SEIZURES

YACOUB BAHOU MD
Professor in neurology at
the University of Jordan

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1. Introduction

Seizures are among the most common problems in neurology

Up to 10% of the population will have a seizure at some time in their lives

In addition, seizures can be among the most dramatic forms of nervous system dysfunction

Although seizures have many different causes and manifestations, by definition a seizure is an abnormal hypersynchronous electrical discharge of neurons in the brain, producing a clinical dysfunction

Epilepsy is defined as a condition in which there is a tendency to have recurrent unprovoked seizures

Practically the diagnosis of epilepsy is often applied after a patient has had two unprovoked seizures

2. Classification

Seizures can arise from one specific focus within the brain(focal) or involve both cerebral hemispheres at the onset (generalized)

The diagnosis and categorization of the seizure is based primarily on the semiology(i.e., signs or symptoms) characterizing the event

Those that arise from one portion of the brain can evolve and spread to involve the whole brain(secondarily generalized)

Among focal seizures, those in which awareness is impaired are termed “ with impaired awareness” (previously complex partial seizures) , whereas those in which awareness is preserved are termed “ aware” (previously simple partial seizures) (table)

TABLE 15-1. Types of Seizures

Focal-onset:	
Motor	Myoclonic (jerking) Epilepsia partialis continua (sustained rhythmic jerking) Clonic (rhythmic movements) Tonic (stiffening) Hypermotor (e.g., running) Focal-onset with secondary generalization (generalized convulsion)
Non-motor	Focal-onset with impaired awareness (old "complex partial') Sensory, e.g., olfactory, somatosensory, or hemianopic Focal-onset with altered cognition, e.g., aphasic, amnestic, 'psychic' / 'emotional' (e.g., altered mood, rage) Autonomic
Generalized—onset:	
Motor	Generalized, tonic (then) clonic, convulsion ('grand mal') Myoclonic Tonic Atonic (lack of tone, with falls)
Non-motor:	Absence Other primary absence-like seizures, eyelid myoclonia Myoclonic—absence Generalized nonconvulsive seizures in comatose or ICU patients

* FOCAL SEIZURES

By definition, focal seizures(previously termed “ partial”) begin in a focal area of the brain and do not impair awareness, at least at the onset(figure)

In general, such seizures lead to positive rather than negative neurologic symptoms(e.g., tingling rather than numbness, visual hallucinations rather than blindness)

The manifestations of focal seizures depend on their site of origin in the brain.

These are designated as motor or nonmotor

Focal motor seizures, in which one part of the body may stiffen or jerk rhythmically, involve the motor cortex in the frontal lobe

The classic Jacksonian march occurs when the electrical activity spread along the motor strip, leading to rhythmic jerking that spreads along body parts following the organization of the motor homunculus

