Neurologic and Neuromuscular Diseases

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Cerebral Palsy
Seizure Disorders
Neuromuscular Diseases
- Developmental Myopathies
- Muscular Dystrophies
- Spinal Muscle Atrophy

Neurologic and neuromuscular disorders represent a substantial percentage of pediatric coexisting disease, and are associated with the need for a variety of surgical procedures during childhood. Cerebral palsy and seizure disorders are very common in the pediatric population, and thus anesthesiologists should be familiar with their clinical characteristics and the pharmacologic agents used for their treatment. Although less common, myopathies are associated with significant morbidity in children, and are noteworthy because of their association with malignant hyperthermia and the potentially catastrophic hyperkalemic response to administration of succinylcholine.

**CEREBRAL PALSY**

Cerebral palsy (CP) is often defined as a static motor encephalopathy. It encompasses a collection of motor system disorders caused by a perinatal or early childhood neurological insult (Table 5-1). The incidence of CP in the United States is approximately 0.7 per 1000 live births and is rising. The contribution of very low birthweight infants to this population of children is significant: approximately 52,000 very low birthweight infants (<1500 g) are born annually. These infants make up more than 25% of the children diagnosed with CP.

Children with CP exhibit a wide variety of clinical manifestations that range from mild (e.g., slight lower-extremity spasticity and normal cognitive function) to severe (e.g., spastic quadriplegia and profound mental retardation). Respiratory system dysfunction usually parallels the overall severity of the disease. Bulbar motor dysfunction causes a loss of normal airway protective mechanisms (cough, gag, etc.) and leads to chronic pulmonary aspiration, recurrent pneumonia, development of reactive airway disease, and parenchymal lung damage. Consequently, children with severe CP will often exhibit a reduced functional residual capacity and lower than normal oxygen saturation. Bulbar dysfunction also causes gastrointestinal symptoms that include gastroesophageal reflux and an inability to swallow oropharyngeal secretions. Gastrostomy tubes are often placed during infancy to optimize nutritional status.

Infants born prematurely may develop areas of brain ischemia secondary to cerebral hemorrhages in the early newborn period. The area of infarction is termed "periventricular leukomalacia" (white matter atrophy surrounding the ventricles) and is associated with development of varying degrees of limb spasticity. Chronic absence of motor input results in progressive development of limb contractures during childhood that worsen with age.

Baclofen, a gamma amino butyric acid (GABA) agonist, reduces pain associated with muscle spasms and slows development of contractures. Most children receive it orally; however, intrathecal administration is possible for severe cases. Side-effects of baclofen include urinary retention and leg weakness, which usually abate when the dose is reduced. Abrupt withdrawal from oral or intrathecal baclofen may cause seizures, hallucinations, disorientation, and dyskinesias. Overdose of baclofen is associated with depressed consciousness and hypotension.

Botulinum toxin is also used to treat spasticity associated with CP. While the child is sedated, it is injected into contracted muscles and produces a functional denervation of the muscle by preventing release of acetylcholine from the presynaptic motor end-plate. This results in a temporary reduction in muscle tone that may last for
months. There are no significant side-effects from its use or known interactions of botulinum toxin with anesthetic agents.

Seizures are present in about 30% of patients with cerebral palsy. Anticonvulsants should be continued until the morning of surgery and reinstituted as quickly as possible during the postoperative period. When it is not feasible to continue oral or gastrostomy anticonvulsant administration, rectal (e.g., phenytoin, valproic acid, and carbamazepine) and intravenous (e.g., phenytoin, valproic acid, and phenobarbital) options are possible. If the surgical procedure causes significant blood loss, anticonvulsant levels should be checked postoperatively, and doses should be adjusted to reestablish optimal levels. Children with CP are often subjected to numerous surgical interventions during childhood. Orthopedic procedures are the most common and include scoliosis repair, and a variety of limb procedures to improve range of motion and decrease progression of contractures. Dorsal rhizotomy may be required to control painful lower limb spasticity. Nissen fundoplication is performed to control chronic gastroesophageal reflux and may include a feeding gastrostomy. This is now performed by laparoscopy in many centers.

