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Epilepsy in children and anesthesia

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Abstract

Epilepsy, also called seizure disorder, is the most common childhood brain disorder in the United States. The aetiology of epilepsy in children is multifactorial with congenital, metabolic, infective, and problems associated with prematurity being common causes. Nearly 3 million Americans have epilepsy. About 450,000 of them are under 17 years old. About 1 in 200 children (0.5%) have epilepsy, a neurological condition where children have a predisposition to recurrent, unprovoked seizures. There are many different types of epilepsy, especially in infancy, childhood and adolescence. Epilepsy can be thought of in terms of either: the site of seizure origin in the brain (generalised or focal seizures), or the underlying cause. Genetic epilepsies (formerly called idiopathic or primary epilepsies) occur in an otherwise normal person and are due to a genetic predisposition to seizures. Some epilepsies are due to an underlying abnormality of the brain structure or chemistry (formerly called symptomatic or secondary epilepsies). Other epilepsies have no known cause. Epilepsy is commonly diagnosed in children and can be confused with other conditions. An accurate diagnosis is essential. A seizure is an excessive surge of electrical activity in the brain that can cause a variety of symptoms, depending on which parts of the brain are involved. Seizures can be provoked or unprovoked. Provoked seizures, caused by fever in a young child or severe hypoglycemia, are not considered to be forms of epilepsy. Unprovoked seizures have no clear cause but can be related to genetics or brain injury. When a child has two or more unprovoked seizures, epilepsy is often the diagnosis. Despite advances in antiepileptic medication therapy, a significant number of pediatric patients with epilepsy have seizures that are not well controlled. Antiepileptic medications interact with anesthetic agents, and common anesthetics can precipitate or suppress seizure activity. There are important pharmacokinetic and pharmacodynamic interactions between AEDs and drugs commonly used in anaesthesia. These affect both drug efficacy and the risk of seizure activity intraoperatively.

Keywords: Epilepsy; Seizures; Anesthesia; Children; Status epilepticus

1. Introduction

Seizures occur when there is a momentary 'imbalance' within electrical and chemical circuits in the brain, such that groups of brain cells act in an excessive fashion. This may create a temporary disturbance in the way the brain controls awareness and responsiveness and may cause unusual sensations or abnormal movements and postures. The International League against Epilepsy (ILAE) has classified seizures into focal (or partial) seizures which arise from one hemisphere and generalized seizures which show electrographic seizure onset over both hemispheres. Lamotrigine and carbamazepine are considered drugs of choice in focal epilepsies, while valproate is probably the most effective drug for primary generalized seizures. If the initial antiepileptic drug (AED) results in adverse effects, an alternative AED is tried as monotherapy. If, on the other hand, seizures continue in spite of adequate doses, combination therapy is often necessary. Seizures may be primary (idiopathic) or more commonly secondary to other conditions. Primary epilepsy has a genetic predisposition with a 1.5–3% risk of paternal inheritance and a 3–9% risk of maternal inheritance. Secondary seizures may be caused by prenatal, perinatal, or post-natal events. Absence epilepsy causes short moments. Rolandic epilepsy (self-limited epilepsy with centrotemporal spikes) affecting an estimated 15% of children diagnosed

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with epilepsy. Juvenile myoclonic epilepsy: common during puberty, myoclonic epilepsy seizures cause uncontrolled muscle movements. Infantile spasms (West syndrome) are a severe type of epilepsy that affects infants. Lennox-Gastaut syndrome (LGS) can cause seizures. Risk factors for epilepsy in children are: history of epilepsy in their biological family history (genetic predisposition); traumatic brain injury; brain infection; other neurological issues. Epileptic seizures ("fits") can present in very different ways: Some only last a few seconds and are hardly noticeable, while others cause severe convulsions (jerking and shaking), sometimes in all of the body. In children, the symptoms are often not diagnosed properly at first. Improvements in epilepsy treatment in recent years have made the condition more manageable. Many new anti-seizure medications are available and more are being tested. In addition to newer medications, alternative treatments such as surgical procedures, medical devices, and dietary therapies, are also available for children and teens who continue to have seizures while on medication. A number of studies have suggested that a ketogenic diet can reduce the number of seizures in children who don't respond well to medication [1-7].