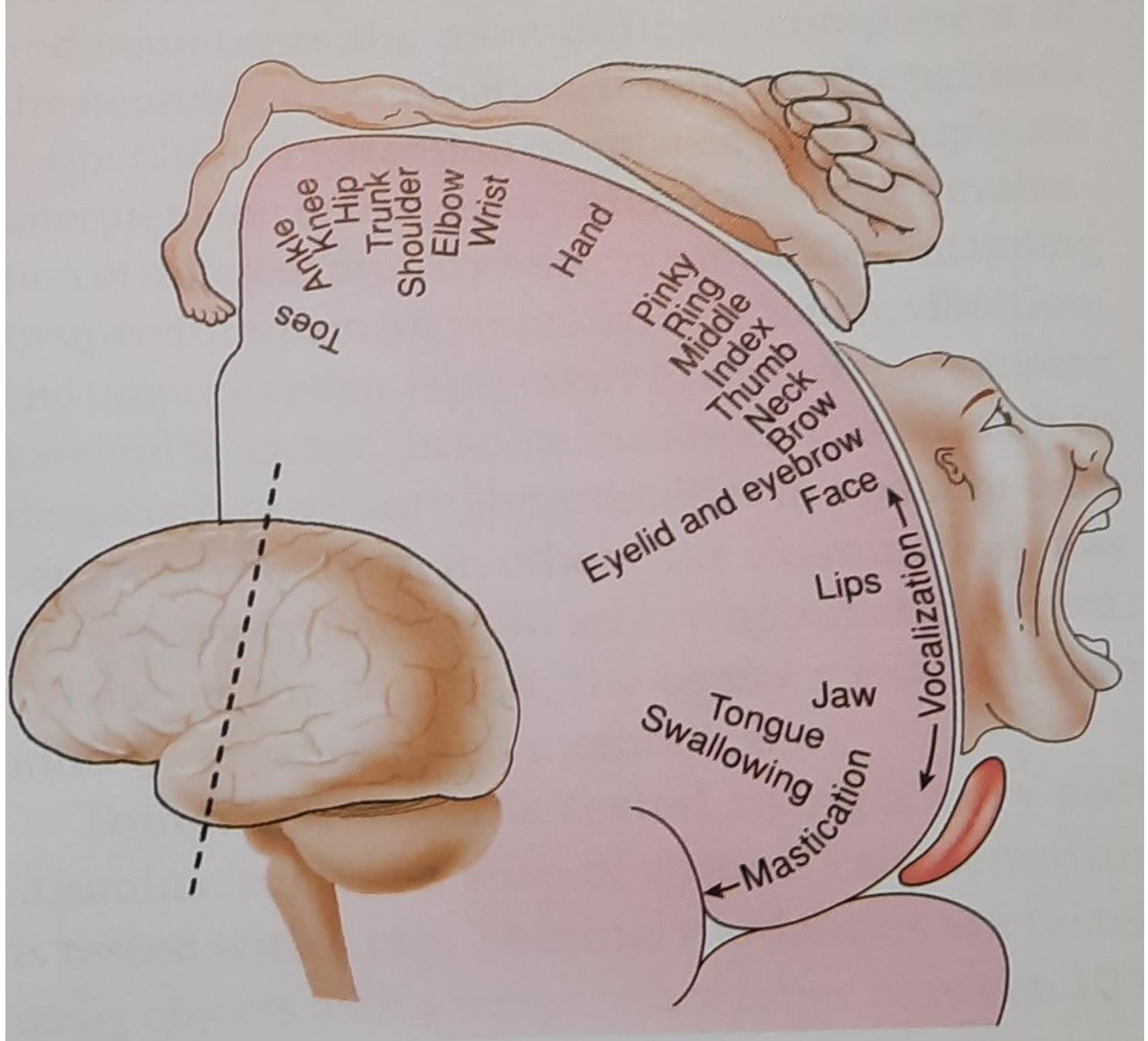
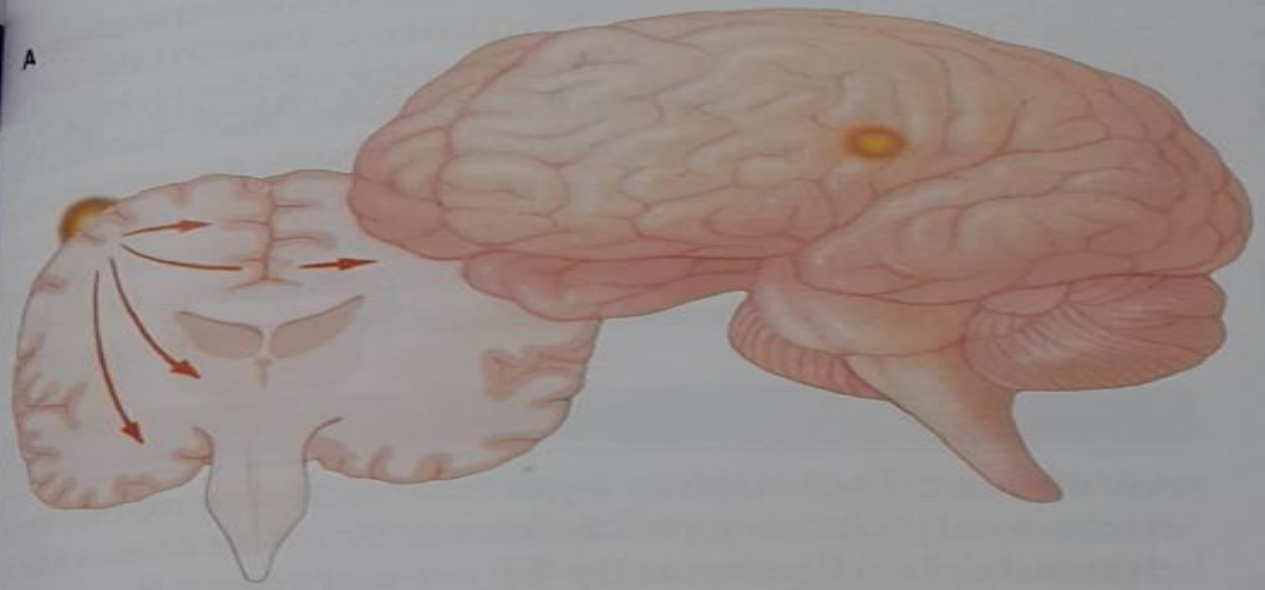


FIGURE 5-4. The homunculus of the motor strip.