Preoperative assessment includes defining and optimizing all systemic medical illnesses. Concurrent upper respiratory infections are poorly tolerated and exacerbate preexisting respiratory disease. Preoperative anxiolysis should be administered to children who are not cognitively impaired. Some children with CP are prone to upper airway obstruction when consciousness is depressed and should be closely monitored after the administration of the premedication. Administration of an anticholinergic agent may decrease pooling of oropharyngeal secretions.

There are no special considerations when choosing an agent for induction or maintenance of general anesthesia. If a gastrostomy tube is present, the stomach should be evacuated prior to induction of general anesthesia. Because of malformation of facial structures, mask ventilation may be difficult, but endotracheal intubation should be straightforward. Presence of gastroesophageal reflux and increased oropharyngeal secretions may encourage the anesthesiologist to rapidly secure the airway using an intravenous induction agent. Children with cerebral palsy demonstrate increased sensitivity to succinylcholine but do not exhibit excessive potassium release after its use. Nevertheless, succinylcholine should be used only to treat life-threatening airway emergencies. Nondepolarizing muscle relaxants are less potent and have a relatively shorter duration of action in children with CP. This may be related to chronic anticonvulsant administration.

Sevoflurane and halothane are relatively more potent (i.e., lower minimum alveolar concentration; MAC) in children with CP. Increased sensitivity to narcotics is present in all but mild forms of cerebral palsy. Doses should be reduced, and greater vigilance at the time of extubation is necessary to ensure the child’s ability to maintain a patent upper airway. Hypothermia is a common intraoperative problem in children with CP. Impaired temperature regulation is caused by hypothalamic dysfunction and the patient’s absence of muscle and subcutaneous fat.

Postoperative regional analgesia may benefit children with CP who have difficulty communicating the severity of their pain. Addition of epidural clonidine may help reduce postoperative lower-limb spasticity. Oral diazepam 0.2–0.3 mg/kg is used as an adjuvant to help alleviate muscles spasms.

### SEIZURE DISORDERS

Seizures are clinical manifestations of a variety of disorders. Febrile seizures represent the most common type of seizure disorder in the pediatric population (5%). Idiopathic epilepsy, which is primarily seen in older children, is much less common, with an estimated incidence of approximately 0.6% of the population. Trauma, hypoxia, and infection are the primary causes of seizures in infants. Additional causes of seizures in children include metabolic disease, hypoglycemia, electrolyte and metabolic abnormalities, toxic ingestions, and congenital or developmental defects. However, in up to 50% of seizure disorders, the etiology remains unknown.

The currently accepted international classification of epileptic seizures divides these disorders into two broad categories: partial and generalized (Box 5-1). Partial seizures are those in which the initial clinical and electroencephalographic (EEG) changes indicate activation of a system of neurons limited to part of one cerebral hemisphere. When consciousness is not impaired, it is labeled a simple partial seizure and indicates a unilateral cerebral event. When consciousness is impaired, it is called a complex partial seizure and indicates a bilateral cerebral event. Partial seizures can consist of a variety of manifestations that includes motor, sensory, autonomic, or psychic phenomena. With partial seizures, there is usually no specific postictal state. Partial seizures can also exhibit progression to generalized seizure activity.

There are four basic types of generalized seizures:

- Absence seizures are also called “petit mal” seizures. They consist of staring spells during which the patient is not responsive, and last usually only a few seconds.
- Myoclonic seizures consist of brief twitching muscle activity that is uncoordinated. There are two types of myoclonic seizures: epileptic are those that originate from cortical or subcortical tissues; nonepileptic
myoclonus originates from the brainstem or spinal cord and is due to loss of cortical inhibition or impaired function of spinal interneurons.

- Tonic-clonic seizures are those with which most people are familiar. They consist of an initial tonic contraction phase, during which it is common for patients to become apneic and cyanotic from the tonic rigidity of the thoracic cavity. This is followed by the clonic, repetitive twitching phase, where breathing resumes but can be shallow and irregular.
- Atonic seizures are characterized by a state of immobility and unresponsiveness.