2. Mechanism of epilepsy

The mechanism of epilepsy is related to (i) loss of post-synaptic inhibition with loss of inhibitory γ-aminobutyric acid (GABA) activity, (ii) new excitatory synaptic connections with increased release of the excitatory amino acid glutamate, and (iii) appearance of pacemaker neurones with abnormal voltage-mediated calcium currents, all leading to abnormal firing of the neurones. Seizures may be partial (focal), or generalized, or they may start as partial and progress to generalized. Partial seizures can be simple, not associated with impaired conscious level or complex (associated with impaired consciousness. Generalized seizures are associated with bilateral symmetrical electric brain activity. They present with transient impaired consciousness (absence or 'petit mal' seizures) or generalized muscle contractions (tonic, clonic, or tonic–clonic 'grand mal' seizures), which are usually associated with impaired consciousness. Several forms of epilepsy: petit mal epilepsy, infantile spasms, myoclonic epilepsy, benign partial epilepsy, and benign childhood epilepsy which carries an excellent prognosis [8-9].

2.1. Types of seizures

Some are very short, lasting only a few seconds, while others can last a few minutes. Some can cause uncontrollable jerking movements, while others cause them to be confused or stare blankly. Seizures are categorized into two main types: focal, which are also called partial seizures, and generalized. Another, rarer, type is progressive myoclonic epilepsy. Infantile-onset epilepsy syndromes and childhood-onset epilepsy syndromes and seizure disorders are both categorized by the age at which symptoms began, among other factors. Finally, genetic and neurologic disorders can also lead to seizures in children. Focal seizures begin with an abnormal electrical discharge in one region of the brain. They are further categorized by their effect on a child's consciousness, responsiveness, and memory. Temporal lobe seizures are the most common type of epilepsy in both children and adults. The temporal lobe is located beneath the temples, on either side of the head. It is responsible for memory, emotions, interpreting sounds, and understanding language. Frontal lobe epilepsy is the second most common form of epilepsy. The frontal lobe is located beneath the forehead and is the part of the brain responsible for decision-making, problem-solving, and emotions. The occipital lobe is located at the back of the brain, behind the parietal and temporal lobes. This is the site of the brain's visual system. Parietal lobe seizures are also relatively rare in children. The parietal lobe, located near the center of the brain, is responsible for processing information about the senses of touch, pain, and space. Symptoms of gelastic epilepsy may include brief, repeated seizures characterized by uncontrollable laughter that has no known cause. Generalized seizures begin with a widespread, excessive electrical discharge that involves both hemispheres, or sides, of the brain at the same time. Symptoms include blinking and staring, loss of muscle tone, stiffening of limbs, and, when the entire brain is involved, rhythmic, full-body jerking. Generalized epilepsies can be divided into two categories: idiopathic generalized epilepsy, in which the child is otherwise behaviorally and neurologically normal between seizures, and developmental and epileptic encephalopathies, in which intellectual and developmental problems occur between seizures. Progressive myoclonic epilepsy is rare and frequently results from hereditary metabolic disorders or neurodegenerative conditions, such as neuronal ceroid lipofuscinosis, Lafora body disease, and mitochondrial encephalopathy. When a disorder has a constellation of features that tend to occur together, it is termed a syndrome. Some children with seizure disorders have certain characteristics in common and have an epilepsy syndrome—defined by the age at which seizures start, seizure types, presence or absence of developmental delay, and findings on the electroencephalogram (EEG). Benign familial neonatal seizures cause recurrent seizures in newborns. The seizures usually begin when the infant is about 3 days old and are brief, lasting 1 to 2 minutes.Ohtahara syndrome is a rare type of epilepsy that develops in newborns, often within the first two weeks of life. The seizures are primarily tonic seizures but may also include partial seizures and myoclonic seizures. Ohtahara syndrome is often caused by metabolic disorders or brain damage, although in many babies the cause cannot be determined. Infantile spasms, also known as West syndrome, are rare. This is a severe type of epilepsy syndrome that begins in children who are 3 to 12 months old. Dravet syndrome is a severe type of epilepsy syndrome often resulting from a gene mutation that causes abnormalities in sodium channels in the brain, which play