A

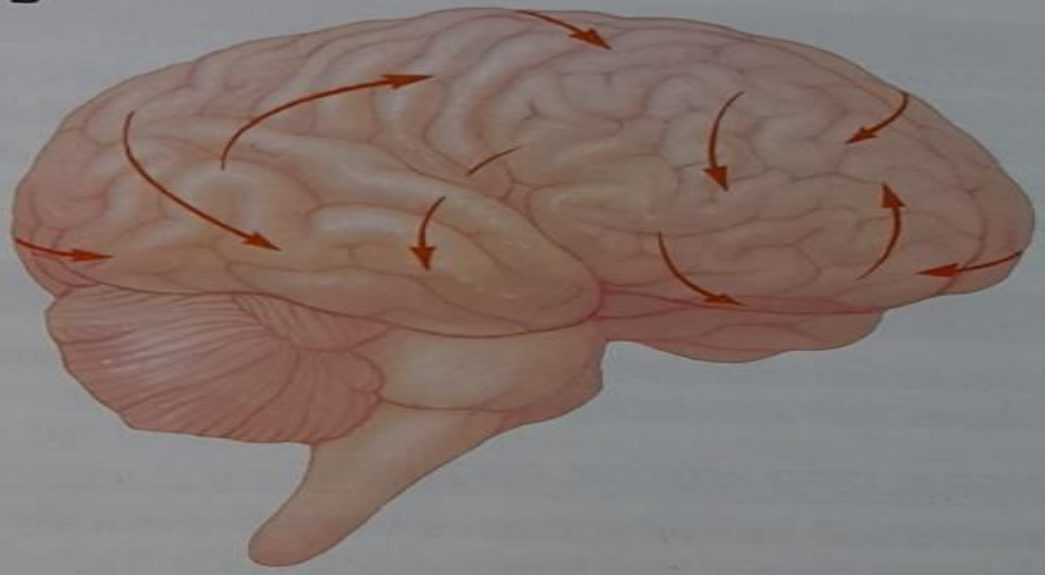


Simple
Consciousness is not impaired, can involve senses (flashing lights or a change in taste or speech) or motor function (uncontrolled stiffening or jerking in one part of the body such as the finger, mouth, hand, or foot), nausea, déjà vu feeling.

Complex
Consciousness is impaired and variable (unconscious repetitive actions), staring gaze, hallucination/delusion.

Focal evolving to generalized
Begins as focal seizure and becomes generalized.

B



Absence
Involve a loss of consciousness with vacant stare or unresponsiveness.

Myoclonic
Involve sudden, forceful contractions of single or multiple groups of muscles.

Clonic
Longer rhythmic jerking activity.

Tonic–clonic
Include alternate contraction (tonic phase) and relaxation (clonic phase) of muscles, a loss of consciousness, and abnormal behavior.

Atonic
Loss of muscle tone; person suddenly drops.

RGURE 15-1. Characteristics of seizure types. (**A**) Focal-onset seizures. (**B**) Generalized seizures. (Reprinted with permission from Ford SM. *Roach's Introductory Clinical Pharmacology*. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017. Figure 29.1.)

Focal nonmotor seizures from other regions of the brain can cause sensory phenomena(sometimes parietal), visual phenomena(usually occipital), or gustatory, olfactory, and psychic phenomena(frequently temporal)

The latter may include déjà vu, jamais vu, or sensations of depersonalization (‘out of body”) or derealization

Focal seizures with impaired awareness

Focal seizures with impaired awareness(previously termed complex partial seizures) have a focal onset and involve impairment of awareness

Many arise in the temporal lobe, but a frontal lobe focus is also common

Focal seizures with impaired awareness may include automatisms

(stereotyped motor actions without clear purpose) such as lip-smacking, chewing movements, or picking at clothing

The patient may have speech arrest or may speak in a nonsensical manner

By definition, the patient does not respond normally to the environment or to questions or commands

Occasionally, patients may continue the activities they were participitating in at the onset of the seizure,sometimes to remarkable lengths

Patients may continue folding laundry during a seizure or even finish driving home

Focal seizures with impaired awareness of frontal lobe origin may involve strange bilateral movements, such as bicycling or kicking, or behavior such as running in circles

If the patient's awareness is not known, the seizure is termed a focal seizure with unknown awareness

The last classification of focal seizures is termed focal to bilateral tonic-clonic

This term refers to the pattern of seizure propagation from one type of focal seizure to bilateral symptoms

Focal to bilateral tonic-clonic was previously termed partial onset with secondary generalization

* GENERALIZED SEIZURES

Generalized seizures include 2 categories: motor seizures and absence seizures (previous figure)

A) Generalized motor seizures

Generalized motor seizures were previously referred to as generalized tonic-clonic (GTC) seizures or grand mal seizures

This is the seizure type with which the lay public is most familiar

They typically begin with a tonic phase, lasting several seconds, in which the entire body becomes stiff(including the chest and pharyngeal muscles, sometimes leading to a vocalization known as the epileptic cry)

This is followed by the clonic phase, in which the limbs jerk rhythmically, more or less symmetrically, typically for less than 1 to 2 minutes

Toward the end of the clonic phase, the frequency of the jerking may decrease and stop as the body becomes flaccid

The patient may bite the tongue and become incontinent of urine during a generalized motor seizure

There is typically a postictal state after the seizure, lasting minutes to hours, during which the patient may be tired or confused, before returning to normal activity slowly

B) ABSENCE SEIZURES (PETIT MAL ABSENCE)

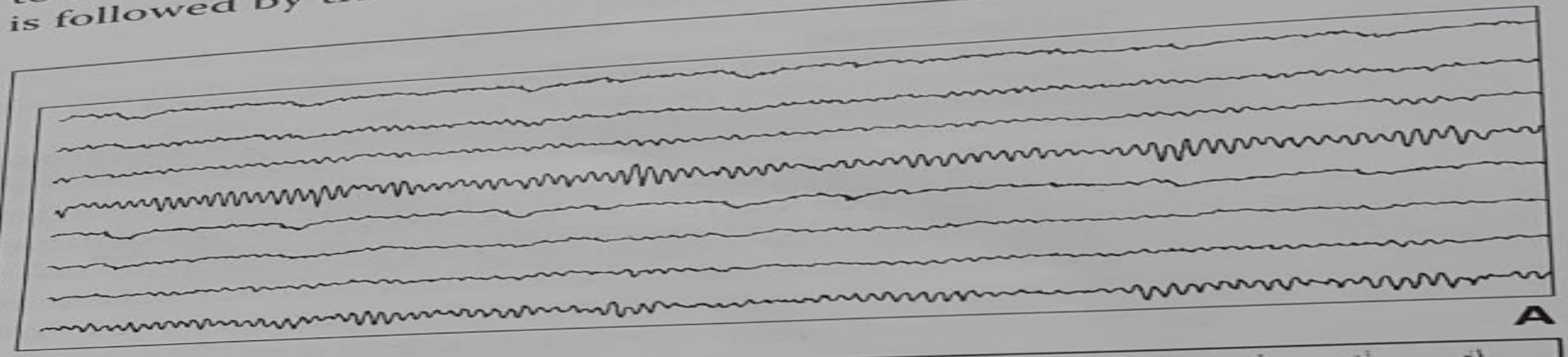
An absence seizure is a generalized seizure that most commonly occurs in children or adolescents and is characterized primarily by an unresponsive period, often with staring, that lasts for several seconds, with immediate recovery thereafter