Infantile spasms (West syndrome) consist of the triad of unique “salaam-like” seizure movements, arrest of psychomotor development, and a characteristic EEG pattern called “hypsarrhythmia.” The onset peaks at between 4 and 7 months of age and almost always occurs before 12 months. It can be associated with a known underlying neurological disorder, or can be idiopathic, and is associated with a poor neurodevelopmental outcome. Lennox–Gastaut syndrome consists of different types of seizures which occur frequently and are difficult to control. It usually manifests itself in the 3- to 5-year age group, and is associated with severe mental retardation. Both infantile spasms and Lennox–Gastaut syndrome are notoriously difficult to control with anticonvulsant agents.

There are a variety of treatment regimens that are individualized for each child and the particular type of seizure disorder (Table 5-2). Anesthesiologists should be familiar with the clinical indications and major side-effects of the most commonly used anticonvulsants.

Anesthetic concerns for children with seizure disorders will depend on coexisting morbidities and will be individualized depending on the mental status of the child. If necessary, children who require strict pharmacologic control of their seizure disorder should have their oral anticonvulsants converted to the intravenous forms (or equivalent medications if intravenous forms are not available) during the preanesthetic fasting interval and during the postoperative period if oral intake is not possible. In most cases preanesthetic anticonvulsant levels are not necessary.

Most anesthetic and analgesic agents can be safely administered to children with seizure disorders. A possible exception is multiple doses of meperidine because its metabolite, normeperidine, possesses proconvulsant properties. Nitrous oxide, sevoflurane, methohexital, etomidate, and all opioids have been anecdotally associated with seizure-like movements in both healthy and epileptic patients, without serious sequelae. In most of these cases these movements were likely a benign form of myoclonus. Virtually all general anesthetic agents are anticonvulsants in doses associated with loss of consciousness.

Higher doses and shorter dosing intervals of neuromuscular blockers are required in patients taking anticonvulsant medications. The precise mechanism of this phenomenon has not been elucidated. However, this resistance is not as prominent for those neuromuscular blockers that are metabolized in the plasma (i.e., atracurium, mivacurium), so it may be related to a pharmacokinetic effect based in the liver. There is also some data and clinical experience indicating that anticonvulsants may cause some resistance to opioids. Although definitive data are lacking, it does not appear that general anesthesia impacts the subsequent frequency or severity of seizures postoperatively.

**NEUROMUSCULAR DISEASES**

Neuromuscular diseases can be broadly divided into disorders of the muscle, and disorders of neuromuscular transmission (Box 5-2). Muscle diseases can be further categorized into developmental myopathies, muscular dystrophies, and metabolic myopathies. Disorders of neuromuscular transmission can be further categorized into diseases of the neuromuscular junction and anterior horn cell diseases. This list is extensive and only the most common and most important in pediatric anesthesia will be reviewed here.

Muscle diseases, or myopathies, are characterized by muscle weakness and atrophy. Many children are symptomatic at birth, while others are normal in early infancy only to develop weakness in the first few years of life. The myopathies are of interest to anesthesiologists for two major reasons. First, some are associated with an increased risk of malignant hyperthermia (see Chapter 21); and second, all are associated with development of life-threatening hyperkalemia after administration of succinylcholine (see Chapter 19). Children with myopathies often require multiple surgical procedures throughout childhood. These include a muscle biopsy as a component of the diagnostic work-up, insertion of a gastrostomy or tracheostomy as weakness worsens, and a variety of orthopedic procedures for alleviation of contractures and scoliosis.

As with neurological diseases, anesthetic considerations for children with muscle diseases will largely depend on the medical condition of the child, as there is a wide spectrum of affliction, even between children with the same diagnosis. Even though central core myopathy is one of the only diseases genetically linked to malignant hyperthermia, most pediatric anesthesiologists will perform a nontriggering anesthetic technique for all children with myopathies. Use of nondepolarizing muscle relaxants will depend on the baseline strength of the child. Careful titration of the neuromuscular blocker based on train-of-monitoring is recommended. Children with muscle weakness are at increased risk for requiring postoperative mechanical ventilation, and thus,
this possibility should be proactively addressed with the parents and child if appropriate.

