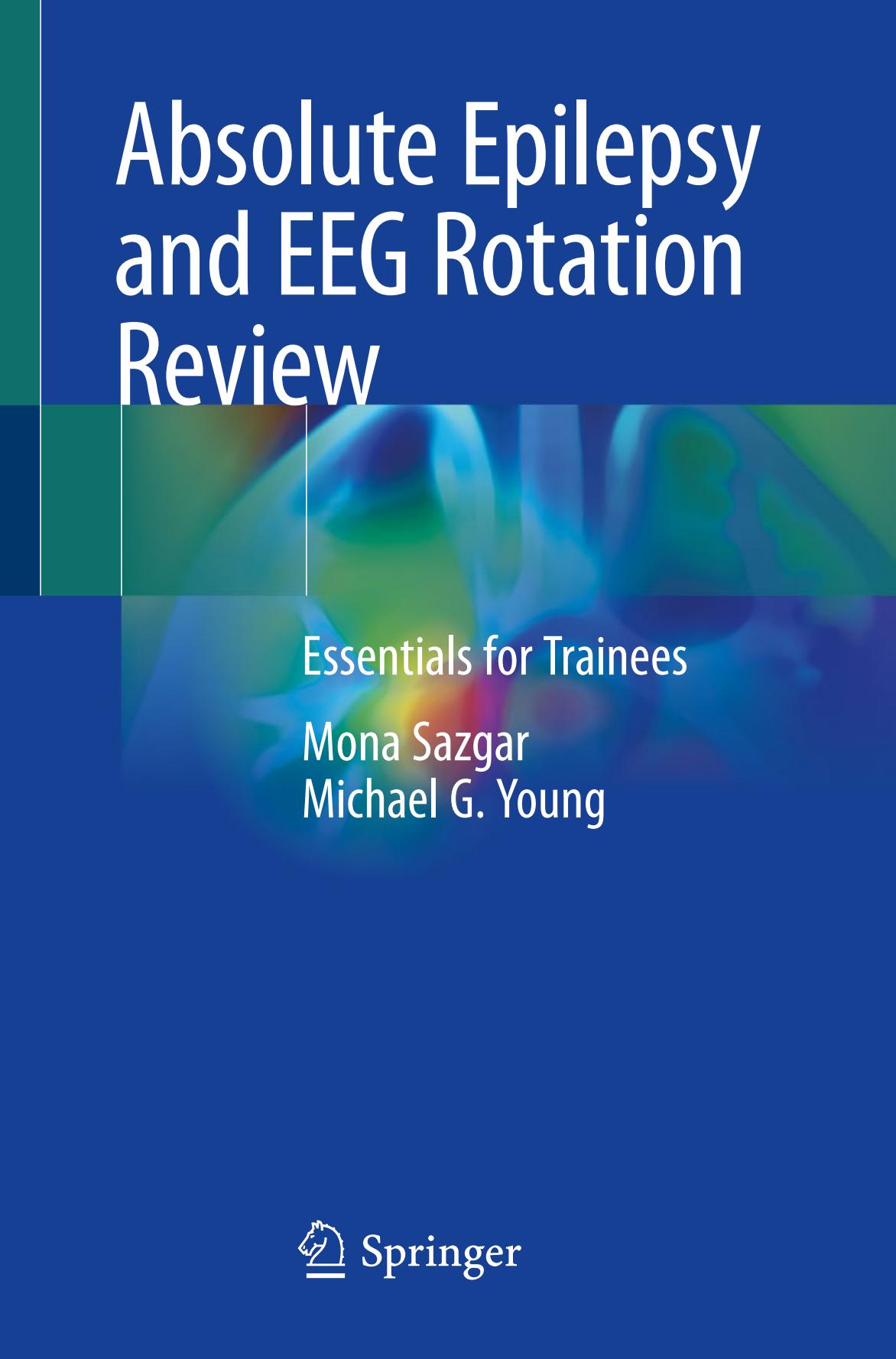


Absolute Epilepsy and EEG Rotation Review



Essentials for Trainees

Mona Sazgar
Michael G. Young



Springer

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Mona Sazgar • Michael G. Young

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*To Behrouz, my love
To Neema, my pride and joy
To mom and dad, my guides*

Mona Sazgar

To Kieu, for her patience and unwavering support; to my parents, Michael and Karina; and to all those in the medical field who continue to inspire me, especially Kieu, Joe, Shaun, and Sergio.

