APPENDIX 1

History of epilepsy

Misunderstandings about epilepsy can be found throughout history and still exist in many cultures around the world. Epilepsy has been depicted in literature for centuries with the first reports occurring around 2000 BC.[1] The explanation of epilepsy has ranged from a religious, sacred experience to one of demonic possession or a curse.

The first scientific explanation of epilepsy generating from the brain was detailed in a text titled *On the Sacred Disease*, written around 400 BC and included in the Hippocratic Corpus.* This piece of literature is thought to have started the understanding of epilepsy as scientific, rather than religious or spiritual. It depicts epilepsy as a medical condition, noting the "sacred disease" has no relation with the divine, but is explained instead by the accumulation of phlegm in the brain.

Despite the description in the Hippocratic Corpus, explanations of epilepsy tied to religion persisted,[2] as shown in a review of epilepsy during the Middle Ages, the Renaissance, and the Enlightenment.[3] The review notes that the primary view of epilepsy during the Middle Ages was one of superstition, most notably endorsed by some religious authorities. The predominant theory was that those with epilepsy were possessed and a religious intervention was the only cure. Epilepsy in the Middle Ages was also thought to be contagious, leading to those with epilepsy being shunned and facing social discrimination. An isolation hospital for people with epilepsy opened in France in 1486, named St. Valentin, after Saint Valentine, the patron saint of epilepsy.[3]

In the 18th and 19th centuries, the broader acceptance of epilepsy as being a medical condition helped to create an understanding of its pathology and dissolved the idea that it was a religious or

* A collection of Ancient Greek medical works associated with Hippocrates and his teachings. The exact authorship of these books is largely unknown.

spiritual condition. This led to the introduction of medical treatment with some of the first therapies for epilepsy. A review of epilepsy research from the same time noted several treatment options, including ingesting substances such as bromides, indigo, belladonna, mistletoe, zinc oxide, and chloroform.[4] Intentionally causing fevers, bloodletting, and surgical procedures involving creating holes in the skull also occurred during this time.

Medical advancements and research have come a long way since the early history of epilepsy, but it is still not completely understood, leading to the continued stigma of the disease, even today. ("Stigma" refers to negative and unfair beliefs people have about something.) In 2019, the World Health Organization, in partnership with various epilepsy organizations, published a comprehensive report, "Epilepsy: a public health imperative," noting this stigma and discrimination. This report encourages improving knowledge and raising awareness in schools, workplaces, and communities. Enacting legislation to uphold human rights standards can help prevent discrimination in this group of individuals.[5]

Addressing the stigma often associated with epilepsy can be best done through education. Knowing what to say to others about epilepsy, particularly for children, can help empower them to not be embarrassed or ashamed of their condition. This education should be provided not just to the individual with epilepsy but the entire family.[6] Increasing education is shown to decrease negative attitudes toward epilepsy. Still, misconceptions and myths exist today.[7]

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APPENDIX 2

Seizure mimics

Not all events that look like a seizure are in fact a seizure. A seizure is often obvious, but sometimes an event characterized by a change in consciousness, physical movement, behavior, sensation, or feeling appears to be a seizure but is not; rather, it is due to another condition. This is referred to as a "seizure mimic" or a "nonepileptic event." To differentiate between seizures and seizure mimics, the medical professional uses the process of differential diagnosis. Meticulously eliminating seizure mimics is done before diagnosing the event as a seizure.

Common seizure mimics are presented in Tables A2.1 to A2.3 by the age group in which they most often occur or start to be noticed. These lists are not exhaustive.

Table A2.1 Seizure mimics in the neonatal period and infancy

CONDITION	DESCRIPTION	SIGNS/SYMPTOMS THAT MIMIC SEIZURES	DISTINGUISHING CHARACTERISTICS	REFERRALS AND ADDITIONAL TESTING
Gastroesophageal reflux disease (GERD); acid reflux	A condition where liquid contents from the stomach go back into the esophagus.[1]	Irritability, excessive crying, sleep disturbances, muscle contractions, low heart rate, apnea (breathing stops momentarily).[2]	Improvement of signs and symptoms with gastric protection medicines.[2]	Gastroenterologist.* pH monitoring.† Upper gastrointestinal endoscopy.‡
Sandifer syndrome	Movement disorder that may occur along with GERD.[5]	Involuntary muscle contractions, back arching, stiffening of the neck, turning and tilting the head.[6,7] Events occur up to 10 times a day and resolve within 3 minutes.[6]	Events typically occur within 30 minutes of feeding, rarely occur in sleep, may improve by sitting up, no impaired awareness.[6] Improvement of signs and symptoms with gastric protection medications.[2,5]	Gastroenterologist.
Breath-holding spells	Vigorous crying episode after which, on expiration, the child holds their breath (as a reflex, not on purpose), sometimes until they pass out.[8]	Body stiffness or convulsions, impaired awareness, cyanosis (bluish skin coloring) or paleness.[6,8]	Triggered by an event that makes the child cry.[8]	Cardiologist (if concern the event may be of a cardiac nature).[8]
Benign spasms§ of infancy	Movements that occur in typically developing infants and resolve on their own in the second year of life.[9]	Brief spasms (1 or 2 seconds) of the head, trunk, shoulders, and arms, which may occur in clusters.[7,9]	Occur while awake and in sleep, no impaired awareness; sudden onset and sudden end.[7,10]	EEG.[9]

* A medical professional who specializes in the care of the gastrointestinal tract and related organs.

† A test to determine whether acid is entering the esophagus from the stomach.[3]

‡ Involves viewing the inside of the gastrointestinal tract with a camera; "upper" refers to the upper part of the gastrointestinal tract, which includes the mouth, esophagus, stomach, and small intestine.[4]

§ "Benign" means something that is not harmful. "Spasms" are brief, involuntary muscle contractions.

Table A2.2 Seizure mimics in childhood

CONDITION	DESCRIPTION	SIGNS/SYMPTOMS THAT MIMIC SEIZURES	DISTINGUISHING CHARACTERISTICS	REFERRALS AND ADDITIONAL TESTING
Cyclic vomiting	A condition that includes repeated bouts of vomiting.[6]	Abdominal pain, pallor (pale skin), and fatigue; may also occur along with migraine headaches.[6]	Often occurs in a very predictable pattern and lasts for a certain number of days, then resolves.[6]	Gastroenterologist* Upper gastrointestinal endoscopy.†[6] Abdominal imaging.[6]
Hypoglycemia	A condition with lower than typical blood glucose (sugar) levels.[11]	Confusion, impaired awareness, lack of coordination, difficulties with speech, and tremors.[12]	Hunger, heart palpitations, sweating.[12] Examination of the preceding circumstances (is the individual fasting, taking medications, or diabetic?).[13]	Endocrinologist.‡
Migraine	A type of headache with moderate to severe throbbing and pulsating pain. It often occurs and the pain may be concentrated on one side of the head.[15]	May be accompanied by an aura (a sensation or symptom experienced at the onset of a neurological event) and may include numbness, alterations in speech, visual disturbances, and dizziness.[16,17]	Family history of migraines.[17] Occurs without motor signs, as often occur with seizures. Migraine auras have a gradual onset (seizure auras tend to be abrupt).[16] Impaired awareness is uncommon.[16]	Imaging or laboratory tests may be recommended.

Cont'd.

* A medical professional who specializes in the care of the gastrointestinal tract and related organs.

† A test to determine whether acid is entering the esophagus from the stomach.[3]

‡ A medical professional who specializes in the treatment of the endocrine system, including organs and glands that regulate hormones.[14]

CONDITION	DESCRIPTION	SIGNS/SYMPTOMS THAT MIMIC SEIZURES	DISTINGUISHING CHARACTERISTICS	REFERRALS AND ADDITIONAL TESTING
Movement disorders	**Stereotypies:** Semivoluntary repetitive movements that are often rhythmic.[6,10]	May include clapping or arm-shaking.	Stereotypies are usually not associated with impaired consciousness and may occur multiple times per day.[10]	EEG[10]
	Tics: Involuntary, sudden, rapid, and repetitive sounds or movements.[10]	Vocal tics may include throat-clearing, coughing, grunting, or yelling. Motor tics may include blinking, eye-rolling, mouth movements, shaking of hands, tapping, kicking, or abnormal postures.[18]	Unlike seizures, tics and stereotypies can be interrupted or suppressed voluntarily for a short period.[10,19]	
Sleep disorders	**Narcolepsy:** A sleep disorder characterized by excessive sleepiness during the day and often presenting with irresistible sleep attacks.[20]	Often (70 percent) accompanied by cataplexy (loss of posture, causing the individual to fall suddenly).	Typically, after an event related to a sleep disorder, the individual is refreshed, unlike after a seizure when they are confused, or tired.[12]	Referral to a sleep specialist. Polysomnogram with EEG.
	Parasomnias: A group of sleep disorders characterized by unusual behaviors that occur just prior to falling asleep, while asleep, or just upon waking,[13, 21, 22] including sleepwalking, night terrors, or confusional arousal.*[21]	Individuals may also experience hallucinations or paralysis upon sleep or when waking.[12] May be accompanied by impaired awareness and the inability to recall the event. [13,21]	Typically occur only once or twice per night, while seizures may occur multiple times in one night.[21]	
Sleep myoclonus	A sudden, involuntary, muscle jerk that occurs during sleep transitions (falling asleep or waking up).[21]	Often accompanied by a hallucination of movement, experienced as a feeling of falling.[23]	Extremely brief, only occurs with sleep.	Typically not needed.