**Developmental Myopathies**

The developmental myopathies consist of a heterogeneous group of congenital myopathies that are mostly nonprogressive, although some patients show slow clinical deterioration. Most of these conditions are hereditary; others are sporadic. These include nemaline rod myopathy, central core myopathy (CCM), and myotubular myopathy. CCM is an autosomal dominant disease characterized by hypotonia and proximal weakness at birth. Unlike other muscle diseases, there appears to be a predisposition of CCM patients to malignant hyperthermia susceptibility in the form of a genetic linkage to the ryanodine receptor on chromosome 19. However, the literature is conflicting, and the subject of myopathies and susceptibility to malignant hyperthermia continues to evolve.

**Muscular Dystrophies**

Although the muscular dystrophies are a group of unrelated disorders, there are four obligatory criteria that distinguish them from other neuromuscular diseases:

1. It is a primary myopathy.
2. It has a genetic basis.
3. The course is progressive.
4. Degeneration and death of muscle fibers occur at some stage in the disease.

Duchenne-type muscular dystrophy (DMD) is an X-linked recessive disease that, although present at birth, usually presents in early childhood as weakness and motor delay. Additional clinical manifestations include pseudohypertrophy of the calves and markedly elevated baseline creatine phosphokinase (CPK). Since weakness is greatest in the proximal muscle groups, the child must rise from the sitting position in two steps: first leaning on the hypertrophied calves and then pushing the trunk up with the arms. This is referred to as Gower's sign, and is nearly pathognomonic for one of the muscular dystrophies. Eventually, progressive and severe muscle atrophy and weakness cause loss of the ability to ambulate. The most serious aspects of DMD include a progressive cardiomyopathy and respiratory failure secondary to ventilatory pump failure. Cognitive abnormalities are usually mild. Most children become wheelchair-bound early in the second decade, with death before age 30 from either respiratory failure or cardiomyopathy.

Although no definitive genetic link to malignant hyperthermia has been found, most pediatric anesthesiologists consider these children to be MH-susceptible based on anecdotal reports, and will perform a nontriggering technique. However, as stated above for CCM, definitive proof of association between myopathies and MH susceptibility is lacking. Use of inhalational agents, albeit for a relatively short period of time, appears to be safe when intravenous access is not available.

A less severe (yet debilitating) related disease is the Becker-type muscular dystrophy. Similar features to DMD include calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of CPK. However, the onset of weakness in Becker-type dystrophy is later in life than with DMD, and death often occurs at a later age than with DMD. The anesthetic considerations are identical to those for DMD.

Myotonic dystrophy is an autosomal dominant muscular dystrophy that is characterized by the persistent contraction of both striated and smooth muscle after its stimulation. Myotonia refers to the slow relaxation of a contracted muscle and is observed in children over the age of 5 years. All muscle tissues in every organ system are affected, leading to widespread disease that begins mildly in the neonatal period but progresses throughout childhood. Additional clinical manifestations include cardiac, respiratory, and gastrointestinal dysfunction, endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, intellectual impairment, and other neurologic abnormalities. Succinylcholine and cholinesterase inhibitors will exacerbate the myotonia.

**Spinal Muscle Atrophy**

Spinal muscle atrophy (SMA) is an inherited autosomal recessive disorder characterized by anterior horn cell degeneration and is found as three clinical syndromes. Type 1 is called Werdnig–Hoffman disease and is the most severe beginning in early infancy. It is characterized by significant muscle weakness and atrophy, except for diaphragmatic sparing which occurs later in life. Type 2 presents at between 6 and 12 months of age and has a more prolonged, slightly milder course. Type 3 is the least debilitating and is called Kugelberg–Welander disease. Cognitive abilities remain unaffected in all forms of the illness. Life-expectancies vary with the severity of the disease; death occurs from repeated aspiration or lung infections.
### Case

An 11-month-old female is scheduled for a diagnostic muscle biopsy and open gastrostomy tube insertion. She has a history of hypotonia, developmental delay, and failure to thrive secondary to poor feeding effort. Chromosomal analysis is normal, and her physicians suspect she may have a mitochondrial myopathy.