Michael G. Young

Foreword

Dear reader,

Oh, how far we have come and thankfully so since I was a neurology trainee! Without revealing my exact vintage, my neurophysiology rotation involved turning the pages of stacks of electroencephalograms (EEGs). As a second year resident in neurology, I remember my attending pointing to sharp-appearing waves in temporal lobe areas and asking me whether the patient has epilepsy. Although the answer seemed obvious, I knew there was a trick to it, otherwise why the question. I was thinking that my guess would have a 50% chance of being correct. This remarkable volume by Drs. Sazgar and Young will ensure that neurology residents and fellows are not at a loss when asked this question and will be able to answer correctly and, further, to understand why. This simple question remains relevant and instructive because human electroencephalography has not fundamentally changed since it was standardized in the 1920s. However, the formats for evaluating and interpreting EEG data have become myriad, to the great benefit of patient care. The educational endeavor of the authors is similarly to evolve a classic approach into something new. They are incorporating into one volume two fields that have been traditionally taught separately, EEG reading and epilepsy care. In the era of epilepsy monitoring units, prolonged ambulatory EEGs and quantitative EEG, as well as syndrome-specific epilepsy treatments, the two topics are completely intertwined; the clinical implications of one are not understood without knowledge of the other. Most trainees participate in both epilepsy patient care and EEG reading during their rotations, and until this book, there was no single resource for such.

Drs. Sazgar and Young have addressed an important gap in neurology training by providing the EEG and epilepsy “essentials” for trainees. This book will be important and truly essential for trainees and for neurologists beyond training who are seeking to advance their skills. The concise format, with the effective use of bullets, allows for quick and ready translation of the educational pearls to clinical implementation. Such a reliable, comprehensive yet circumscribed scholastic source is sought out in this information age.

Dr. Mona Sazgar is a valued friend and academic colleague. She is an esteemed and respected neurology educator and a gifted clinician. She has a keen and dedicated interest in furthering the best care for women with epilepsy. I had the great pleasure of writing and editing a book with Dr. Sazgar, and during that collaboration, I experienced her persistence and grace firsthand. She once told me that one of

her character flaws is to be “pathologically early” for every appointment, which is one of the most laudable traits I can think of. Her timing for publishing this book could not be better, given that many academic programs are onboarding the ACGME-accredited epilepsy fellowship. Dr. Sazgar had the insight to involve a recent epilepsy fellowship graduate and current junior attending, Dr. Michael G. Young, as a co author for the *Essentials*. His perspective ensures that the educational content meets the “boots-on-the-ground” needs, in a manner that connects knowledge with practicality. It is my great honor to be part of this publication. And finally, as to answer my attending’s question, the trick was that the sharp waves were actually normal variants called wicket spikes explained in Chap. 7 of the book, and the patient did not have epilepsy.

New York, NY, USA

Cynthia L. Harden

Preface

Throughout my academic career as an epileptologist, I had the pleasure of teaching epilepsy and EEG to more than 30 epilepsy and clinical neurophysiology fellows and hundreds of neurology residents and students. I passionately encouraged trainees to take up a career in epilepsy and attempted to make the subject simplified and desirable. My goal was that the trainees do not treat learning epilepsy and EEG as another hurdle to overcome before they graduate. I wanted them to enjoy their learning experience. One question that consistently came up in every encounter was which textbook to read as a reference. Of course, there are many comprehensive textbooks of epilepsy and atlases of EEGs published by my accomplished colleagues over the years. However, for trainees with extremely busy schedule who spend a month or a couple of weeks doing a clinical rotation, it is almost impossible to read through a comprehensive textbook. Their consistent feedback was that my lectures and take-home information they received during my rounds were most practical and what they needed to learn. It occurred to me that I can help thousands of residents, fellows, students, and clinicians to have access to my years of experience in teaching epilepsy and EEG by giving them a concise, yet comprehensive collection of the crucial points they need to know when time is short. I invited my young and astute colleague, Dr. Michael G. Young, to join me in this endeavor as co author and to contribute his invaluable fresh perspective. We hope that our book will put the readers at ease and give them confidence that they have learned what they needed to know about epilepsy and EEG in an uncomplicated way.