* A sudden arousal from sleep accompanied by confusion.[21]

Table A2.3 Seizure mimics in adolescence and adulthood

CONDITION	DESCRIPTION	SIGNS/SYMPTOMS THAT MIMIC SEIZURES	DISTINGUISHING CHARACTERISTICS	REFERRALS AND ADDITIONAL TESTING
Behavioral, psychological, and psychiatric	May include dissociative disorders,* panic attacks, hyperventilation, and episodic dyscontrol.†	Aggression, hallucination, auras, thrashing movements, tremors, dizziness, fear.[13,16]	May be brought on by personal or environmental stressors and typically do not involve a change in consciousness. Episodic dyscontrol events typically come on abruptly, are short in duration, without impaired consciousness, and are followed by exhaustion and difficulty recalling the event.[25] Panic attacks tend to last longer than seizures.	Referral to mental health and psychiatric medical professionals.[13]
Cardiovascular	Conditions that involve the heart and vascular system, including heart abnormalities (long QT syndrome‡), high blood pressure, or postural orthostatic tachycardia syndrome (POTS).§	An individual with long QT syndrome may become pale, or limp (or rigid), and may have impaired consciousness.[26] POTS results in chest pain, rapid heartbeat, lightheadedness, blurred vision, and abdominal pain.[7,27]	Long QT episodes may be triggered by exercise or fear.[7] POTS is triggered by standing and resolves with sitting or lying down.[27]	Cardiologist. ECG/EKG (electrocardiogram; tracing of the electrical activity of the heart). Imaging such as vessel ultrasound, echocardiogram (an ultrasound showing pictures of the heart and valves).[12]

Cont'd.

* Psychiatric conditions involving "problems with memory, identity, emotion, perception, behavior, and sense of self"[24]

† Recurrent attacks of uncontrollable rage and violence that result in damage to people or property; also known as intermittent explosive disorder.[25]

‡ A condition of abnormal cardiac rhythm, causing syncope (fainting) and may lead to death.[26]

§ A group of conditions where blood flows to the heart after a change of position, resulting in a symptom known as orthostatic intolerance. Individuals with orthostatic intolerance feel faint or lightheaded when they move from lying to standing.

CONDITION	DESCRIPTION	SIGNS/SYMPTOMS THAT MIMIC SEIZURES	DISTINGUISHING CHARACTERISTICS	REFERRALS AND ADDITIONAL TESTING
Cerebrovascular	Conditions that involve the brain and vascular system and include brain abnormalities, strokes, or transient ischemic attacks (TIAs)*	Difficulty with speech, vision, or lack of movement on one side of the body.	Lack of movement occurs instead of extra movements as occurs with seizures.	Imaging.
Psychogenic nonepileptic seizures (PNES)†	Involuntary events that may last for several minutes (sometimes 15 to 30 minutes or longer).	Impaired awareness and motor signs such as irregular jerking or shaking of the limbs and falling.[30]	Personal or environmental stressors, or trauma, may be triggers.[30]	EEG. May result in significant impact on quality of life and require interdisciplinary management including psychotherapy, behavioral management, and screening and treatment of mental health conditions, as appropriate.[31]
Syncope (fainting spell)	A condition that involves self-limiting† transient (temporary) loss of consciousness with the inability to maintain a standing or unsupported posture and may be accompanied by brief jerking movements.[32,33,34]	Limp posture or jerking movements, impaired consciousness.[34]	Typically occurs from standing, not from a sitting or lying down position, unlike seizures.[32] May be triggered by pain, emotions, prolonged standing, or a hot environment and often preceded by dizziness, nausea, paleness, or sweating.[12, 34, 35] Consciousness regained quickly.[36]	Cardiologist.[32]

* A condition when a blood vessel in the brain is either blocked or ruptured. This leads to damage in the brain and causes symptoms such as paralysis, speech problems, and memory loss.[28] A TIA is a transient, or temporary blockage, which resolves on its own, and may cause temporary symptoms similar to a stroke.[29]

† Refers to something that limits itself or spontaneously resolves.

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APPENDIX 3

Seizure and epilepsy terminology

The terminology for seizures and epilepsy has changed over the years, and both "old" and "new" terms can be found in the literature. Table A3.1 shows common terms in both their old and new forms.[1,2] This book uses the new terms, listed in the table in the order they are discussed in the text.

Table A3.1 Old and new terms for seizures and epilepsy

NEW TERM	OLD TERM
Focal onset seizure	Partial seizure
Focal aware seizure	Simple partial seizure
Focal impaired awareness seizure	Complex partial seizure
Focal to bilateral tonic-clonic seizure	Focal seizure with secondary generalization
Generalized tonic-clonic seizure	Grand mal seizure
Absence seizure	Petit mal seizure
Atonic	Akinetic or drop attacks
Hyperkinetic	Hypermotor
Epileptic spasm	Infantile spasm
Nonepileptic psychogenic seizure (PNES)	Psychogenic seizure, pseudoseizure

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APPENDIX 4

Neurons and seizures

Neurons are the smallest unit of the nervous system, and there are billions of them in the brain and spinal cord. They are electrically excitable cells and carry information (signals) between the central nervous system and the rest of the body as electrical impulses through a web-like structure from neuron to neuron, or from neurons to other cells in the body.[1]

Electrical activity moves through and out of a neuron to the next neuron or cell via a complex process, known as an "action potential."

The inside of a neuron at rest (not sending or receiving any signals) is negatively charged compared to the fluid surrounding it (containing ions). This is referred to as the "resting membrane potential" and is a measurement of the difference in electrical charge (voltage) between the inside and the outside of the neuron.

Figure A4.1 illustrates this concept for a typical resting membrane potential for a neuron.

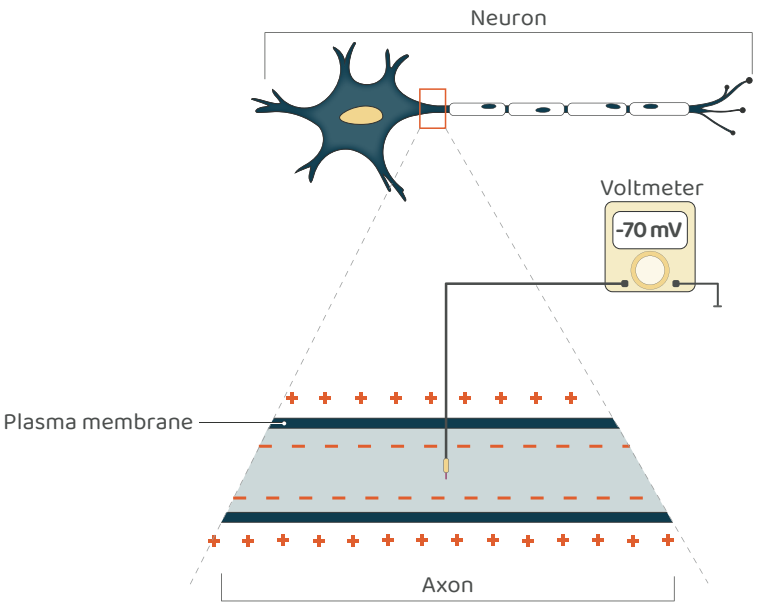

Figure A4.1 Resting membrane potential in a neuron. The plus (+) and minus (–) signs represent the net electrical charges of the ions inside and outside the cell. The barrier between the two spaces is the plasma, or cell, membrane. The net electrical charge outside the cell is positive, while net electrical charge inside the cell is negative. The resting membrane potential (–70 mV on the voltmeter*) is the difference between the inside of the cell relative to the outside of the cell.