Absence seizures can occur tens or even hundreds of times a day and may be noticed first by schoolteachers and assumed to be daydreaming or difficulty concentrating

A classic 3 –per-second generalized spike –and-wave electroencephalogram (EEG) pattern accompanies absence seizures

(figure). Hyperventilation is a common trigger

is followed by the



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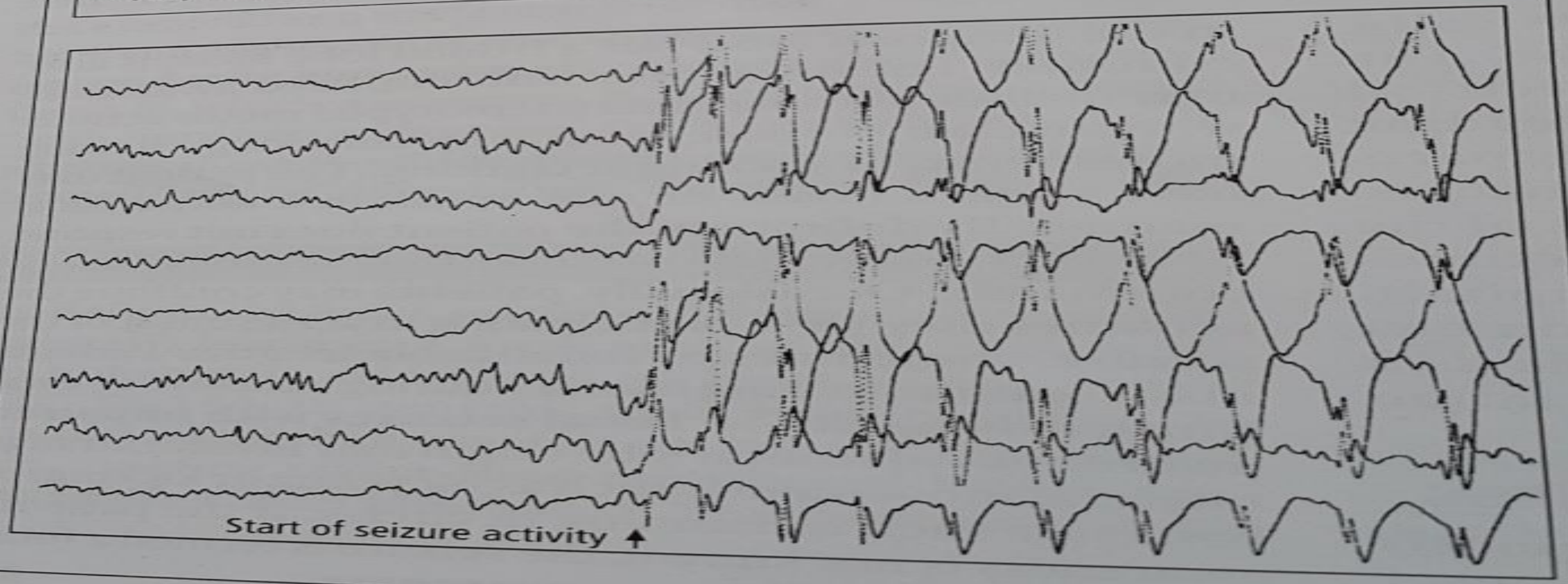

B

C) Juvenile myoclonic epilepsy (Janz syndrome)

This is increasingly recognized as a common form of primary generalized epilepsy

Age of onset is typically in the teens

Patients have the clinical triad of:

- infrequent generalized seizures, often on waking

- daytime absences

- sudden,shock-like, involuntary jerking movements (myoclonus), usually in the morning. Patients may therefore, apparently inexplicably spill their breakfast or throw it across the room (" Kellog's epilepsy")

The EEG shows polyspike-wave discharges and photosensitivity

Treatment with sodium valproate is often successful , but recurrence is likely if medication is stopped

Alternative drugs include clonazepam,levetiracetam and lamotrigine

This benign condition must be distinguished from childhood conditions where severe myoclonus and epilepsy are associated with underlying degenerative disease of the brain(progressive myoclonic epilepsies)

Recognition of juvenile myoclonic epilepsy is important, as patients treated incorrectly with carbamazepine than valproate, may worsen

D) Other generalized seizure types

Less common seizure types include myoclonic-atonic, clonic-tonic clonic, myoclonic absence, and absence with eyelid myoclonia, all of which are generalized in onset(table)