Together, we offer this simplified, bullet format collection of the essentials of epilepsy and EEG to the trainees and clinicians to take home.

Irvine, CA, USA

Mona Sazgar

Acknowledgment

We would like to express our sincere appreciation to Dr. Anton Hasso, professor of radiologic sciences and director of neuroimaging research at the University of California, Irvine, for his contribution to some of the neuroimaging cases used in this book. Also, our appreciation goes to our dear colleagues at the UCI Comprehensive Epilepsy Program for their suggestions regarding patient cases including Dr. Lilit Mnatsakanyan, Dr. Indranil Sen-Gupta, Dr. Jack Lin, and Dr. Xiaoying Lu.

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Part I

Epilepsy



What Is Not a Seizure?

1

1.1 Evaluating a Spell

- Not all episodes of shaking or loss of awareness/consciousness are seizures
- Due to their wide variation in presentation, seizures can be easily misdiagnosed
- Other non-epileptic etiologies should always be considered
- Correct diagnosis of a spell is critical to ensure that the proper treatment is initiated
- A detailed history provided by a witness of the event is key in diagnosis of a spell
- *To arrive at proper diagnosis ask about:*
 - Precipitating factors (What were the circumstances before the event?)
 - Prodrome (What did the patient experience prior to the event?)
 - Time course (short or long)
 - Stereotypy (Do the events happen the same way every time?)
 - Behavior during episode
 - Ameliorating factors
 - Nature of recovery (prolonged confusion vs. rapid recovery)
- Video-EEG monitoring is often necessary for characterization of the event

1.2 Seizure Mimickers

1.2.1 Syncope

- Most common causes: vasovagal vs. cardiogenic vs. hypotension [1]
- Prodrome of lightheadedness, dizziness, vision changes, diaphoresis, etc
- Often patient appears pale

- May be triggered by emotion (vasovagal), positional change (orthostatic hypotension), Valsalva maneuvers
- Often accompanied by a few clonic, myoclonic jerks, or brief tonic posturing
- Quick return to baseline

1.2.2 Migraine

- Migraine with aura is typically associated with positive symptoms (paresthesias, vision changes, i.e., fortification spectrum)
- Aura spreads gradually over ≥ 5 min and lasts < 60 min
- Occipital and temporo-occipital lobe seizures can also cause visual hallucinations
- Migraine or headache with migraine features often follows a seizure
- An epileptic seizure may occur during or after a migraine; however, the role of migraines in triggering seizures is controversial [2]
- Migraines and epilepsy are often comorbid conditions [3–6]

1.2.3 Transient Ischemic Attacks (TIAs)

- Typically lasts < 1 h
- Tend to cause “negative” signs and symptoms (weakness, numbness, aphasia, vision loss)
- Seizures usually result in “positive” symptoms (clonic movements, tingling, visual hallucinations)
- Seizures may cause postictal negative symptoms (Todd’s paralysis), therefore confused with TIAs
- Limb-shaking TIAs may be confused with focal motor seizures
 - Often associated with severe carotid occlusive disease [7]
 - Symptoms may be provoked by maneuvers that decrease cerebral blood flow

1.2.4 Sleep Disorders

- May be confused with frontal lobe epilepsy
- Parasomnias involve arousal from non-REM sleep
- Parasomnias may resemble nocturnal seizures:
 - Vocalization (sleep talking) and somnambulism (sleep walking) can mimic postictal or ictal wandering and confusion
 - Night terrors may be confused with nocturnal seizures, especially occipital epilepsy in children
 - Patients arousing from stage N3 of sleep may be confused
- REM sleep behavior disorder manifests with dream enactment (often violent)
 - This may be confused with hypermotor behavior during a nocturnal frontal lobe seizure
- Cataplexy in narcoleptics may be confused with an atonic seizure