The action potential process can be divided into stages. The neuron starts at the resting membrane potential phase and is then activated, causing a brief change from negative to positive, and then back to negative again. These stages are shown in Figure A4.2 and described below:[2]

- **Depolarization:** An event where a neuron's membrane potential briefly becomes less negative (for about 1 millisecond, or 1,000th of a second). This results when the cell body of a neuron receives enough signals to activate (when the threshold is met), causing a portion of the axon nearest the cell body to depolarize—becomes less negative for a moment (in about 1 millisecond).
- **Repolarization:** This occurs after the firing of the axon reaches the peak positive value and switches back to a more negative state by the movement of ions.
- **Hyperpolarization:** This is when the membrane falls below the resting potential based on movement of ions. While brief, this action is notable because the amount of stimulus needed to reactivate (or depolarize) this same neuron would be more than what triggered it to begin with, making it less likely that this same neuron would be immediately triggered again (within the next few milliseconds).

Additional terms related to action potentials and depicted in Figure A4.2 include:

- **Resting potential:** When no impulse is being received or sent and the neuron is "at rest." The voltage of the resting membrane potential is –70mV in the figure.

* An instrument that measures voltage. The unit of measurement for a membrane potential is a millivolt (1/1000th of a volt), expressed as mV.

- **Threshold:** The voltage at which the signals are of a large enough intensity to produce the effect (–55 mV in the figure).
- **Failed initiations:** The result of signals being insufficient to cause the membrane potential to reach the threshold, so depolarization does not occur. The action potential is an all-or-nothing process; that is, if the threshold is not reached, an action potential does not result, and no message is sent. Some failed initiations are depicted in the figure. Notice the peaks are below the threshold, so no depolarization occurs.

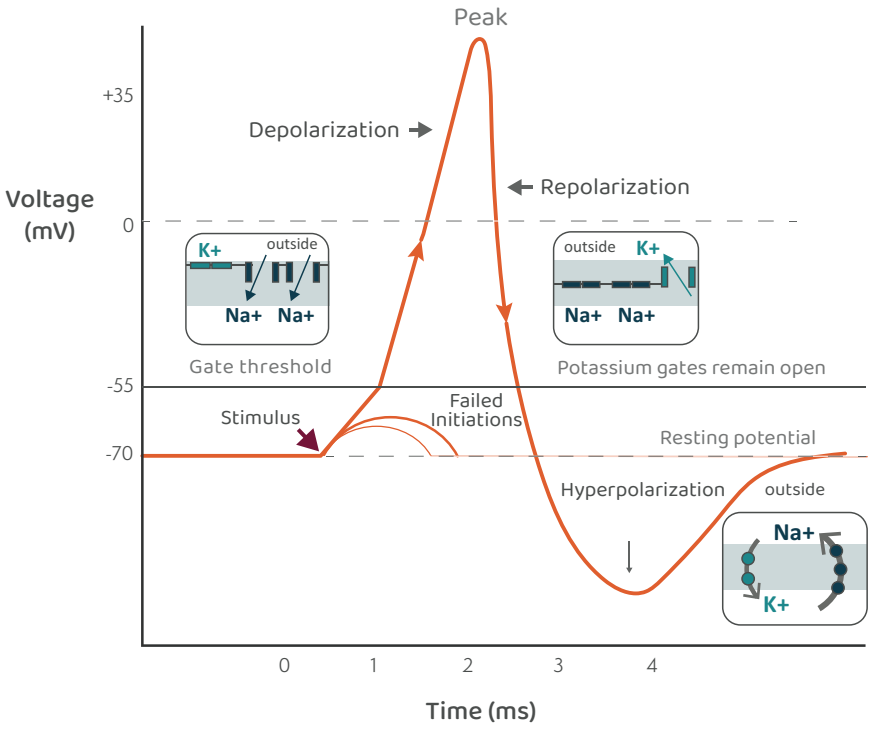

Figure A4.2 Stages of an action potential. Na+ = sodium; K+ = potassium.

The action potential process continues down the axon of the neuron with the changes from one segment of the axon triggering depolarization in the next section and so on until it reaches the end of the axon.

Many ions exist in the body and in and around the neurons, and the movement of these ions (traveling in the impulse) across the axon's membrane (the outer surface) creates the action potential. Action potentials allow neurons to communicate signals rapidly and efficiently. However, during a seizure, neurons fire excessively and uncontrollably, and the ability of the neurons to regulate signals is disrupted. This leads to uncontrolled electrical activity, seen as a seizure.

Most often, sodium and potassium ions generate the action potentials. A "sodium-potassium pump" is an energy-consuming mechanism within cells that moves these ions in and out of the cells, changing the net electrical charge, allowing the membrane to return to the resting potential and prepare for another action potential. The action potential process is illustrated in Figure A4.3.

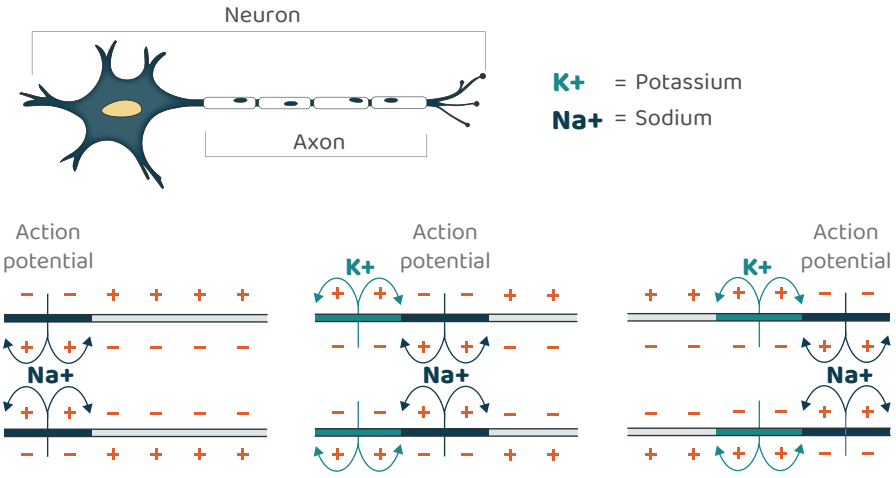

Figure A4.3 Action potential traveling down a neuron's axon. Potassium (K+) and sodium (Na+) ions move into and out of the neuron (the double lines represent the plasma, or cell, membrane, with the inside of the cell located between the lines) as the electrical charge changes. The three images along the bottom represent a sequence at three time points: the curved arrows indicate the movement of the ions, and the color of the plasma membrane signifies the specific ion moving. In this way, the message, or impulse, moves down the length of the axon from left to right.

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APPENDIX 5

Genetic testing and epilepsy

Genetic testing may be recommended for individuals with epilepsy. Having an overview of DNA, genes, and chromosomes, and their relationship to one another is helpful to understanding the process of genetic testing.

This relationship is depicted in Figure A5.1 and terms are described below:[1]

- **DNA:** The building block of genes.
- **Gene:** A segment of DNA.
- **Chromosomes:** Units of packaged genetic materials made up of DNA and proteins. Chromosomes exist in pairs,* with both males and females† having 23 pairs of chromosomes (46 total, in each cell‡); one pair in the set are sex chromosomes, differing males from females. Males have both an X and a Y sex chromosome while females have two X sex chromosomes. A child will inherit one copy of each chromosome from the female parent and one copy of each chromosome from the male parent, thereby inheriting 50 percent of the genetic material from the female parent and 50 percent from the male parent. Since females do not have a Y chromosome, males always inherit the Y chromosome from the male parent.
- **Nucleus:** Found in the center of the cell and contains most of the genetic material; responsible for controlling and regulating the activities of the cell.

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* In this description, the sex chromosomes are considered a pair; although the male has two different chromosomes (X and Y), which are not an exact pair. Another way to describe the number of chromosomes is to state that humans have 22 sets of autosomes (nonsex chromosomes) and one set of sex chromosomes.

† "Male" and "female" refer to biologic sex, not gender.

‡ Sperm cells and egg cells contain only half the genetic material (just one copy of each chromosome) as other cells in the human body.[2]

- **Mitochondria:** The structure that surrounds the nucleus of the cell and contains some genetic material; responsible for supplying the cell with energy. Genetic material from the mitochondria is primarily inherited by a child from the female parent.[3]
- **Nucleotides:** The building blocks of DNA. The order of nucleotides in DNA is examined (called sequencing) in genetic testing.[4] Multiple nucleotides are found in DNA (listed in the figure).