Seizures that are myoclonic (without other features) may be generalized or focal

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3. Epidemiology and etiologies

Seizures have a U-shaped distribution in age of onset – they are more common in the very young and the very old

Etiologies vary depending on the age of onset

In infants, a variety of neonatal infections, hypoxic-ischemic insults, genetic syndromes, and congenital brain malformations are common causes of seizures

Febrile seizures are a special case

They are the most common cause of seizures in children, affecting up to 3% to 9% of this age group

They occur between 6 months and 5 years of age in the setting of a febrile illness without evidence of intracranial infection and are usually generalized in onset

Most children with febrile seizures do not have neurologic deficit

For the event to be considered a febrile seizure, the fever may be present before the seizure or must develop in the immediate postictal period

The risk of subsequent epilepsy is relatively small unless the seizures are prolonged or focal in onset or if other neurologic abnormalities or a family history of epilepsy is present

Older children may also develop seizures related to head injury, meningitis,encephalitis, or vascular diseases, and genetic syndromes continue to be a significant etiology at this age group

Among young adults, head injury, substance use, and excessive alcohol use are common causes of new-onset seizures, but brain tumors and strokes become more common etiologies by middle age

In the elderly, strokes become the most common etiology, but substance abuse and alcohol are not uncommon causes

Metabolic disturbances from systemic problems such as severe hypo-or hyperglycemia, hepatic failure, or renal failure are also frequent causes

Frequently , seizures occur in children(and sometimes adults) as part of a syndrome that may include specific seizure types, EEG patterns, and associated neurologic abnormalities

Many of these are called " idiopathic generalized epilepsies"-usually considered to be genetic conditions in almost all cases

The diagnosis of a specific syndrome may have implications both for genetic testing and for the proper choice of pharmacologic treatments

Examples are outlined in the table

TABLE 15–2. Epilepsy Syndromes: Features and Treatment

Selected Epilepsy Syndromes	Age of Onset	Seizure Types	Associated Findings	EEG Findings	Commonly Used Treatments
Lennox–Gastaut syndrome	Childhood	Tonic, atonic, myoclonic, generalized tonic–clonic, absence	Major cognitive impairment and disability	Slow (1- to 2-per-second) spike-and-wave discharges	Valproic acid, lamotrigine, felbamate, rufinamide, clobazam
Focal motor seizure, e.g., benign rolandic epilepsy	Childhood	Simple partial seizure involving the mouth and face, infrequent generalized tonic–clonic	Nocturnal preponderance of seizures	Centrotemporal spikes	Carbamazepine, sometimes no treatment necessary
Absence epilepsy	Childhood and adolescence	Absence; sometimes, generalized tonic–clonic seizures	Hyperventilation as trigger	3-per-second generalized spike-and-wave	Ethosuximide, valproic acid, lamotrigine
Juvenile myoclonic epilepsy	Adolescence and young adulthood	Myoclonic, absence, generalized tonic–clonic	Early morning preponderance of seizures	4- to 6-per-second polyspike-and-wave	Valproic acid, lamotrigine, levetiracetam

EEG, electroencephalogram.

4. CLINICAL MANIFESTATIONS

A) History

The diagnosis of seizures is a clinical one

Most commonly the patient is seen after an event has occurred, and the diagnosis must be made on the history alone

In these cases, the patient (and more importantly, witnesses, if the seizure was generalized in onset) must be questioned for an exact description of the event itself(and especially the onset), any premonitory symptoms, and the character of the recovery period in order for the clinician to decide whether the event was a seizure

and, if so, what type of seizure it was

The clinical details should allow differentiation of seizures from other paroxysmal neurologic events (table)

TABLE 15-3. Characteristics of Focal Seizures and Other Paroxysmal Neurologic Events

	Focal Seizures	Transient Ischemic Attacks	Migraine
Onset	Progression of symptoms over seconds	Sudden onset of symptoms	Progression of symptoms over 15–20 min
Neurologic symptoms	Positive motor or sensory symptoms; "psychic" symptoms such as déjà vu	Negative motor, sensory, or visual symptoms (loss of function)	Positive sensory and, especially, visual symptoms such as scintillating scotomata
Duration	Usually less than a few minutes	Usually less than 30 min, always less than 24 h	Symptoms for 15–20 min, typically followed by headache for hours
Consciousness	Preserved or impaired	Preserved	Preserved
Headache	Occasionally postictal	Infrequent	Throbbing pain, often unilateral, following the progression of initial symptoms
			Fatigue common
Recovery	Postictal confusion, sleepiness	Rapid	
Risk factors	Structural brain lesion, family history of seizures	Hypertension, hyperlipidemia, smoking, diabetes, atrial fibrillation, stenotic intracranial or extracranial vessels, hypercoagulability	Family history of migraines

B) Physical examination

The neurologic examination is most helpful diagnostically in the

(relatively uncommon) instances in which the patient is observed during the event or shortly thereafter

In the latter case, a postictal hemiparesis, or Todd's paralysis, may be detected after a bilateral tonic, then clonic seizure; this suggests that the seizure was of focal onset, even if not apparent to observers at that time

Other abnormalities on neurologic examination may also suggest the presence of a focal brain lesion

Of course, the general physical exam may yield findings suggestive of infection or other systemic disease that might explain a new-onset seizure