1.2.5 Paroxysmal Movement Disorders (PMD)

- PMD include episodic ataxias and paroxysmal dyskinesias [8]
- Attacks of dystonia, chorea, athetosis, and other hyperkinetic movement disorders:
 - Paroxysmal kinesigenic dyskinesia
 - Paroxysmal nonkinesigenic dyskinesia
 - Paroxysmal exertion-induced dyskinesia
 - Paroxysmal hypnogenic dyskinesia
- Usually autosomal dominant genetic conditions but may occur sporadically
- Supplementary motor area seizures can be challenging to discern from paroxysmal kinesigenic dyskinesia [8]

1.2.6 Psychogenic Non-epileptic Events or Seizures (PNES)

- Psychogenic non-epileptic *event* is preferred as the term “seizure” which is misleading
- Often confused with epileptic seizures due to generalized shaking and/or reported “loss of consciousness”
- May appear to be “postictal” after the episode
- Episodes are typically longer (several minutes) than epileptic seizures
- May coexist with epileptic seizures
- A presumed seizure disorder that does not respond to treatment with antiepileptic drugs (AEDs) may be non-epileptic and warrants further investigation
- A history of significant psychosocial trauma and abuse may be found
- Video EEG is often necessary to help differentiate epileptic from non-epileptic events
- *Distinguishing red flags to suspect PNES:*
 - Eye closure
 - Non-rhythmic shaking
 - Side-to-side or up-and-down head movements
 - Vocal stuttering
 - Back-arching
 - Pelvic thrusting
 - Waxing and waning features
 - Post ictal crying or shouting
 - Features vary from one event to the next
 - Lack of significant injury
 - Tip of tongue laceration (lateral tongue biting occurs with epileptic seizures)
 - Suggestibility (patient can be talked into having a spell)

Table 1.1 summarizes the conditions which closely mimic epileptic seizures and their distinguishing features.

Table 1.1 Seizure differential diagnosis

Event	Clinical features	Duration	Post-event symptoms	Diagnostic hints/work-up
Syncope	Prodrome of lightheadedness, dizziness, etc. followed by brief LOC; vasovagal usually triggered by strong emotion; few myoclonic jerks may be seen	Seconds to a few minutes	Quick return to baseline	Tilt table testing; EKG, event (i.e., Holter) monitor, echocardiogram
Migraine	Unilateral throbbing headache with N/V, etc.; positive symptoms (fortification spectrum, paresthesia) spreads gradually ≥ 5 min	Migraine aura lasts 5–60 min	Headache	Personal or family history of migraines
TIA	Rapid onset of negative symptoms (numbness, weakness, aphasia); rare positive symptoms (limb-shaking TIA)	<60 min	None	Cerebrovascular disease risk factors, MRI brain, MRA/CTA of the head and neck
Parasomnia	Arousal from non-REM sleep with confusion +/- vocalization or ambulation	Minutes	Confusion	Polysomnogram
Psychogenic nonepileptic seizure	Eye closure, back arching, pelvic thrusting, vocal stuttering, side to side head jerking, waxing and waning course, suggestibility, lack of injury	Minutes; often >5–10 min	None, but may appear "postictal"	Video EEG to capture events
Focal aware seizure	Brief aura (visual distortions, epigastric rising, <i>déjà vu</i> , fear, etc.) or sensory/motor disturbance (paresthesia, clonic activity)	10–30 s	None	MRI brain, EEG; <25% have EEG correlate [9]
Focal seizure with impaired awareness	May be preceded by focal aware seizure; eyes open, staring, automatisms; may progress to bilateral tonic clonic seizure	30–180 s	Confusion, fatigue, amnesia, incontinence	MRI brain, EEG may show IEDs
Generalized tonic-clonic seizure	May be generalized at onset or progress to bilateral tonic clonic; eyes open, tonic posturing followed by rhythmic clonic jerks	1–3 min	Confusion, fatigue, amnesia, incontinence, tongue biting, muscle soreness	MRI brain, EEG may show focal or generalized IEDs

IED Interictal Epileptiform Discharge

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Seizures and Epilepsy

2

2.1 Definition of Seizure and Epilepsy

The International League Against Epilepsy (ILAE) established both conceptual and operational clinical definitions for seizures and epilepsy.