**What is a mitochondrial myopathy? Is it associated with unique considerations for administration of general anesthesia?**

A mitochondrial myopathy is a type of genetic disease that is encompassed within a broad category of entities whose origin is a defect in mitochondrial function, and thus interfere with normal adenosine triphosphate (ATP) production. Although mitochondrial defects can affect almost every organ system, those organs with high metabolic rates – such as the heart, brain, and skeletal muscle – are particularly vulnerable. ATP depletion results in accumulation of lactate, a byproduct of anaerobic metabolism. Clinical manifestations include abnormalities of the heart (e.g., cardiomyopathy, conduction defects), skeletal muscle (e.g., atrophy, weakness), and central nervous system (e.g., seizures, encephalopathy, peripheral neuropathies, ophthalmologic manifestations), among many others. Examples of mitochondrial diseases include chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, Leigh’s disease, Leber’s hereditary optic neuropathy (LHON), mitochondrial myopathy, and myoclonic epilepsy with lactic acidosis and stroke-like episodes (MELAS syndrome). Treatment options are limited, and primarily supportive. Carnitine may lessen muscle weakness and fatigue in some children, and does not interact with anesthetic agents.

Preanesthetic assessment of a child with a suspected or confirmed mitochondrial disease includes evaluation of comorbidities – in particular, cardiac, respiratory, hepatic, and renal function. Premedication should be tailored to the individual patient; respiratory depressants should be avoided in children with weak ventilatory drive. The overall goal of anesthetic management is avoidance of metabolic stressors, such as hypoxemia and hypoglycemia, which may potentially exacerbate lactic acidosis. Clear glucose-containing liquids should be administered 2 hours prior to the anticipated induction of anesthesia. All anesthetic agents have been used safely in patients with mitochondrial diseases, although prolonged use of propofol should be avoided because of its association with lactic acidosis in the critical care setting. Neuromuscular blockers should be carefully titrated to maintain one or two twitches on train-of-four monitoring, as patients with myopathies may demonstrate a unique sensitivity to these drugs. Steroidal neuromuscular blockers, which depend on adequate liver function for metabolism and termination of action, should probably be avoided.

**Should this patient be considered malignant hyperthermia (MH)-susceptible?**

There is no definitive genetic link between mitochondrial disease and MH susceptibility. In the presence of muscle atrophy, elective use of succinylcholine is contraindicated, as it may cause life-threatening hyperkalemia. Inhalational agents have been used safely in patients with mitochondrial diseases.

**How would you induce and maintain general anesthesia? Is a muscle relaxant necessary?**

Induction and maintenance of general anesthesia will be routine: inhaled sevoflurane and N₂O for induction of anesthesia, or an intravenous induction agent if the child has intravenous access. Since this child has preexisting hypotonia, I don’t expect that he will be able to adequately ventilate and oxygenate using a spontaneous ventilation technique. Therefore, I will likely use controlled ventilation, using either a laryngeal mask airway (LMA) or an endotracheal tube. Depending on the severity of the child’s hypotonia, I may choose to omit neuromuscular blockade from the induction regimen, since there are no surgical requirements for paralysis.