In particular, signs of meningitis should be sought in any patient who has had a seizure

5. Diagnostic evaluation

A) Laboratory studies

Laboratory testing may show an underlying metabolic abnormality, such as hyponatremia or hypocalcemia, that explains new-onset seizure

After a generalized seizure, there is commonly a lactic acidosis, resulting in decreased serum bicarbonate

A toxicology screen for common substances of abuse, as well as an alcohol level, should be done in all patients

Female patients of reproductive age should also have a pregnancy test

In cases where infection is suspected, a lumbar puncture should be performed

B) Brain imaging

An uncomplicated seizure in a patient with known epilepsy does not generally warrant brain imaging

With rare exceptions, however, neuroimaging should be performed in patients with new-onset seizures

For seizures of probable focal onset, a magnetic resonance imaging

(MRI) is a necessary part of the diagnostic workup, to look for a structural abnormality that is the focus for that seizure

A CT Brain scan may suffice in the urgent setting

C) Electroencephalography(EEG)

An EEG may be useful for several reasons:

- It may identify a potential focus of seizure onset

- It may show abnormalities characteristic of a specific epilepsy syndrome(e.g., with rapid, narrow, generalized spike and polyspike discharges in a patient with " primary generalized epilepsy")

- and it may establish whether a patient who has had a seizure and is not regaining alertness promptly is postictal or is having ongoing continuous nonconvulsive seizures

The diagnosis of whether a particular paroxysmal event was a seizure or not, however, rests primarily on clinical grounds

In patients with known epilepsy, up to 50% of routine EEGs are normal

6. TREATMENT

A) Drugs

The mainstay of epilepsy treatment is pharmacologic

The number of available antiseizure drugs (ASD) has more than doubled in recent years, and there is now a large selection of agents from which to choose, each with its own set of indications and possible adverse effects (table)