- *Conceptual definitions [1]*
 - “An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.”
 - “Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.”
- *Operational (practical) clinical definition of epilepsy [2]*
 - Epilepsy is a disease of the brain defined by any of the following conditions:
 - At least two unprovoked (or reflex) seizures occurring >24 h apart
 - One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
 - Diagnosis of an epilepsy syndrome

Provoked seizures occur as the result of the seizure threshold being transiently lowered by some disturbance.

- Do *NOT* count toward a diagnosis of epilepsy
- Provoked seizures are usually *generalized* convulsive seizures

- Causes of provoked seizures:
 - Medications [3]
 - Antidepressants (Bupropion, TCAs, Venlafaxine)
 - Tramadol
 - Diphenhydramine
 - Isoniazid
 - Theophylline
 - Imipenem
 - Antipsychotics
 - Recreational drugs:
 - Amphetamines, cocaine, MDMA, phencyclidine
 - Alcohol withdrawal
 - Barbiturate or benzodiazepine withdrawal
 - Metabolic
 - Hypoglycemia or hyperglycemia
 - Hyponatremia
 - Hypocalcemia

Reflex seizures are provoked seizures which meet criteria for epilepsy due to their perpetual and abnormal tendency to have seizures caused by that stimulus.

- Photic-induced seizures (seizures provoked by flashing lights) are considered reflex seizures

2.2 Seizure Types and Classification

In 2017, the ILAE released a new seizure classification system that includes both a basic and expanded version [4]. The expanded version provides more subcategories for more detailed characterization of the seizures.

2.2.1 ILAE 2017 Basic Classification of Seizure Types

- Seizures are named by onset (focal vs. generalized vs. unknown) (Fig. 2.1)
- Focal onset – originating within the networks of one hemisphere
- Generalized onset – originating from and rapidly engaging networks of both hemispheres
- The term “onset” is presumed and omitted, with the exception of “unknown onset.”
- Focal seizures may be further classified by level of awareness (aware vs. impaired awareness) and/or motor vs. non-motor onset
 - Awareness pertains to knowledge of self and environment during a seizure
- Level of awareness is omitted for focal seizures if unknown or not applicable

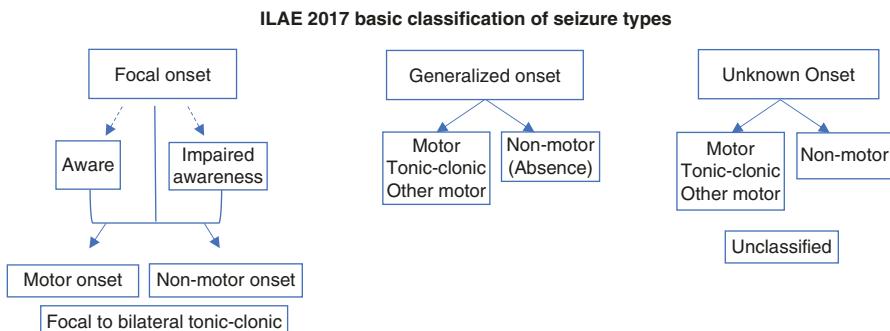


Fig. 2.1 ILAE 2017 Basic seizure classification

- Seizures may be “unclassified” due to insufficient information or inability to place in other categories
- Examples:
 - Focal aware seizure (previously simple partial seizure)
 - Focal seizure with impaired awareness (previously complex partial seizure)
 - Focal to bilateral tonic-clonic seizure (previously secondarily generalized tonic-clonic seizure)

2.2.2 ILAE 2017 Expanded Classification of Seizure Types

- Same as the basic classification with additional modifiers for more precise characterization (Fig. 2.2)
- Motor or non-motor modifiers are chosen according to the earliest prominent sign or symptom
 - Can be used to further characterize focal aware or impaired awareness seizures
 - Alternatively, motor/non-motor modifiers can be used without specifying level of awareness (i.e., focal myoclonic seizure)
- Since behavioral arrest is common in many seizure types, focal behavioral arrest seizure should only be used if behavioral arrest is the predominant aspect of the entire seizure
- Cognitive seizures imply impairment of any cognitive domain (i.e., language) or positive symptoms (*déjà vu*, hallucinations, etc.) or perceptual distortions
- Emotional seizures may involve feelings (fear, anxiety, etc.) or the appearance of affect without subjective emotions
- *Atypical absence seizures* should meet one of the following:
 - Slow onset or offset
 - <3 Hz spike-wave activity
 - Marked change in tone