a role in nerve cell communication. Seizures generally begin before a child is 1 year old and can be difficult to control. These types of seizures often affect a baby's cognitive development. Certain other types of seizures and epilepsy syndromes more commonly start in childhood. They include febrile seizures, Landau-Kleffner syndrome, Lennox-Gastaut syndrome, Rasmussen syndrome, benign Rolandic epilepsy, benign occipital epilepsy, childhood absence epilepsy, and juvenile myoclonic epilepsy. Febrile seizure occurs when a child between 6 months and 6 years old has a tonic-clonic seizure plus a high fever, which may occur as a result of a viral illness. Landau-Kleffner syndrome, also called acquired epileptic aphasia, is a rare disorder in which a child loses their ability to speak and understand others' speech. Lennox-Gastaut syndrome is an uncommon form of epilepsy that causes difficult-to-control seizures, including tonic, atonic, prolonged absences, and generalized convulsions. Almost all children who have Lennox-Gastaut syndrome have cognitive and developmental delays. Rasmussen syndrome is rare and usually begins in children who are 14 months to 14 years old. The condition is associated with progressive neurologic deterioration and seizures. Benign Rolandic epilepsy, also called benign epilepsy of childhood with centrotemporal spikes, is one of the most common childhood seizure disorders. Seizures typically begin when children are 2 to 13 years old. There are two subtypes of benign occipital epilepsy—Panayiotopoulos syndrome and Gastaut-type syndrome. The type depends on your child's age when symptoms begin. Panayiotopoulos syndrome begins when a child is 3 to 5 years old, while Gastaut-type syndrome can start at any age throughout childhood but tends to peak around the age of 8 or 9. Absence seizures are generalized seizures that usually occur in children who are 5 to 9 years old. Many disorders that affect the structure and function of the brain in early life can lead to epilepsy, causing seizures in children. Some genetic and neurologic disorders may lead to seizures, along with other neurologic, development, and behavioral symptoms. Rett syndrome is a neurodevelopmental disorder that causes seizures. This genetic condition typically affects girls and begins when a child is 6 to 18 months old. Angelman syndrome is a type of epilepsy syndrome that causes learning difficulties, speech delays, and certain behavioral characteristics, such as a cheerful mood and bursts of sudden and unexplained laughter. The condition is a genetic disorder that usually develops when babies are 6 to 12 months old. Seizures occur in children with Sturge-Weber syndrome, a congenital neurological disorder, due to abnormalities in the blood vessels lining the brain. Children with Sturge-Weber syndrome often have a port wine stain birthmark on the forehead and upper eyelid of one side of the face. There is a greater likelihood of intellectual impairment when seizures start before a child is 2 years old and are resistant to treatment. Symptoms of FOXG1 syndrome typically develop in the second month of life and include irritability and seizures. Delayed development, difficulty walking and sitting, intellectual disability, and problems with speech and vision are also symptoms of the disorder. Most children with this syndrome have microcephaly, or a smaller head size. Children who have Dup15q syndrome, a developmental disorder, have weak muscle tone, delays in sitting and walking, and problems with speech, language, and social interaction. Seizures, which may be difficult to control, typically develop between the ages of 6 months and 9 years. Children who have KBG syndrome are short for their age and may have underdeveloped bones of the spine, arms, leg, head, and face. They may also experience developmental and intellectual delays. Symptoms may include seizures, starting as early as infancy or as late as the teen years. Seizures may respond to medication. Some children with KBG syndrome outgrow seizures [10-15].

