is maintained either with low end-tidal volatile agents (minimum alveolar concentration (MAC) 1) or with total IV anaesthesia (TIVA), along with short-acting opioids (fentanyl or remifentanyl), inhaled nitrous oxide and controlled ventilation. Sevoflurane has almost replaced halothane as an agent for induction; isoflurane, sevoflurane or desflurane is used for maintenance of anaesthesia. Sevoflurane provides smooth induction followed by a rapid recovery. Neuromuscular blockade with non-depolarising muscle relaxants is given to prevent patient movement and minimise the amount of anaesthetic agent required. Fentanyl is the most commonly used opioids, but its half-life increases with repeated dosing. It requires hepatic metabolism which is immature in premature infants. The sedative and respiratory depressive effects of fentanyl may be prolonged in these children. Remifentanyl is unique in the sense it is cleared rapidly by the plasma esterases, but the associated rapid recovery may be accompanied by delirium and inadequate analgesia. However, it requires supplementation of other analgesics during postoperative period. The goal is "rapid awakening" in order to help early neurological assessment, haemodynamic stability, and minimal coughing and straining in the ETT. Sevoflurane provides better recovery profile, as compared to isoflurane in children. The anaesthetic concerns in epilepsy surgery, include perioperative seizures and the effects of anticonvulsants. Chronic use of anticonvulsants induces rapid metabolism and clears anaesthetic agents such as neuromuscular blockers and opioids, thereby increasing the anaesthetic requirements. Anaesthesia for children undergoing neurosurgery requires knowledge on cerebral pathophysiology and the interaction of anaesthetic agents on brain [8-19].

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### 3. Neurodevelopmental disorders

More than 600 neurological disorders can affect people of all ages. Some conditions that can affect newborns, infants, children and teens include: Cerebral palsy: This group of disorders affects muscle control, causing difficulty with muscle movements. Cerebral palsy results from an injury or illness that affects brain development before birth. Seizures and epilepsy: Seizures are surges of electrical activity in the brain that affect behavior, sensations, movements or consciousness. Headache and migraine: Headaches and migraine can make learning difficult and affect a child's daily activities and quality of life. Sleep disorders: Children, especially teens, can have sleep disorders, which can lead to other problems such as daytime sleepiness and poor performance in school. Neurodegenerative diseases: These conditions occur when brain cells become damaged or begin to die. Neurological disorders in newborns: These conditions occur when an injury or other problem affects brain development before, during or shortly after birth. Neurodevelopmental disorders affect a child's development, causing physical, behavioral, learning and other difficulties. Attention-

deficit/hyperactivity disorder (ADHD): This condition causes behavior issues, such as self-control and ability to focus and concentrate. Autism spectrum disorder: This disorder affects a child's ability to develop healthy social and communication skills. Learning disabilities: This group of disorders causes difficulty with written and spoken language, math and other subjects. Rett syndrome: This genetic disorder occurs mostly in girls, affecting learning, social behaviors, speaking, balance and movement. Speech, language and swallowing disorders: Aphasia is a type of neurological disorder that affects the ability to read, write, speak and understand speech. Dysphagia, or difficulty swallowing, affects your ability to eat and drink. Tourette syndrome: This neurological disorder involves tics, which are sudden, repeated, involuntary (unintentional) movements or sounds. The disease manifest as a set of three of impaired social interaction, impairment of verbal (spoken) and non-verbal (unspoken) communication, alongside confined, repetitive patterns of behavior with a lot of adherence to routines and limited interests. Epilepsy is a common problem tracked down in individuals of all ages. This is a chronic condition characterized by the occurrence of multiple seizures. A seizure is caused as a result of a brief disturbance in the brain cells. Epilepsy might be caused by hereditary factors, developmental problems, infectious illnesses and injury caused to the brain preceding birth. Most headaches in aren't symptoms of neurological problems, nonetheless, at times they might be caused by a serious underlying issue. Headaches can be caused by changes in the brain or in the body which send pain messages to the brain and result in headaches. It is important to screen headaches especially when accompanied by other symptoms like reduced alertness, vomiting, clumsiness. Attention Deficit Hyperactivity Disorder (ADHD), one of the most widely known neurological problem than might in fact go on until adolescents in ADHD; frequently left undiagnosed and marked as naughty given the symptoms they experience like forgetfulness and fantasizing. Dyspraxia is a condition which makes it difficult to coordinate physical movements. Children with dyslexia can read to upto average levels, whenever diagnosed early. Cerebral Palsy influences motor skills and is brought about by brain damage caused before or during birth or childhood life. Pediatric Stroke, one in around 4000 new borns are affected by this condition of pediatric stroke. New born infants or children with sickle cell anemia, immune disorders or blood clotting troubles might be prone to this condition [19-24].