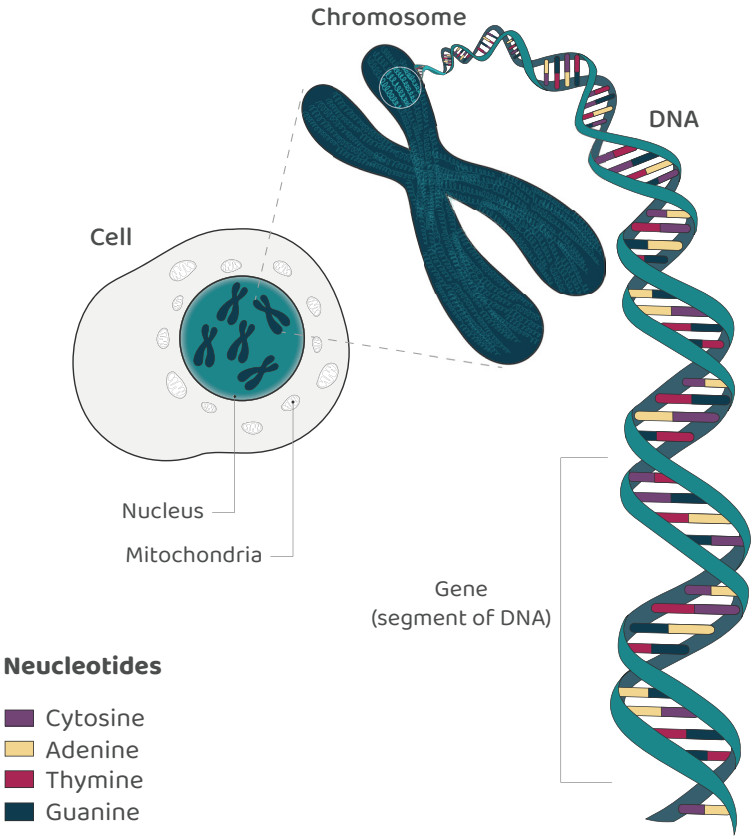

Figure A5.1 DNA, genes, and chromosomes.

Genetic tests used in individuals with epilepsy include:

- **Karyotype:** Produces a picture of the pairs of chromosomes in an individual. Karyotypes are useful in identifying missing, extra, or large structural changes in chromosomes.[5]
- **Chromosomal microarray analysis** (CMA, also known as comparative genomic hybridization): Produces a high resolution molecular karyotype and helps detect atypical, small changes related to the number of chromosomes, the shape of the chromosomes, or extra or missing segments of chromosomes.[6] CMA detects changes known as copy number variants on stretches of DNA. CMA has replaced karyotype as a first-line genetic test in most genetic settings.
- **Gene panel:** A test that targets and investigates specific genes known to be involved in specific conditions:[7] for example, epilepsy. An epilepsy gene panel is used when a specific type of epilepsy known to be associated with a particular gene is suspected.

- **Whole exome sequencing:** A test sequencing all the protein-coding regions of genes in the genome, known as the exome. The exome makes up only about 1.5 percent of the entire genome, but is associated with 85 percent of all variants.[8,9,10]
- **Mitochondrial DNA sequencing:** A genomic technique for sequencing the genes located on the mitochondrial DNA.
- **Whole genome sequencing:** A technique involving sequencing of all the protein-coding regions and nonprotein-coding regions of genes in a genome.[5]

Genetic testing typically produces one of the following results:

- **No abnormalities detected:** This result is also known as normal, negative, or benign (not harmful). In an individual with epilepsy, this means a genetic cause of epilepsy was not identified using the genetic test performed. It does not completely rule out the possibility of genetic cause, however, and more testing may be recommended.[11]
- **Pathogenic variants detected:** This result is also known as abnormal, positive, or as disease-causative. In an individual with epilepsy, this means the genetic change is identified as the cause of epilepsy.[11]
- **Variant of uncertain significance detected:** This result is also known as genetic variant of uncertain significance (VUS) and means a genetic change was detected, but the meaning of the finding is not fully understood. In this situation, it may be recommended that other family members be tested, other in-depth testing be done, and/or the results be reevaluated later (in one to two years). With ongoing research, genetic causes may be identified in the future. A VUS today might later be reclassified as normal, as a genetic epilepsy, or another condition.[11]

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APPENDIX 6

Epilepsy syndromes

Table A6.1 Onset in neonatal period and infancy

SELF-LIMITED FOCAL EPILEPSY SYNDROMES	SELF-LIMITED NEONATAL SEIZURES AND SELF-LIMITED FAMILIAL NEONATAL EPILEPSY (SeLNE)
Age at onset	2 to 7 days.
Resolves by	6 weeks; may persist up to 6 months; up to one-third will have seizures later in life.
Seizures	Focal tonic seizures, most often affecting the head, face, and limbs. May experience vocalization or automatisms, and about one-third will present with cyanosis (bluish skin color) and apnea (breathing stops). Seizures are brief but frequent, appearing in clusters and may occur over hours or several days.[1]
Management and treatment	Antiseizure medication (carbamazepine is usually used for *KCNQ2*); often able to stop within weeks without recurrence.[1]
Cause	Genetic.
Genes	*KCNQ2, KCNQ3*.
Inheritance pattern	Inherited or *de novo*.[1]
Developmental impact	Typical development.[1]
Comorbidities	A minority of individuals may have learning difficulties or mild motor impairment.[1]

Cont'd.

SELF-LIMITED FOCAL EPILEPSY SYNDROMES

SELF-LIMITED FAMILIAL INFANTILE EPILEPSY AND SELF-LIMITED INFANTILE EPILEPSY (SeLIE)	
Age at onset	3 to 20 months.[1]
Resolves by	Typically within 1 year of onset.[1]
Seizures	Focal seizures with behavioral arrest, staring, cyanosis, clonic movements often frequent (5 to 10 per day over several days). Seizures may progress from focal to bilateral tonic-clonic.[1]
Management and treatment	Antiseizure medication.
Cause	Genetic.
Genes	*PRRT2, SCN2A, KCNQ2, KCNQ3*.[1]
Inheritance pattern	Inherited or *de novo*.[1]
Developmental impact	Typical development.[1]
Comorbidities	Movement disorders may develop later in life.[2]
GENETIC EPILEPSY WITH FEBRILE SEIZURES PLUS (GEFS+)	
Age at onset	Under 6 months.[1]
Resolves by	May resolve by puberty.[1]
Seizures	Febrile seizures occurring outside the typical time frame for febrile seizures (i.e., before 6 months of age, or after 6 years of age); additional generalized or focal seizures also occur.[1]
Management and treatment	Antiseizure medication.
Cause	Genetic.
Genes	*SCN1A, SCN1B, GABA, PCDH19, STX1B*.[1]
Inheritance pattern	Typically inherited, may be *de novo*.[1]
Developmental impact	Developmental delay may occur.[1]
Comorbidities	Typically none associated.
MYOCLONIC EPILEPSY IN INFANCY	
Age at onset	6 months to 2 years.[3]
Resolves by	6 months to 5 years from onset;[3] approximately 10 percent of individuals will develop another type of epilepsy during late childhood or adolescence.[1]

Cont'd.

SELF-LIMITED FOCAL EPILEPSY SYNDROMES	**Seizures**	Myoclonic seizures occurring in frequent clusters involving the head and upper arms; may be triggered by sound, light, or touch.[4]
	Management and treatment	Antiseizure medication, which can often be stopped after 3 to 5 years.[4]
	Cause	Likely genetic.
	Genes	None identified.
	Inheritance pattern	Family history of febrile seizures or epilepsy in about 10 percent.
	Developmental impact	Developmental progress is typically normal before onset of seizures; 60 to 85 percent have normal developmental progress at long-term follow-up.[1]
	Comorbidities	Mild learning difficulties and attention problems may occur.[1]
DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES (DEES)	**EARLY-INFANTILE DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY (EIDEE) (OHTAHARA SYNDROME OR EARLY MYOCLONIC ENCEPHALOPATHY)**	
	Age at onset	First 3 months of life.[1]
	Seizures	Generalized or focal, tonic (Ohtahara syndrome), or myoclonic (early myoclonic encephalopathy). Other types of seizures might be seen, such as epileptic spasms. Seizures occur frequently in clusters. Interictal EEG is abnormal.[1] May progress to West syndrome or Lennox-Gastaut syndrome.[5]
	Management and treatment	Often drug-resistant seizures. May be treated with ACTH,* high-dose steroids, antiseizure medication, ketogenic diet, neuromodulation device (vagus nerve stimulator), or epilepsy surgery.[1,6]
	Cause	Genetic, structural, metabolic.[1,7]
	Genes	*SCN2A, SCN8A, KCNQ2, STXBP1, CDKL5, KCNT1, UBA5*.[1]
	Inheritance pattern	Family history not usually present; *de novo*.[7, 8]
	Developmental impact	Developmental delay may occur prior to onset of seizures; moderate to profound developmental delay develops over time.[1]
	Comorbidities	Intellectual disability, movement disorders, or abnormal tone often present.[1,6]
	EPILEPSY OF INFANCY WITH MIGRATING FOCAL SEIZURES	
	Age at onset	First 6 months of life.[1]
	Seizures	Focal clonic or tonic that migrate to multiple areas of the brain; seizures may increase in frequency over time and may lead to status epilepticus.[9]
	Management and treatment	Drug-resistant seizures; multiple antiseizure medications may be tried. Ketogenic diet or neuromodulation (vagus nerve stimulation) may be options.[10]
	Cause	Genetic.
	Genes	*KCNT1, SCNA1, SCNA2, TBC1D24,* and others.[1]

Cont'd.