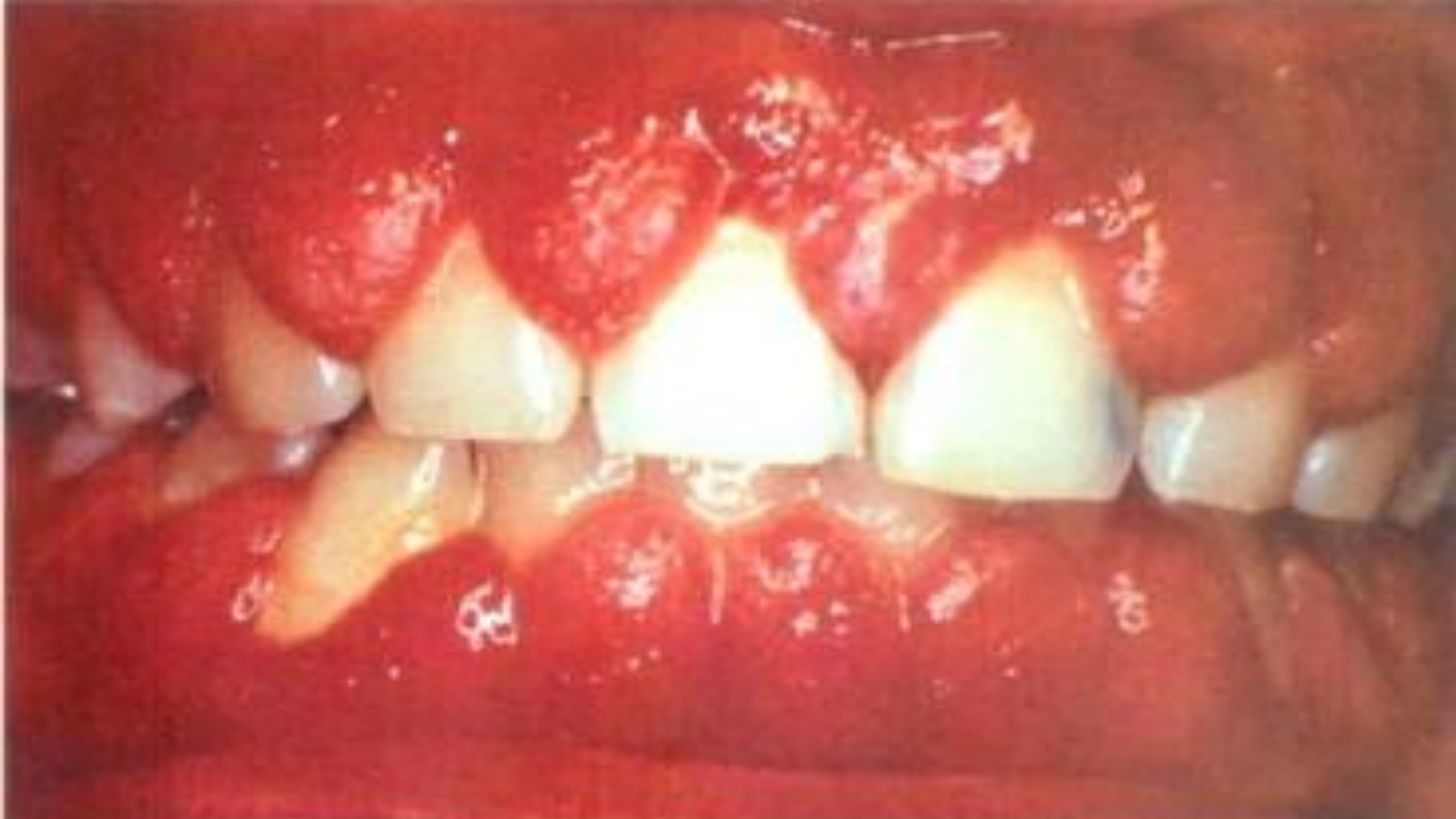
logic. The
(ASDs) has more than

TABLE 15–4. Selected Antiseizure Drugs

	Site of Action	Seizure Types Treated[a]	Characteristic Side Effects
Phenytoin (Dilantin)	Na^+ channel	Focal[a]	Gingival hyperplasia, coarsening of facial features, ataxia
Carbamazepine (Tegretol)	Na^+ channel	Focal	Hyponatremia, diplopia
Valproic acid (Depakote)	Na^+ channel, GABA receptor	Focal, generalized	GI symptoms, tremor, weight gain, hair loss, hepatotoxicity, thrombocytopenia, teratogenicity
Phenobarbital	GABA receptor	Focal, generalized	Sedation
Ethosuximide (Zarontin)	T-type Ca^{2+} channel	Absence	GI symptoms
Gabapentin (Neurontin)	Unknown, possibly voltage-gated Ca^{2+} channel	Focal	Sedation, weight gain (occasional)
Lamotrigine (Lamictal)	Na^+ channel, glutamate receptor	Focal, generalized	Diplopia, rash (rare Stevens–Johnson syndrome; more with rapid introduction)
Topiramate (Topamax)	Na^+ channel, GABA activity	Focal, generalized	Word-finding difficulty, renal stones, weight loss
Tiagabine (Gabitril)	GABA reuptake	Focal	Sedation
Levetiracetam (Keppra)	Poorly understood (synaptic vesicle modulation of neurotransmitter effects)	Focal, generalized	Insomnia, anxiety, irritability
Oxcarbazepine (Trileptal)	Na^+ channel	Focal	Sedation, diplopia, hyponatremia
Zonisamide (Zonegran)	Unknown; probably multiple mechanisms	Focal, generalized	Sedation, renal stones, weight loss
Lacosamide (Vimpat)	Na^+ channel	Focal	Sedation, headache, syncope
Pregabalin (Lyrica)	Voltage-gated Ca^{2+} channel	Focal	Sedation, peripheral edema, weight gain
Clobazam (Onfi)	Benzodiazepine receptor	Generalized	Sedation, mood symptoms, fever

[a]Drugs effective for focal seizures are also used for secondarily generalized

GABA, gamma-aminobutyric acid; GI, gastroint



An ASD is typically not started after a single seizure unless there is a reason to believe that a 2nd seizure is likely

This applies especially to symptomatic seizures i.e.,those due to a treatable or reversible condition, such as meningitis, alcohol withdrawal, or hyponatremia

Most neurologists would not start an ASD after a single seizure for which no underlying cause is found

ASD treatment is usually begun after 2 seizures that are not provoked

The primary goals of ASD treatment are to eliminate seizures and avoid side effects, ideally with monotherapy- i.e., using a single drug

Most neurologists increase the dose of a single drug until either seizure control is achieved or adverse effects become intolerable

If the latter occurs, the dose is lowered and a 2nd drug may be added

If seizure control is achieved, an attempt is often made to taper the 1st drug , leaving the second as monotherapy

For about 70% of epilepsy patients, seizures will be well controlled on ASDs, often with the 1st drugs tried

For the remainder, 2 or more ASDs may be required, or the seizures remain refractory to medical therapy

B) Ketogenic diet

The ketogenic diet is a high-fat, high-protein , low-carbohydrate diet often considered for treatment of patients with epilepsy

It produces urine and plasma ketones, which are used for monitoring therapy

It can be effective in reducing the seizure frequency in both adult and pediatric patients

There are several epilepsy syndromes , mostly pediatric, for which there is good evidence of efficacy of the ketogenic diet

It can be difficult for patients to tolerate and is not known to be safe for other medical comorbidities, including lipid disorders

C) Vagus nerve stimulation

The vagus nerve stimulator is a device shown to be effective in the treatment of partial and generalized seizures

It is implanted subcutaneously below the clavicle and stimulates the left vagus nerve through programmed electrical impulses delivered through leads placed in the neck

Various devices for direct brain stimulation including transcutaneous magnetic stimulation and deep brain stimulation also have promise for epilepsy treatment in the future, but they are still under development

D) Surgery

Patients refractory to medical management may be candidates for epilepsy surgery

Exactly what constitutes being medically refractory will depend on an individual patient's characteristics

Contributing factors typically include seizure type and frequency, tolerance of ASD therapy, number of ASDs tried and the effect on the patient's quality of life

The most common surgical procedure is resection of the epileptogenic area, typically following a presurgical evaluation in which continuous video-EEG monitoring combined with neuroimaging and other tests is used to identify the focus of seizure onset

For seizures of medial temporal lobe origin(the most common target of epilepsy surgery), the rate of complete seizure freedom following resective surgery can be over 60%

Other less commonly used surgical procedures include corpus callosotomy, hemispherectomy, or multiple subpial transection