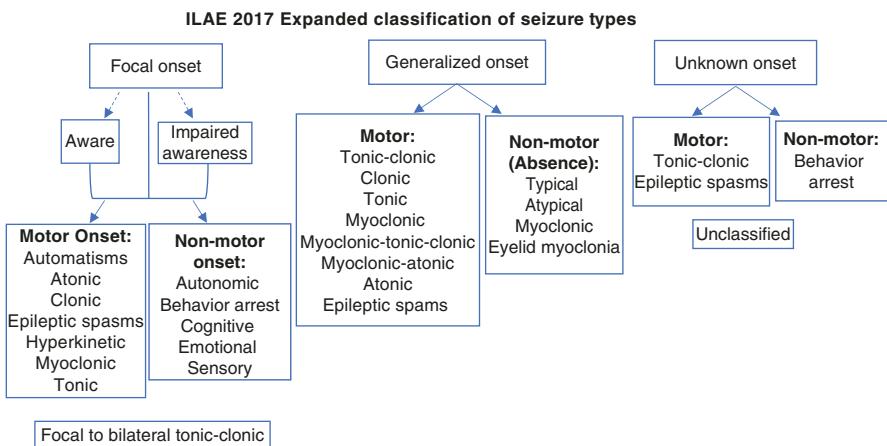


Fig. 2.2 ILAE 2017 expanded seizure classification

2.3 Risk Factors for Epilepsy

- Complex febrile seizures
 - Duration >15 min
 - >1 seizure in 24 h or during the same illness
 - Focal seizure
- Family history of epilepsy
- Head trauma with LOC
- Meningitis/encephalitis
- Perinatal distress

2.4 Causes of Seizures

- It is important to identify the etiology of a seizure for both treatment and prognosis. Keep in mind that some epilepsies may fit into more than one category

2.4.1 Genetic

- Approximately 15% of people with epilepsy have a positive family history (first-degree relative with epilepsy)
- Risk of epilepsy is about threefold higher if a first-degree relative has epilepsy [5]
- Genetic (formerly idiopathic or primary) generalized epilepsies account for 15–20% of all epilepsies [6]
- Several genes are implicated in various epilepsy syndromes (Table 2.1)

Table 2.1 Genetic epilepsies

Syndrome	Gene	Inheritance	Clinical features
Epilepsy syndromes of early onset (before 1 year)			
Benign familial neonatal seizures	KCNQ2 KCNQ3	AD	Onset within first few days of life Usually does not require treatment Normal developmental outcome
Benign familial infantile seizures	SCN2A PRRT2	AD	Onset between 3–10 months Usually does not require treatment Normal developmental outcome
Ohtahara syndrome (EIEE) [7]	STXBP1 KCNQ2 ARX CDKL5 Erbb4	Various	Onset within first few months Tonic spasms > focal motor, GTC seizures EEG – continuous suppression-burst pattern Most cases are associated with a structural brain abnormality
Early myoclonic encephalopathy (EME) [7]			Onset within first few months Myoclonic seizures > focal motor, tonic spasms EEG – suppression-burst predominantly during sleep
ARX	X-linked	Affects males	Tonic spasms Often associated with lissencephaly, agenesis of corpus callosum
CDKL5 [8]	X-linked		Ohtahara syndrome (EIEE) Onset within first 3 months Predominantly affects females Early tonic seizures Normal interictal EEG initially Severe hypotonia May have Rett-like features (deceleration of head growth, stereotypies)
STXBP1	Various		Most develop epileptic spasms Ohtahara syndrome (EIEE) Tonic seizures, epileptic spasms, or tonic-clonic seizures Ohtahara syndrome (EIEE)
Epilepsy syndromes associated with febrile seizures			

(continued)

Table 2.1 (continued)