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES (DEES)	**Inheritance pattern**	Typically *de novo*.[10]
	Developmental impact	Developmental delay is severe. Typically, a poor prognosis with decreased life expectancy.[1]
	Comorbidities	Intellectual disability, microcephaly,† movement disorders, gastrointestinal disorders.[10,1]
	INFANTILE EPILEPTIC SPASMS SYNDROME (IESS) (WEST SYNDROME)	
	Age at onset	3 to 12 months.[7]
	Seizures	Epileptic spasms ranging from a few to over a hundred in clusters while awake or during sleep. Focal seizures may also occur at the beginning or end of the spasms. [1,7] Hypsarrhythmia on interictal.[12] Individuals with this syndrome often develop other epilepsy syndromes.
	Management and treatment	ACTH/high-dose steroids and/or antiseizure medication (e.g., in case of tuberous sclerosis, vigabatrin might be a good option); ketogenic diet might be considered.[13]
	Cause	Structural (30 percent), genetic, metabolic.[14,15]
	Genes/ chromosomes	*ARX*, *CDKL5*, *STXBP1*, *SPTAN1*, *IQSEC2*, *TSC1*, *TSC2*, Trisomy 21.
	Inheritance pattern	Family history is rare, typically *de novo* when genetic cause.
	Developmental impact	Developmental progress is typically normal before onset of seizures; developmental delay occurs over time.[1]
	Comorbidities	Down syndrome and tuberous sclerosis are associated with this syndrome.[14] Intellectual disability develops in most.[15] Autism spectrum disorder may develop.[15]
	DRAVET SYNDROME (PREVIOUSLY KNOWN AS SEVERE MYOCLONIC EPILEPSY OF INFANCY)	
	Age at onset	First year of life.[16]
	Seizures	Focal, focal to bilateral tonic-clonic seizures and generalized seizures that are often prolonged and may lead to status epilepticus.[17] Myoclonic and absence seizures may also occur. Febrile seizures are the first seizure in about 60 percent of individuals.[16] Seizures may be triggered by vaccines, fever, flashing lights, or stress. Drug-resistant seizures which are lifelong.[17]
	Management and treatment	Antiseizure medication, but avoid sodium channel blockers,‡ medical cannabis, ketogenic diet may be tried.[18]
	Cause	Genetic.
	Genes	*SCNA1*.[16]
	Inheritance pattern	May be inherited and family history of seizures present in 30 to 50 percent; most are *de novo*.[17]
	Developmental impact	Developmental delay occurs after seizures begin and are typically apparent by age 3.[1,18]
	Comorbidities	Multiple comorbidities including intellectual disabilities, movement disorders, and sleep disorders.[16, 18]

Cont'd.

ETIOLOGY-SPECIFIC EPILEPSY SYNDROMES

KCNQ2-DEE	
Age at onset	Within the first few days of life.[1]
Seizures	Tonic, myoclonic, or focal seizures that are often accompanied by apnea (breathing stops).[1]
Management and treatment	Antiseizure medication such as carbamazepine or oxcarbazepine; seizures are often resistant to typical first-line antiseizure medications[1]
Cause	Genetic.
Genes	*KCNQ2*.[1]
Inheritance pattern	*De novo*.[1]
Developmental impact	Developmental delay is moderate to severe.[1]
Comorbidities	Intellectual disability, movement disorders, autism spectrum disorder, behavior disorders, and sleep disorders.[19]
PYRIDOXINE DEPENDENT (ALDH7A1)-DEE (PD-DEE) AND PYRIDOX(AM)INE-5'-PHOPHATE DEFICIENCY (PNPO)-DEE (P5PD-DEE)	
Age at onset	May occur before birth with intrauterine convulsions or within the first few days of life; about 25 percent present after the neonatal period, up to 3 years; often born prematurely.[1]
Seizures	Myoclonus, focal, epileptic spasms, generalized tonic-clonic; seizures are frequent and often prolonged and may lead to status epilepticus.[1]
Management and treatment	Seizures are often resistant to antiseizure medications but respond well to supplements of pyridoxine or pyridoxal-5' phosphate, which may be needed lifelong. Sometimes leucovorin (a form of folic acid) might be needed.[1,20]
Cause	Metabolic, genetic.[1]
Genes	*ALDH7A1, PLBP, PNPO*.[1]
Inheritance pattern	Inherited.[21]
Developmental impact	Developmental delay.[21]
Comorbidities	Intellectual disabilities range from mild to severe in most individuals.[1]
CDKL5-DEE	
Age at onset	Within the first 6 weeks of life.
Seizures	Tonic, focal, generalized tonic-clonic, epileptic spasms, stereotyped hand movements.[1,22]
Management and treatment	Drug-resistant seizures; sustained benefit has not been shown with antiseizure medication. Ganaxolone, a synthetic neuroactive steroid, is approved by the US Food and Drug Administration (FDA) to treat seizures in individuals who are 2 years or older.

Cont'd.

ETIOLOGY-SPECIFIC EPILEPSY SYNDROMES		
	Cause	Genetic.
	Genes	*CDKL5*; an X-linked gene, seen predominantly in females (4:1).[1]
	Inheritance pattern	Typically *de novo*, may be inherited.[23]
	Developmental impact	Developmental delay is severe, and less than 25 percent of individuals will be able to walk independently or speak single words.[1]
	PCDH19 CLUSTERING EPILEPSY	
	Age at onset	Within the first year of life.
	Seizures	Focal impaired aware (may include screaming), tonic-clonic; seizures may be triggered by fever and often occur in clusters; may lead to status epilepticus. Seizures may resolve in at least 25 percent in adolescence or later.[1]
	Management and treatment	Drug-resistant seizures, often requiring multiple antiseizure medications.[24]
	Cause	Genetic
	Genes	*PCDH19*; an X-linked gene, seen predominantly in females.[1]
	Inheritance pattern	Inherited or *de novo*; approximately half are *de novo*.[1]
	Developmental impact	Developmental delay is common; microcephaly may occur.[1]
	Comorbidities	Intellectual disability, movement disorders, and migraines.[1]
	STURGE-WEBER SYNDROME	
	Age at onset	Condition is present at birth, but seizures typically begin within the first 6 months of life.
	Seizures	Focal, focal to bilateral tonic-clonic, epileptic spasms, status epilepticus; seizures present in 75 to 85 percent of individuals.[1]
	Management and treatment	Antiseizure medication such as carbamazepine, oxcarbazepine, and levetiracetam often provide good seizure control. If drug-resistant seizures develop, epilepsy surgery may be recommended. Ketogenic diet may be recommended.[1, 25] Low-dose aspirin beginning in infancy may be given to prevent stroke-like events.[26]
	Cause	Structural, genetic.
	Genes	*GNAQ*.27
	Inheritance pattern	*De novo*.[27]
	Developmental impact	Developmental delay is common.[26]
	Comorbidities	Angiomas (lesions caused by atypical growth of blood vessels) may be present in the brain, in the eye, and as capillary malformations on the face. When these appear on the face they are referred to as port-wine stains. Stroke-like events resulting in hemiparesis (weakness or partial paralysis on one side of the body) may occur.[26] Learning disorders, psychiatric and behavioral conditions, headaches, and intellectual disability may occur.[1]

Cont'd.

ETIOLOGY-SPECIFIC EPILEPSY SYNDROMES

GELASTIC SEIZURES WITH HYPOTHALAMIC HAMARTOMA	
Age at onset	Within the first year of life in 85 percent of individuals.[1]
Seizures	Gelastic (laughing episodes) or dacrystic (crying episodes) seizures; may also progress over time to focal impaired awareness and generalized seizures.[1]
Management and treatment	Drug-resistant seizures; epilepsy surgery may be an option for treatment.[1]
Cause	Structural (lesions in the hypothalamus§ that are present at birth); genetic.
Genes	About 5 percent are associated with *GL13*.[1]
Inheritance pattern	Typically *de novo*[28]
Developmental impact	Developmental delay may occur.[29]
Comorbidities	Intellectual disability, behavioral disorders, and psychiatric disorders may occur.[29]

* ACTH (adrenocorticotropic hormone) is a medication given over several weeks, often along with antiseizure medications, and is particularly effective in the treatment of infantile spasms.[30]

† A condition in which the individual's head is much smaller than typical and may be caused by lack of brain development and growth.