2.2. Anesthesia

Seizures can occur under anaesthesia and are managed by immediate deepening of anaesthesia, administration of an anticonvulsant agent, and subsequent correction of any reversible precipitating factor. Seizures are episodes of abnormal synchronized electrical brain activity. It is estimated that 2% of all people will experience a seizure during their lifetime. Epilepsy is the most common serious neurological disorder, with a prevalence of 0.5–1% of the population. While the traditional antiepileptic drugs (AEDs) still play a significant role in treatment of seizures, there has been an influx of newer agents over the last 20 yr, which are now in common usage. Patients with epilepsy often require anaesthesia for elective and emergency surgery. Appropriate perioperative management of AED therapy is vital in maintaining seizure control in these patients. Anaesthesia is usually maintained with a volatile agent, with or without nitrous oxide and an opioid. Less frequently, total i.v. anaesthesia (TIVA) is used. Phenytoin, phenobarbital, and carbamazepine cause hepatic enzyme induction. This results in increased metabolism of halogenated anaesthetics, which increases the risk of halothane hepatitis and urinary fluoride excretion. Enzyme induction may cause increased opioid requirements, whereas gabapentin has a morphine-sparing effect. Anaesthetic agents with epileptogenic potential, e.g. ketamine and alfentanil, and those with epileptogenic metabolites, e.g. meperidine, should be avoided. Seizures under anesthesia, should be managed by immediate deepening of anaesthesia, administration of an anticonvulsant agent such as propofol, thiopental, or a benzodiazepine, administration of 100% oxygen, and correction of any reversible precipitating factors, including hypoxia, hypercarbia, hypocapnoea, hyponatraemia, and hypoglycaemia. Normal saline solution should be used in these patients, with close monitoring of the acid–base status. Plasma levels of AEDs must be checked if there is any delay in restarting them or if perioperative seizures occur. Seizures are more common in the postoperative period. They may be precipitated by the use of proconvulsant anaesthetic agents, hypoxia, hypercapnoea, electrolyte disturbances (hyponatraemia, hypocalcaemia and hypomagnesaemia),

hypoglycaemia, uraemia, subtherapeutic levels of AEDs, or local anaesthetic toxicity. The occurrence of epileptic seizures after an intracranial neurosurgical operation is a well-known phenomenon, occurring in 5% to 20% of patients undergoing brain surgery. Several risk factors have been propounded to explain such an event the type of lesion, low grade gliomas, meningioma, abscess, aneurysm, or chronic subdural hemorrhage; its location; an age less than 2 years; some comorbidities, e.g., postoperative electrolytic imbalance in children, presence of cognitive impairment in adults; cortical damage related to the surgical approach. Many anaesthetic agents affect the propensity to seizures, both in patients with epilepsy and in those with no prior history of seizures. In patients taking AEDs, drug interactions and maintenance dosing of AEDs during periods of starvation are important considerations in the perioperative period [16-22].

2.3. Status epilepticus

Status epilepticus is defined as seizure lasting more than 30 min, or two or more seizures without complete recovery of consciousness between them. Status epilepticus is a neurological emergency associated with 25% overall mortality; 8% in children, 30% in adults, and 40–50% in elderly. Status epilepticus is a neurological emergency associated with significant mortality in children. In the early phase, the increased metabolic demands of the brain are met by an increase in arterial pressure, increased cerebral blood flow, increased minute ventilation, and increased blood glucose level. After 30 min, cerebral auto-regulation fails, with decreased cerebral blood flow, increased intracranial pressure, and a decrease in arterial pressure. Treatment guidelines are as follow: Supportive (ABC); Ensure patent airway; Ensure adequate ventilation and oxygenation; Secure large-bore i.v. access to facilitate blood tests (full blood count, clotting, glucose, AED levels, renal and liver function tests, calcium, and magnesium) and administration of i.v. fluids; Perform arterial blood gas analyses; Use i.v. vasopressors if required; Specific: consider aetiology and exclude alternative cause of seizures; First line: benzodiazepines; i.v. lorazepam 0.1 mg kg−1 over 30–60 s. This can be repeated once if seizures continue for 10 min. If i.v. access is not established; rectal diazepam 0.5 mg kg−1. If seizures continue for 10 min, lorazepam is used if i.v. access established, otherwise rectal paraldehyde 0.4 mg kg−1 in an equal volume of olive oil; Second line: phenytoin 15–20 mg kg−1 i.v. over 20 min with ECG and arterial pressure monitoring. If i.v. access is not yet established, use an intra-osseous needle. If the patient already on phenytoin, give phenobarbital 20 mg kg−1 over 20 min and send blood for phenytoin level. Use rectal paraldehyde if not already given; Third line (refractory seizures): induction of general anaesthesia (GA) with thiopental 4–5 mg kg−1, followed by 3–5 mg kg−1 h−1 infusion or midazolam 0.1 mg kg−1, followed by 2–20 μg kg−1 min−1 infusion and transfer to an intensive care unit.