**What are appropriate extubation criteria for this patient?**

Exudation criteria for patients with hypotonia or developmental delay are ill-defined. The three criteria that are used in healthy children are: (1) sufficient muscle strength to maintain upper airway patency; (2) a regular respiratory pattern; and (3) wakefulness (e.g., spontaneous eye opening, following commands). The child in this case may demonstrate abnormalities for one or more of these criteria. Tracheal extubation will therefore become incumbent on the child attaining their preoperative or baseline parameters.
ARTICLES TO KNOW


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**Box 5-1 International Classification of Epileptic Seizures**

**Partial Seizures**

- Simple partial (intact consciousness)
  - Motor
  - Sensory
  - Autonomic
  - Psychic
- Complex partial (impaired consciousness)

**Generalized Seizures**

- Absence
- Tonic
- Clonic
- Tonic-clonic
- Myoclonic
- Atonic

**Unclassified Seizures**

- Infantile spasms (West syndrome)
- Lennox-Gastaut syndrome

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**Box 5-2 Classification of Neuromuscular Diseases of Childhood**

**Muscle Diseases**

- Developmental
  - Nemaline rod myopathy
  - Central core myopathy
  - Myotubular myopathy
- Muscular dystrophies
  - Duchenne muscular dystrophy
  - Becker muscular dystrophy
  - Myotonic dystrophy
- Limb-girdle muscular dystrophy
- Facioscapulohumeral muscular dystrophy
- Congenital muscular dystrophy
- Metabolic myopathies
  - Potassium-related periodic paralysis
  - Glycogenoses
  - Mitochondrial myopathies
  - Lipid myopathies

**Diseases of Neuromuscular Transmission**

- Neuromuscular junction disorders
  - Myasthenia gravis
  - Organophosphate poisoning
  - Botulism
- Tick paralysis
- Anterior horn cell diseases
  - Spinal muscular atrophies (SMA)
  - Poliomyelitis
### Table 5-1  Types of Cerebral Palsy

<table>
<thead>
<tr>
<th>Type</th>
<th>Anatomical Location of Pathology</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic (most common: 70%)</td>
<td>Cerebrum</td>
<td>Quadriplegia, diplegia, and hemiplegia The number of extremities affected and the degree of spasticity correlate with level of intelligence.</td>
</tr>
<tr>
<td>Dyskinetic</td>
<td>Basal ganglia; associated with kernicterus (severe hyperbilirubinemia in the newborn period).</td>
<td>Dystonia (twisting position of torso), athetosis (purposeless movements of extremities), and chorea (quick, jerky proximal movements of extremities); seizures.</td>
</tr>
<tr>
<td>Ataxic</td>
<td>Cerebellum</td>
<td>Tremor, loss of balance and speech.</td>
</tr>
<tr>
<td>Mixed</td>
<td>Cerebrum and cerebellum</td>
<td>Spasticity and athetoid movements.</td>
</tr>
</tbody>
</table>

### Table 5-2  Indications for and Side-effects of Anticonvulsants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indications</th>
<th>Side-effects/Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Partial, tonic-clonic</td>
<td>Diplopia, nausea and vomiting, ataxia, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin)</td>
<td>Absence</td>
<td>Rash, anorexia, leukopenia, aplastic anemia</td>
</tr>
<tr>
<td>Phenobarbital (Luminal)</td>
<td>Tonic-clonic, partial</td>
<td>Hyperactivity, sedation, nystagmus, ataxia</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>Tonic-clonic, partial</td>
<td>Rash, nystagmus, ataxia, drug-induced lupus, gingival hyperplasia, anemia, leukopenia, polyneuropathy</td>
</tr>
<tr>
<td>Valproic acid (Depakote)</td>
<td>Tonic-clonic, partial, absence</td>
<td>Hepatotoxicity, nausea and vomiting, abdominal pain, weight loss, weight gain, anemia, leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Recently Developed Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>Partial</td>
<td>Somnolence, dizziness, ataxia, fatigue</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>Tonic-clonic, partial, absence, Lennox–Gastaut syndrome</td>
<td>Dizziness, ataxia, blurred or double vision, nausea, vomiting, and rash. A few cases of Stevens-Johnson syndrome reported.</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>Partial</td>
<td>Somnolence, asthenia, dizziness</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>Partial</td>
<td>Dizziness, somnolence, and tremor. May make absence epilepsy worse</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>Tonic-clonic, partial, Lennox–Gastaut syndrome, infantile spasms</td>
<td>Somnolence, fatigue, weight loss, nervousness</td>
</tr>
</tbody>
</table>