‡ A type of antiseizure medication that blocks sodium ions from flowing in and out of neurons, inhibiting seizure activity.[31]

§ A structure in the brain that helps to maintain a stable environment in the body by controlling hormones and the autonomic nervous system, including body temperature, blood pressure, hunger, thirst, mood, and sleep.[32]

Table A6.2 Onset in childhood

SELF-LIMITED FOCAL EPILEPSY SYNDROMES		
	SELF-LIMITED EPILEPSY WITH CENTROTEMPORAL SPIKES (SeLECTS) (PREVIOUSLY KNOWN AS ROLANDIC EPILEPSY)	
	Age at onset	3 to 14 years.[33]
	Resolves by	Puberty (age 13); may persist until 18 years.[33]
	Seizures	Brief focal clonic or tonic seizures that involve the throat and/or tongue and one side of the bottom half of the face; may progress to focal to bilateral tonic-clonic;[33] often sporadic.[7]
	Management and treatment	Antiseizure medication; often can be stopped 2 to 4 years after starting. Complete remission is common.[34]
	Cause	Genetic cause is suspected but is not yet well characterized.[33]
	Genes	None identified.
	Inheritance pattern	Family history of epilepsy or febrile seizures may exist, but typically not a family history of SeLECTS.[33]
	Developmental impact	Typical development.[33]
	Comorbidities	Behavior disorders and language impairment may occur but often improve after the epilepsy resolves.[33]
	SELF-LIMITED EPILEPSY WITH AUTONOMIC SEIZURES (SeLEAS) (PREVIOUSLY KNOWN AS PANAYIOTOPOULOS SYNDROME)	
	Age at onset	3 to 6 years.[33]
	Resolves by	1 to 2 years after onset.
	Seizures	Focal autonomic seizures; vomiting is a frequent sign (75 percent of individuals); seizures are infrequent and 25 percent have only a single seizure.[33] Seizures occur with sleep and may be prolonged, lasting more than 30 minutes
	Management and treatment	Antiseizure medication; often able to be stopped within 1 to 2 years. Approximately 20 percent of individuals will develop another epilepsy syndrome.[33]
	Cause	Unknown.
	Genes	None identified.
	Inheritance pattern	Minority have a family history of epilepsy.[35]
	Developmental impact	Typical development.[33]
	Comorbidities	May have mild language impairment that often improves after the epilepsy resolves.[36]

Cont'd.

SELF-LIMITED FOCAL EPILEPSY SYNDROMES		
	CHILDHOOD OCCIPITAL VISUAL EPILEPSY (COVE)	
	Age at onset	8 to 9 years.[33]
	Resolves by	Puberty.[33]
	Seizures	Focal aware or impaired awareness seizures with or without motor signs occur while awake and are often accompanied by sensory phenomena; may be frequent and brief with hallucinations or migraines.[33] Typical absence seizures may also occur.[33] Vision changes, visual hallucinations, eye pain, repetitive eye movements may also occur.[37] Postical headache is common.[33]
	Management and treatment	Antiseizure medication if seizures recur; complete remission of seizures in 50 to 80 percent of individuals with or without antiseizure medication occurs by puberty.[33]
	Cause	Genetic cause is suspected but is not yet well characterized.[33]
	Genes	None identified.
	Inheritance pattern	Family history of febrile seizures or epilepsy in one-third of individuals and family history of migraine in 9 to 16 percent of individuals.[33]
	Developmental impact	Typical development.[33]
	Comorbidities	Typically none associated.[38]
	PHOTOSENSITIVE OCCIPITAL LOBE EPILEPSY (POLE)	
	Age at onset	4 to 17 years.[39]
	Resolves by	Varies.
	Seizures	Focal aware seizures with sensory phenomena; seizures are brief and rarely progress to a focal to bilateral tonic-clonic seizure.[40] Seizures are often triggered by light sources (e.g., TV, video games, flickering sunlight.[41]
	Management and treatment	Antiseizure medication; avoid known triggers.
	Cause	Genetic cause suspected.[42]
	Genes	None identified.
	Inheritance pattern	Family history of the syndrome is present in one-third of individuals.[39]
	Developmental impact	Developmental delays may exist.[40]
	Comorbidities	Typically none associated.

Cont'd.

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES (DEES)

EPILEPSY WITH MYOCLONIC-ATONIC SEIZURES (EMAtS) (PREVIOUSLY KNOWN AS DOOSE SYNDROME; ALSO KNOWN AS EPILEPSY WITH MYOCLONIC-ASTATIC SEIZURES)	
Age at onset	2 to 6 years.[33]
Seizures	Generalized tonic-clonic, myoclonic, myoclonic-atonic, absence; onset of seizures is often abrupt and explosive and may include status epilepticus;[33] may have a history of febrile seizures.[43]
Management and treatment	Ketogenic diet may be successful; antiseizure medication. Drug-resistant seizures that may resolve in about two-thirds of individuals; antiseizure medication can be stopped.[33]
Cause	Genetic.
Genes	*SCN1A, SCN1B, SCN2A, STX1B, SLC6A1, CHD2, SYNGAP1, NEXMIF, KIAA2022, SLC2A1*.[33]
Inheritance pattern	Family history of febrile seizures in 50 percent of individuals.[44]
Developmental impact	Developmental delay or regression may occur, which may improve once seizures resolve.[33]
Comorbidities	Intellectual disability, behavior disorders, sleep disorders, or movement disorders.[33]
LENNOX-GASTAUT SYNDROME	
Age at onset	18 months to 8 years.[33]
Seizures	Tonic, atonic, atypical absence seizures, often subtle, along with multiple seizure types.[45] Ten to 30 percent of individuals have another epilepsy syndrome[45] diagnosed prior to Lennox-Gastaut syndrome, and 80 to 90 percent will continue to have seizures into adulthood.[46]
Management and treatment	No definitive treatment; may try antiseizure medication, steroids, ketogenic diet, medical cannabis, neuromodulation (vagal nerve stimulator),[13] or epilepsy surgery (corpus callosotomy).
Cause	Structural (70 percent), genetic.[33, 45]
Genes	None identified.[45]
Inheritance pattern	Typically occurs without any family history;[33] *de novo* mutation possible.[47]
Developmental impact	Developmental delay is severe and may be present before the onset of seizures.[45]
Comorbidities	Intellectual disability, behavior disorders, sleep disorders, and autism spectrum disorder are common.[48]
LANDAU KLEFFNER SYNDROME (CONSIDERED A SUBTYPE OF EE-SWAS)	
Age at onset	3 to 8 years.[49]
Seizures	Obvious seizures occur in 70 percent of individuals and are often present as absence or focal seizures. Seizures are often self-limiting. Presents with progressive loss of speech and comprehension of speech.
Management and treatment	Antiseizure medication, steroids, epilepsy surgery;[49] seizures may resolve.

Cont'd.

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES (DEES)		
	Cause	Genetic.[49]
	Genes	*GRIN2A*.[50]
	Inheritance pattern	Unknown; family history usually not present.[7]
	Developmental impact	Significant regression in language, and even if seizures resolve language impairment persists in over 80 percent of individuals.[7]
	Comorbidities	Language impairment, behavior disorders, cognitive impairment, ADHD, depression, anxiety, sleep disorders.
	DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHY WITH CONTINUOUS SPIKE-WAVE ACTIVATION IN SLEEP (DEE-SWAS), AND EPILEPTIC ENCEPHALOPATHY WITH SPIKE-WAVE ACTIVATION IN SLEEP (EE-SWAS) (PREVIOUSLY KNOWN AS ELECTRICAL STATUS EPILEPTICUS IN SLEEP [ESES])	
	Age at onset	2 to 12 years.[33]
	Seizures	Focal aware or impaired awareness and focal to bilateral tonic-clonic seizures, absence, atonic; seizure activity occurs during sleep or times of drowsiness; multiple types of seizures may occur or in some individuals, no clinical seizures occur (only electrographic seizures).[33] Seizures typically resolve by puberty.[33,51]
	Management and treatment	Antiseizure medication, steroids, epilepsy surgery, or ketogenic diet.[33,51]
	Cause	Structural, genetic, metabolic, or unknown.[52]
	Genes	*GRIN2A*.[33]
	Inheritance pattern	Family history of seizures in up to 50 percent of individuals;[33] *de novo* mutation possible.[53]
	Developmental impact	Developmental delay is often present before the onset of seizures and continues to progress after the onset. Developmental delay may persist even if seizures resolve, although improvement may occur, particularly when the seizures last less than two years.[33]
	Comorbidities	Cognitive impairment, language impairment, movement disorders, behavioral disorders, autism spectrum disorder, and psychiatric disorders may occur.[33, 52]
	HEMICONVULSION-HEMIPLEGIA-EPILEPSY SYNDROME (HHE)	
	Age at onset	Under 4 years.[33]
	Seizures	Focal clonic status epilepticus. Seizures occur in an acute stage (febrile seizure that progresses to status epilepticus) and a chronic stage (focal seizures, focal to bilateral tonic-clonic). Seizures lead to swelling and atrophy* in half of the brain.[33]
	Management and treatment	Drug-resistant seizures; antiseizure medication, or epilepsy surgery.[33]
	Cause	Unknown.
	Genes	None identified.
	Inheritance pattern	Unknown.