2.4. Local anaesthetic toxicity

Local anaesthetic toxicity can present with tonic–clonic seizures, and if this is suspected in a child, it should be managed as follows: Stop injecting local anaesthetic and call for help; ABC: maintain the airway and, if necessary, secure with a tracheal tube. Give 100% oxygen and ensure adequate ventilation. Confirm or establish i.v. access; Control seizures: give benzodiazepine, thiopental, or propofol in small incremental doses; Management of cardiac arrest associated with LA injection: Start cardiopulmonary resuscitation bearing in mind that prolonged resuscitation may be necessary and cardiac arrhythmias may be refractory; Consider treatment with lipid emulsion: Give an i.v. bolus injection of Intralipid® 20% 1.5 ml kg−1 over 1 min followed by an infusion of 0.25 ml kg−1 min−1. Repeat the bolus injection twice at 5 min intervals if adequate circulation has not been restored. If adequate circulation still not restored after another 5 min, increase rate to 0.5 ml kg−1 min−1. Continue infusion until a stable and adequate circulation restored; Consider the use of cardiopulmonary bypass if available.

3. Discussion

Traditional AEDs exert antiseizure activity by the following mechanisms: reduce the inward voltage-gated positive currents (Na+, Ca2+); increase inhibitory neurotransmitter activity (GABA); decrease excitatory neurotransmitter activity (glutamate, aspartate). Pharmacological treatment with antiepileptic drugs (AEDs) depends on the type and frequency of seizures, age of the patient, and drug side-effects. Therapy is usually started with one anticonvulsant drug at a dose likely to result in therapeutic plasma level, after which the dose can be optimized as required. AEDs should be continued up to the time of the surgery and should be restarted as soon as possible after operation. Traditional anticonvulsant drugs including phenobarbital, phenytoin, carbamazepine, and sodium valproate are potent hepatic enzyme inducers, whereas felbamate, not available in the UK, is a hepatic enzyme inhibitor. Sodium valproate, carbamazepine, and ethosuximide can be associated with hepatotoxic effects. The latter three drugs, and primidone, are associated with thrombocytopenia and platelet abnormalities. Topiramate is associated with asymptomatic high anion gap metabolic acidosis. In a child with epileptic seizures, a recording of brainwave activity (EEG) and a picture of the brain (MRI) may be obtained, where necessary. Common generalized onset seizures: Generalized tonic-clonic seizures (previously called "grand mal seizures") involve abnormal electrical activity in the whole brain. They are the most dramatic type of seizure; they cause rhythmic and sometimes violent jerking movements in both sides of the body with

loss of consciousness. These seizures usually last for 2 to 3 minutes and will almost always end on their own. Absence seizures (previously called "petit mal seizures") are very short episodes with a vacant stare or a brief (few seconds) lapse of attention. They may also include other subtle symptoms like eyelid fluttering, rapid eye blinking or lip smacking. Focal onset seizures. Focal onset seizures, previously called "complex partial seizures", involve abnormal electrical activity in one part of the brain. During these seizures, a person may be aware of what is going on (called a "focal aware seizure"), or they may not be aware of what is happening, called a "focal seizure with impaired awareness". Epilepsy surgery encompasses a wide variety of treatments performed by neurosurgeons to eliminate the source of seizures, prevent the spread of seizures, stimulate the brain to stop seizures, or otherwise change seizure circuits. The goal of surgery is to eliminate seizures or reduce the number and severity of seizures.

4. Conclusion

Seizure occurs when one or more parts of the brain has a burst of abnormal electrical signals that interrupt normal signals. There are many types of seizures. Each can cause different kinds of symptoms. These range from slight body movements to loss of consciousness and convulsions. The most common treatment of recurrent seizures is pharmacologic with antiepileptic medication (AED). Approximately 70% of patients respond to AED management. Those who continue to have seizures are considered to have medically refractory epilepsy, and are at risk for adverse effects on quality of life, brain development, learning, language, and injury. For children with uncontrolled epilepsy, that is epilepsy in which seizures are not adequately controlled by medication, other treatments are available, including: rectal diazepam or intranasal/ buccal midazolam, for treatment of prolonged seizures and seizure clusters; new antiepileptic medications, available in clinical drug trials or through special access schemes; epilepsy surgery; ketogenic diet; vagus nerve stimulation; alternative therapies

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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