7. STATUS EPILEPTICUS

Status epilepticus(SE) is an abnormal state in which either seizure is continuous for a prolonged period or seizures are so frequent that there is no recovery of consciousness between them

There are several types of SE, including the generalised convulsive form(ongoing clonic movements of the limbs) and more subtle forms in which the patient may be unresponsive and might have subtle motor signs such as eyelid twitching or nystagmus

Potential causes of SE include acute metabolic disturbances, toxic or infectious insults, hypoxic-ischemic damage to the brain, and underlying epilepsy

Morbidity from SE can be high; outcome depends largely on etiology and duration

SE is a medical emergency, the management of which centers on stopping the seizure activity and preventing the occurrence of systemic complications(table)

TABLE 15-5. Management of Status Epilepticus

Phases	Timing	Steps	Monitoring
Stabilization	0–5 min	• Airway • Breathing • Circulation • Oxygen Blood glucose (finger stick) • Thiamine and D5W if glucose <60 mg/dL	• ECG • IV access • Labs studies: CBC, chemistry, toxicology screen, antiseizure drug level, if known to be on treatment
If seizures continue:			
Initial treatment	5–20 min	Administer benzodiazepines. *One of the following:* • IM midazolam • IV lorazepam • IV diazepam	
If seizures continue:			
Second treatment	20–40 min	Administer antiseizure drug. *One of the following:* • IV fosphenytoin • IV valproic acid • IV levetiracetam • IV lacosamide • IV phenobarbital	
If seizures continue:			
Third treatment	40–60 min	Repeat treatments in second phase or sufficient continuous IV infusion of seizure-suppressing ("anesthetic") medications: midazolam, propofol, or pentobarbital (or thiopental)	• Initiate continuou EEG monitoring • Admit to ICU • If continuous IV infusion of sedating drugs is administered, patient requires intubation

These steps to stabilize a patient

It is particularly important to consider the possibility of ongoing nonconvulsive seizures in patients whose convulsions have ceased but whose mental status has not improved, or in whom the mental status is disproportionately impaired to what is expected from other comorbidities

It is also important to note that a cluster of frequent seizures may warrant similarly aggressive management, particularly because this condition may evolve to SE quickly

There are evidence-based guidelines on how to approach adults and children in SE.These guidelines are updated on a regular basis as new ASDs and procedures become available

8. Special topics

A) First aid for seizures

All physicians should be familiar with first aid measures for patients having a seizure

In general,the goal is to prevent the patient from becoming injured

(and to prevent well-meaning bystanders from intervening unwisely)

The patient with complex partial seizures may wander or make semipurposeful movements; if necessary he or she should be gently guided out of harm's way

More aggressive attempts at restraint may provoke a violent reaction

The patient with GTCs should be laid on his or her side, if possible, so that vomiting does not lead to aspiration

Tight clothing should be loosened

Nothing should be placed in the mouth

Most GTCs stop within 1 or 2 minutes; immediate medical attention should be sought if a seizure becomes more prolonged

B) Sudden unexpected death in epilepsy

Sudden unexpected death in epilepsy(SUDEP) is a rare and devastating outcome from epilepsy

It is defined as a " sudden, unexpected death of a person with epilepsy who is otherwise healthy" (AAN Guideline)

SUDEP in children is rare, occurring in 1 every 4500 children with epilepsy

In adults, SUDEP is more common, resulting in the death of 1 in 1000 adults with epilepsy per year

Risk factors include the following:

- GTCs , especially with a high frequency of GTCs(effectively treating and reducing the frequency of seizures results in a decreased risk of SUDEP)
- Longer duration of the diagnosis of epilepsy
- Age: 18 to 40 years
- Alcohol use
- Missing ASD doses

Although this can be anxiety provoking to discuss, patients and families should be counseled about the risk of SUDEP and that adherence to effective ASD treatment probably decreases the risk

B) Seizures and driving

Each state in the USA has its own licensing requirements for people with epilepsy

Physicians who care for seizure patients should be aware of them

Most states require a specific seizure-free interval before a patient may drive

Exceptions can sometimes be made for purely nocturnal seizures or those with a prolonged focal onset that provides the patient with a warning without impaired awareness

A few states require physicians to report patients with seizures to the department of motor vehicles

All patients should be counseled about driving restrictions

C) Antiseizure drugs and pregnancy

Women taking ASDs have a somewhat higher risk of fetal malformations than does the general population, but the absolute risk is still low

Valproic acid has been specifically associated with a higher rate of neural tube defects

All women with epilepsy who are considering becoming pregnant should take folic acid (at least 1 mg per day)

It is reasonable to consider modifying the ASD regimen prior to conception, depending on the severity of a women's epilepsy, but the risk of ASD-related teratogenicity must be balanced with the risk of seizures during pregnancy

D) Psychogenic nonepileptic seizures

A reported 10% to 30% of patients evaluated at tertiary referral centers for medically refractory epilepsy actually have events that have no EEG correlate and are psychogenic in nature

These are referred to as psychogenic nonepileptic seizures

Some of these patients may have “ true” epileptic seizures at other times

Many patients with psychogenic events have comorbid psychiatric illnesses or a history of abuse

Continuous video-EEG monitoring to record the typical events is usually the most reliable method of differentiating psychogenic events from epileptic seizures