Cont'd.

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES (DEES)	**Developmental impact**	Developmental delay may occur and may be present before the first seizure.[33]
	Comorbidities	Hemiparesis (half of the body is paralyzed) may result; in the majority of individuals, this is permanent; in 20 percent this resolves within a year.[33] Language impairment may occur and typically resolves within two months.[33] disability may occur.[33]
	RASMUSSEN SYNDROME	
	Age at onset	1 to 10 years;[54] in 10 percent of individuals, onset is in adolescence or adulthood.[33]
	Seizures	Focal aware or impaired aware motor, focal atonic, focal to bilateral tonic-clonic; seizures increase in frequency and severity over time.[33,54]
	Management and treatment	Drug-resistant seizures; antiseizure medication,[55] steroids, immunologic therapies, or epilepsy surgery.[54]
	Cause	Unknown.
	Genes	None identified.
	Inheritance pattern	Unknown.
	Developmental impact	Developmental delay is common.[55]
	Comorbidities	Progressive weakness on one side of the body; cognitive, memory and language impairment.[56]
GENERALIZED EPILEPSY SYNDROMES	**CHILDHOOD ABSENCE EPILEPSY**	
	Age at onset	2 to 13 years;[57] seizures may resolve by age 10 to 14.
	Seizures	Absence seizures; occur multiple times per day and last less than 20 seconds; may be provoked by hyperventilation; history of febrile seizures in 10 to 15 percent.[57] may later develop juvenile myoclonic epilepsy or juvenile absence epilepsy.
	Management and treatment	Antiseizure medication.
	Cause	Presumed genetic cause; idiopathic generalized epilepsy.
	Genes	None identified.
	Inheritance pattern	Family history of absence seizures or other generalized seizures present in about one-third of individuals.[58]
	Developmental impact	Developmental delays may occur.[59]
	Comorbidities	ADHD, learning impairment, behavior disorders, or psychiatric disorders may occur.[59–61]
	EPILEPSY WITH MYOCLONIC ABSENCES	
	Age at onset	2 to 12 years.[62]
	Seizures	Myoclonic absences, generalized tonic-clonic, atonic; seizures are frequent (several times a day) and last 10 to 60 seconds; may be triggered by hyperventilation.[62,63] Seizures persist into adulthood in more than 50 percent of individuals.[62]

Cont'd.

GENERALIZED EPILEPSY SYNDROMES		
	Management and treatment	Drug-resistant seizures; antiseizure medications.[64]
	Cause	Genetic, structural.
	Genes	None identified.
	Inheritance pattern	Family history of seizures present in 20 percent of individuals.[33]
	Developmental impact	Developmental delays may occur.
	Comorbidities	Intellectual disability;[33] learning impairment is present in 70 percent.[62]
	EPILEPSY WITH EYELID MYOCLONIAS (PREVIOUSLY KNOWN AS JEAVONS SYNDROME)	
	Age at onset	2 to 14 years.[65]
	Seizures	Myoclonic jerks in the eyelids that last 1 to 3 seconds and are repetitive; absence seizures, generalized tonic-clonic.[33] Seizures triggered by eye closure, sunlight, or flashing lights.[65,66] Seizures often persist lifelong.[33]
	Management and treatment	Drug-resistant seizures; antiseizure medication.[33] Ketogenic diet may help as well as the use of blue lenses.[66]
	Cause	Genetic.
	Genes	None identified.
	Inheritance pattern	Family history of seizures or epilepsy in 40 to 80 percent of individuals.[65]
	Developmental impact	Typical development.[65]
	Comorbidities	Mild learning impairment and attention problems may occur.[67]

* Atrophy refers to the shrinking or degeneration of tissues. Brain (cerebral) atrophy specifically is the loss of neurons and their communicating networks, often accompanied by a loss in the overall brain volume.

Table A6.3 Onset in adolescence and adulthood

FOCAL EPILEPSY SYNDROMES	**AUTOSOMAL DOMINANT EPILEPSY WITH AUDITORY FEATURES**	
	Age at onset	10 to 30 years.[68]
	Seizures	Focal seizures with sensory phenomena (mostly sounds), aphasia; seizures are mild and infrequent. mainly occurring at night.[68]
	Management and treatment	Antiseizure medication; seizures well controlled.[68]
	Cause	Genetic.
	Gene	*LGI1, RELN.*[69]
	Inheritance pattern	Inherited; family history typically present.[69]
	Developmental impact	Typical development.[69]
	Comorbidities	Typically none associated.
	OTHER FAMILIAL TEMPORAL LOBE EPILEPSIES	
	Age at onset	Older than 10 years.[70]
	Seizures	Focal aware or impaired awareness with sensory phenomena (visual or sound hallucinations); seizures are often mild and infrequent; focal to bilateral tonic-clonic seizures in two-thirds of individuals.[70]
	Management and treatment	Antiseizure medication; seizures well controlled.[70]
	Cause	Genetic.
	Gene	Rarely *DEPDC5*.[70]
	Inheritance pattern	Inherited; family history in 60 percent of individuals.[70]
	Developmental impact	Typical development.
	Comorbidities	Typically none associated.
GENERALIZED EPILEPSY SYNDROMES	**JUVENILE ABSENCE EPILEPSY**	
	Age at onset	8 to 20 years.[71]
	Seizures	Absence, generalized tonic-clonic, myoclonic jerks.[71,72] May evolve into juvenile myoclonic epilepsy.[72]
	Management and treatment	Antiseizure medication; required lifelong.[71]
	Cause	Presumed genetic cause; idiopathic generalized epilepsy (IGE).
	Gene	None identified.
	Inheritance pattern	Family history of seizures or epilepsy in 42 percent.[72]

Cont'd.

GENERALIZED EPILEPSY SYNDROMES	**Developmental impact**	Typical development.[71]
	Comorbidities	ADHD, learning impairment.73
	JUVENILE MYOCLONIC EPILEPSY	
	Age at onset	8 to 40 years.[74]
	Seizures	Myoclonic, generalized tonic-clonic, absence; seizures often occur within 1 to 2 hours of waking. Seizures may be triggered by sleep deprivation, stress, or flashing lights.[74] May evolve from childhood absence epilepsy.[74]
	Management and treatment	Antiseizure medication.
	Cause	Presumed genetic cause; idiopathic generalized epilepsy (IGE).
	Gene	None identified.
	Inheritance pattern	Family history occasionally present.[75]
	Developmental impact	Typical development.
	Comorbidities	ADHD, learning impairment.[61, 73]
	EPILEPSY WITH GENERALIZED TONIC-CLONIC SEIZURES ALONE	
	Age at onset	5 to 40 years.[76]
	Seizures	Generalized tonic-clonic; seizures occur within 1 to 2 hours of awakening; may be triggered by sleep deprivation.[76] History febrile seizures may be present.
	Management and treatment	Antiseizure medication; required lifelong.[76]
	Cause	Presumed genetic cause; idiopathic generalized epilepsy (IGE).
	Gene	None identified.
	Inheritance pattern	Family history of epilepsy may be present.76
	Developmental impact	Typical development.
	Comorbidities	Typically none associated.