Syndrome	Gene	Inheritance	Clinical features
Genetic epilepsy with febrile seizures plus (GEFS+)	SCN1A SCN1B SCN2A GABRG2 GABRD SCN1A	AD AD	Febrile and afebrile seizures or febrile seizures after 6 years of age Onset between 6 months and 6 years Typically resolves by puberty Normal development Onset before 18 months Triggered by fever Myoclonic, focal motor, absence, GTC seizures Prolonged focal febrile seizures Seizures often switch sides Affects females Clusters of GTC or focal seizures with febrile illness Autism
Dravet syndrome (SMEI)	PCDH19	X-linked	
			Myoclonic seizures, GTC seizures Progressive neurological deterioration Cerebellar signs Dementia
Genes associated with progressive myoclonic epilepsies (PMEs)			Most common PME High prevalence in Finland [9] Onset from childhood to adolescence Ataxia, mild cognitive decline Occipital seizures Rapid cognitive decline Most die within 10 years of onset [9] Lafora bodies – periodic-acid-Schiff (+) intracellular polyglucosan inclusion bodies found in neurons, heart, skeletal muscle, liver, sweat gland duct cells [9]
Unverricht-Lundborg disease	EPM1 (cystatin B)	AR	
Lafora body disease	EPM2A, EPM2B	AR	

Sialidosis	NEU1	AR	Onset: childhood to adolescence (type 1) 0–10 months (type 2, infantile form) Adolescence (type 2, juvenile form) Decreased vision, cherry red spot Burning extremity pain Coarse facies (type 2)
Neuronal ceroid lipofuscinosis	C1N1-8	AR AD (adult-onset form)	Onset from infancy to adulthood Macular degeneration and vision loss, except adult-onset NCL [9] Ataxia, rapidly progressive dementia Pyramidal & extrapyramidal signs CLN5 occurs almost exclusively in Finland [9]
Denatorubral-pallidoluysian atrophy (DRPLA)	ATN1	AD	Onset from childhood to elderly Three clinical forms: PME, ataxochoreoathetoid, pseudo-Huntington [9] PME phenotype typically has onset before 20 y/o [9]
Myoclonic epilepsy with ragged red fibers (MERRF) [9]	MTTK	Maternal	Onset is variable and can occur at any age Myopathy, neuropathy, hearing loss, dementia, short stature, optic atrophy EEG – slow background, 2–5 Hz generalized SW discharges Muscle biopsy – ragged red fibers in ≥90%
Genetic (idiopathic) generalized epilepsies	EFHC1 BRD2 Cx36 CACNB4 GABRA1 CLCN2 ME2	AD or AR	Onset in adolescence Myoclonic, GTC, ± absence seizures Photosensitivity EEG: 4–6 Hz polyspike and wave discharges
			(continued)

Table 2.1 (continued)

Syndrome	Gene	Inheritance	Clinical features
GLUT1 deficiency	SLC2A1	AD	Onset 1 month to 2 years Myoclonic-ataxic, atonic, atypical absence seizures Acquired microcephaly Low CSF glucose, low to normal CSF lactate, low CSF/plasma glucose ratio Txmt. – ketogenic diet
Focal epilepsies			
Autosomal dominant nocturnal frontal lobe epilepsy	CHRNA4 CHRNA2 CHRNB2	AD	Neuronal nicotinic acetylcholine receptor Onset from infancy to adulthood Multiple stereotyped brief motor seizures at night
Autosomal dominant partial epilepsy with auditory features	LGI1	AD	Aka ADLTE Peak onset from adolescence to adulthood Auditory aura (buzzing, ringing, humming) Ictal receptive aphasia
Others			
Rett syndrome	MECP2	X-linked	Normal development until 6–18 months Regression of speech & purposeful hand movement Acquired microcephaly Stereotypies (hand wringing) Autism
Alpers syndrome [11]	POLG1 (mitochondrial DNA polymerase gamma)	AR	Onset from infancy to childhood Hepatic dysfunction – valproic acid is contraindicated Often presents w/convulsive status epilepticus EEG – rhythmic high amplitude delta with superimposed polyspikes MRI – cortical and thalamic involvement
Tuberous sclerosis complex	TSC1 (hamartin) TSC2 (tuberin)	AD	Peak onset within first few years of life Focal > generalized seizures Epileptic spasms are more common with TSC2 Txmt. – Vigabatrin for epileptic spasms

Abbreviations: EIEE early infantile epileptic encephalopathy, EME early myoclonic epilepsy of infancy, ADLTE autosomal dominant lateral temporal lobe epilepsy