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#### 4. Anesthesiology complications

The risk of postoperative anesthetic complications in patients with SN depends on the patient's ASA classification, clinical condition, type of anesthetic used and type of surgical procedure performed. About 4.2% of cases have moderate complications, such as hypotension. Airway obstruction is the most common complication, followed by nausea and vomiting. All drugs used may produce sedation and respiratory depression and should always be administered under supervision and monitoring. Anti-epileptic drugs cause a prolonged awakening time from anesthesia, but these drugs should not be discontinued during the preoperative in order to reduce perioperative seizures. Monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs) have an increased risk of hypo/hypertension and prolonged awakening after general anesthesia. Risperidone can cause hypotension under general anesthesia and can lead arrhythmias. It may be appropriate to discontinue long-acting antipsychotics and switch to short-acting or lower dose antipsychotics after consultation with the psychiatrist. During anesthesia, Clozapine can cause agranulocytosis, hyperthermia, cardiac conduction problems and hypotension. Psychostimulants can: increase the dose of sedative needed during anesthesia and the risk of hypertension and arrhythmias, lower the seizure threshold and interact with vasopressor. Congenital heart disease affects approximately 50% of patients with DS and this can increase the risk of complications during anesthesia, such as bradycardia. The incidence of bradycardia in DS patients is approximately 3.7%, significantly higher rate than the approximately 0.36% found in healthy patients. Congenital heart disease can also lead to other complications such as pulmonary hypertension. Airway management can be difficult for patients with cerebral palsy due to excessive secretions and the risk of aspiration during anesthesia due to gastroesophageal reflux. These patients also have a greater risk of hypoxia during general anesthesia. In addition, about 30% of patients with cerebral palsy take home anti-comital therapy with an increased risk of drug interactions. General anesthetics mitigate distress and exaggerated hemodynamic responses to pain and stressful stimulation, allowing surgery and diagnostic procedures to be performed worldwide in millions of children every year. The safety of pediatric anesthesia has increased over the past several decades with improved monitoring, equipment, medications, and growing subspecialization and regionalization of pediatric care. Despite these advances, anesthetic-related complications occur more often in children compared to adults [25-43].

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#### 5. Discussion and Outcomes

The nervous system is the brain, spinal cord and nerves, which work together to control the body. Neurological diseases and disorders are conditions that affect the nervous system. They can range from minor issues, such as a headache, to life-threatening conditions, such as stroke or seizure. Causes of these conditions include genetic disorders, developmental issues, injuries and infections. Depending on which areas of the nervous system are affected, neurological disorders can cause problems with: muscle movement, thinking and learning, speaking and swallowing,

mood, behavior and sleep. Children are either born with the disorder, such as spina bifida or hydrocephalus (fluid in the brain), or they acquire the disorder later in life; the result of a traumatic injury or serious infection. Most studies induced or maintained a surgical plane of anesthesia with the application of multiple types of anesthetic drugs in combination. Despite their limitations, extant studies suggest that single brief anesthetic exposures do not appear to produce a measurable effect whereas repeated exposures consistently demonstrate associations between exposure and subsequent deficits in learning and behavior. It is still difficult to draw a definitive conclusion about the relationship between anesthesia and neurodevelopment based on the available studies. In the aspect of outcome measure, we need further exploration into a sensitive and stable outcome to estimate the neurocognitive harm in children. It's consistently certified in most studies covering prolonged exposure that a longer duration contributes to a higher risk of long-term diminution of neurocognitive function. However, longer cumulative duration and multiple exposures may be closely linked. Most studies leaving a lack of strong evidence for the validity of measuring neurodevelopmental changes due to anesthesia, probably because considering the complexity of its design, the difficulty of its implementation, the large human and financial resources required, and the associated ethical issues. To provide optimal neuroanaesthesia care, the anaesthesiologist must have the knowledge of basic neurophysiology of developing brain and effects of various drugs on cerebral haemodynamics. Some studies observed no correlation between multiple anesthesia exposures and neurodevelopmental deficits, while others reported that even a single exposure could increase the risk of deficits.

The anesthetic technique can play a significant role in altering the state of the brain during neurosurgical procedures through effects on the cerebral circulation and metabolism. Pre-existing neuromuscular disease may also have specific anesthetic implications such as cardiorespiratory involvement (eg, myotonia dystrophica), the potential for drug interactions (eg, myasthenia gravis) or abnormal responses to commonly used drugs (eg, malignant hyperthermia).

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## 6. Conclusion

A neurologic disorder is caused by a dysfunction in the brain or nervous system (i.e. spinal cord and nerves). This dysfunction can result in physical and psychological symptoms. Due to their clinical history, and the lack of collaboration, in pediatric non-cooperative patients with Special Needs (SN), the anesthesiological risk may result difficult to assess, despite the fact that they meet the criteria of the outpatient management applied for the patient without disabilities. Reasons for this increased anesthetic risk in young children are multifactorial and include limited cardiopulmonary reserve, multiorgan immaturity, altered total body water composition relative to adults, limited pharmacokinetic and pharmacodynamics data on commonly used medications in children, altered sensitivity to drugs relative to older children, temperature lability, care team experience, and monitoring difficulties. Millions of children experienced surgery procedures requiring general anesthesia. Any potential neurodevelopmental risks of pediatric anesthesia can be a serious public health issue. Based on current studies, it is necessary to endeavor to limit the duration and numbers of anesthesia and the dose of anesthetic agents.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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