Table A6.4 Onset at a variable age

FAMILIAL FOCAL EPILEPSY WITH VARIABLE FOCI	
Age at onset	1 to 52 years.[77]
Seizures	Focal, focal to bilateral tonic-clonic seizures
Management and treatment	Antiseizure medication; seizures well controlled.[77]
Cause	Genetic, genetic-structural.
Gene	*DEPDC5, NPRL2, NPRL3, TSC1, TSC2.*[77]
Inheritance pattern	Family history required for diagnosis.[77]
Developmental impact	Typical development; may have mild developmental impact.
Comorbidities	May have mild intellectual disability, autism spectrum disorders, and behavior disorders.
REFLEX EPILEPSY (EPILEPSY WITH READING-INDUCED SEIZURES)	
Age at onset	10 to 46 years.
Seizures	Seizures occur in response to particular stimuli (e.g., reading) rather than spontaneously. Myoclonic jerks, generalized tonic-clonic; reflex seizures.
Management and treatment	Antiseizure medication; limit reading.
Cause	Genetic.
Gene	None identified.
Inheritance pattern	Family history in 20 to 40 percent of individuals.[78]
Developmental impact	Typical development.
Comorbidities	Typically none associated.
PROGRESSIVE MYOCLONUS EPILEPSY	
Age at onset	2 to 50 years.[55]
Seizures	Myoclonic, generalized tonic-clonic.
Management and treatment	Drug-resistant seizures; antiseizure medication.
Cause	Variable; genetic and metabolic.
Gene	Depends on the cause.
Inheritance pattern	Depends on the cause.
Developmental impact	Developmental delay is common and progressive.[55]
Comorbidities	Poor long-term prognosis.[79] Motor impairment, intellectual disability.[79]

Cont'd.

SLEEP-RELATED HYPERMOTOR (HYPERKINETIC) EPILEPSY (SHE) (PREVIOUSLY KNOWN AS NOCTURNAL FRONTAL LOBE EPILEPSY)	
Age at onset	1 to 60 years of age.[80]
Seizures	Focal, motor; seizures are brief (typically about 30 seconds) and occur during sleep.[55, 80]
Management and treatment	Antiseizure medications or epilepsy surgery; 30 percent of individuals have drug-resistant seizures.[55, 80]
Cause	Structural, genetic.
Gene	*KCNT1, DEPDC5, CHRNA4, CHRNB2, CHRNA2.*[80]
Inheritance pattern	Inherited, may be *de novo*.[55]
Developmental impact	Typical development.
Comorbidities	Intellectual disability, sleep disorders, or behavioral disorders may occur.[80]
MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS (MTLE-HS)	
Age at onset	Variable; most common in adolescents and young adults.[55]
Seizures	Focal aware or impaired awareness, tonic-clonic; autonomic signs and symptoms, automatisms, behavioral arrest, sensory phenomena.[55] May develop after prolonged febrile seizures. Seizures may be drug-resistant.[81]
Management and treatment	Antiseizure medication or epilepsy surgery; epilepsy surgery may provide full remission of this syndrome.[55]
Cause	Structural.
Gene	None identified.
Inheritance pattern	None.
Developmental impact	Typical development.
Comorbidities	Psychiatric disorders, cognitive and memory impairment.[55]
FEBRILE INFECTION-RELATED EPILEPSY SYNDROME (FIRES)	
Age at onset	2 to 17 years of age.[82]
Seizures	Focal impaired awareness, focal to bilateral tonic-clonic, status epilepticus; seizures occur 1 to 14 days after an illness with a fever.[82] Often leads to brain atrophy.[7] Seizures may be drug resistant.
Management and treatment	Antiseizure medication; often requires medically induced coma.[82]
Cause	Unknown.
Gene	None identified.
Inheritance pattern	None.
Developmental impact	Developmental delay is common.[82]
Comorbidities	Intellectual disability, motor impairment, and behavior disorders. A poor prognosis and death occurs in 10 percent of individuals.[33]

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APPENDIX 7

Mechanism of action of antiseizure medications

"Mechanism of action" is how a medication works in the body to achieve a desired effect. As it relates to antiseizure medications, it is what the medication does to reduce, prevent, or stop seizures.

The mechanism of action of antiseizure medications often occurs in the area of the synapse, which is the space between neurons in which neurotransmitters carry messages (for chemical synapses). Seizures result when too many excitatory neurotransmitters cause excessive firing of neurons, or too few inhibitory neurotransmitters exist to stop excessive firing of neurons. Figure A7.1 depicts neuron-to-neuron communication in the area of a chemical synapse and the general mechanism of action of various antiseizure medications.

Antiseizure medications may work to manage or control the imbalance of excitatory and inhibitory neurotransmitters.[1] They may also work by altering the ion channels (in the axon terminal) and postsynaptic channel receptors (in the dendrite), and by blocking the ions from moving in and out of the neurons, stopping the neuron from excessively firing. NMDA receptors, AMPA receptors, and GABA receptors are postsynaptic channel receptors that act as control centers within the neurons and are targets for antiseizure medications.

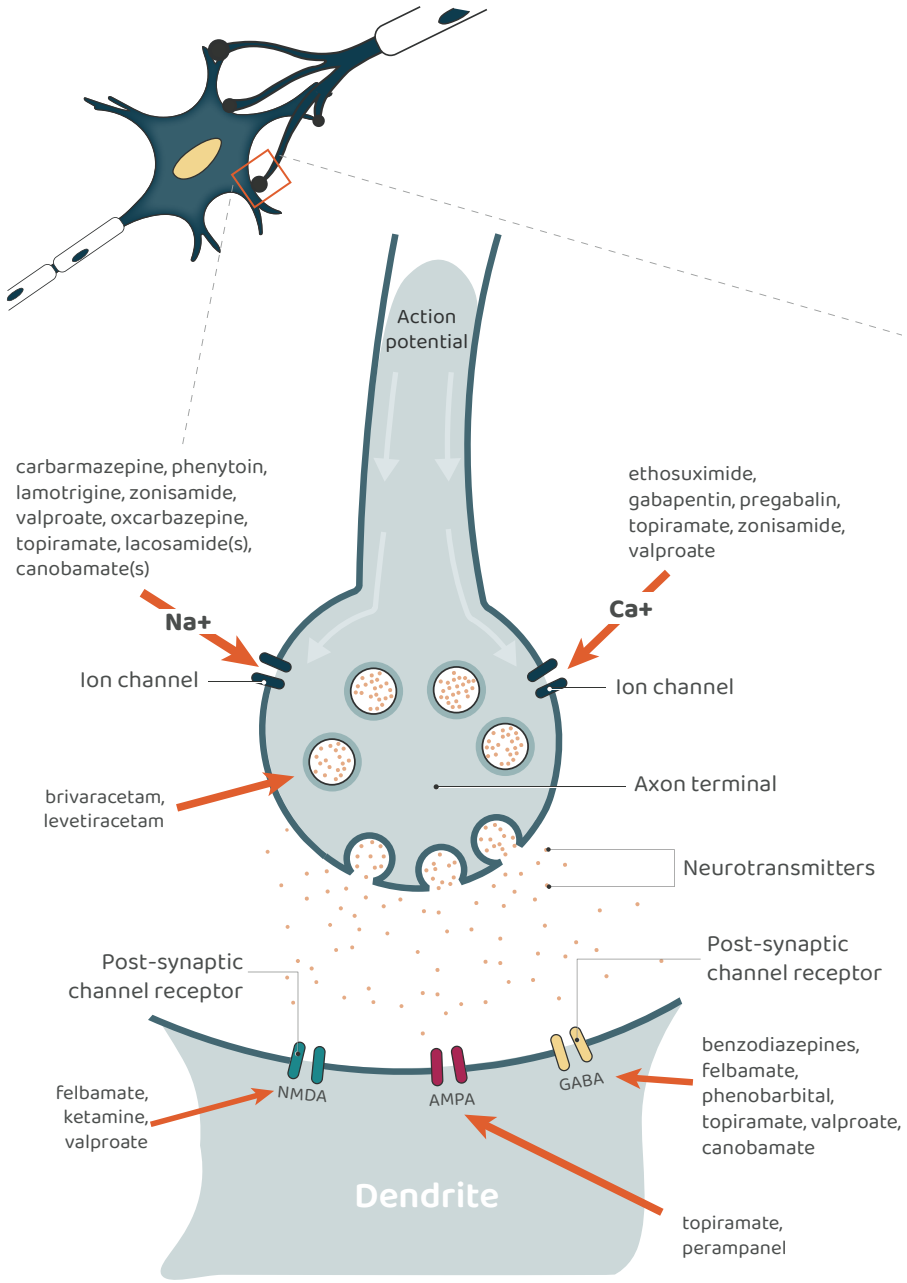

Figure A7.1 Mechanism of action of antiseizure medications. Na+ = sodium; Ca+ = calcium.

References

1 Sheffler MF, Reddy V, Pillarisetty LS (2023) *Physiology, Neurotransmitters*. [e-book] Treasure Island (FL), StatPearls. Available at: https://www.ncbi.nlm.nih.gov/books/NBK539894/> [Accessed December 16 2024].