2.4.2 Metabolic

- Epilepsy is common in disorders resulting from inborn errors of metabolism
- Many metabolic epilepsies (Table 2.2) are considered *epileptic encephalopathies* wherein the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone, and that these can worsen over time [12]

2.4.3 Structural

2.4.3.1 Malformations of Cortical Development

Focal Cortical Dysplasia (FCD)

- Seizures usually begin in childhood and are drug-resistant [13]
- Most epilepsy surgery cases in patients <3 y/o involve FCD [14]
- Classification [13] (Fig. 2.3):
 - FCD type I – abnormal radial and/or tangential cortical lamination
 - Most often temporal and lobar/focal [14]
 - FCD type II – dysmorphic neurons ± balloon cells
 - Most often extratemporal or hemispheric [14]
 - FCD type III – associated with a lesion
- EEG findings often do not localize to the MRI lesion:
 - Scalp interictal findings are localizing in ~50% [14]
 - Scalp ictal EEG is localizing in 68% [14]
 - Seizure onset zone is often diffuse or ill-defined even with intracranial electrodes [14]
- MRI is abnormal and demonstrates signs specific for FCD in ~65% of cases [14]
- MRI abnormalities are more common in FCD type II compared to type I (90–100% vs. 15–60%, respectively)
- MRI characteristics [13]:
 - Cortical thickening
 - Blurring of the gray-white matter junction
 - Hyperintense T2/FLAIR signal in subcortical white matter
 - Transmantle sign – radially oriented T2 hyperintensity extending from the cortex to the ventricle (typically seen with FCD type IIb) [13]
 - Cortical thinning
 - Localized atrophy
- Epileptogenic zone often extends beyond lesion visualized on MRI
- Those with normal MRI are more likely to have an abnormal FDG-PET (especially if coregistered with MRI), ictal SPECT, and MEG (magnetoencephalography) localized to the area of FCD [14, 15]

Table 2.2 Metabolic disorders associated with epilepsy

Disorder	Onset	Clinical presentation	Diagnosis	Treatment
Vitamin B responsive disorders				
Pyridoxine dependent seizures	Neonatal	Prolonged seizures that respond to pyridoxine; hypothermia, poor tone; intrauterine fetal seizures may occur	↑ α-aminoacidic semialdehyde in serum, CSF, urine; Genetic testing: ALDH7A1 gene	Pyridoxine 50–200 mg daily
Pyridoxal phosphate (PLP) dependent epilepsy	Neonatal	Refractory seizures that respond to pyridoxal 5'-phosphate (PLP); usually born premature; lactic acidosis, hypoglycemia	↓ PLP in CSF Genetic testing: PNPO gene	PLP 30–50 mg/kg/d divided in 4–6 doses
Folinic acid responsive seizures	First week of life	Myoclonic or clonic seizures that respond to folic acid; apnea	CSF high performance liquid chromatography with abnormal peaks; ↑ α-aminoacidic semialdehyde in CSF; ↑ serum pipecolic acid; genetic testing: ALDH7A1 gene	PO folinic acid 3–5 mg/kg/d
Cerebral folate deficiency	Childhood, adolescence	Refractory seizures, mental retardation, microcephaly, dyskinesias	↓ CSF methyltetrahydrofolate Genetic testing: FOLR1 gene	PO folinic acid 0.5–5 mg/kg/d
Disorders of amino acid metabolism				
Nonketotic hyperglycinemia (NKH)	Neonatal or infancy	Classical neonatal NKH presents in first week of life w/ seizures, lethargy, severe hypotonia, apnea; hiccups	↑ CSF/serum glycine >0.8, ↑ glycine in CSF & serum; Genetic testing: GLDC, AMT, GCSH	PO sodium benzoate 250–750 mg/kg/d and dextromethorphan; restriction of glycine and serine; exchange transfusions
Serine deficiency disorders	Neonatal	Microcephaly, seizures, neurodevelopmental delay, spasticity	↓ serine in CSF and serum	L-serine 500–700 mg/kg/d
Phenylketonuria (PKU)	Neonatal	Refractory epileptic spasms or GTC seizures; musty or mousy odor; failure to thrive, microcephaly	Serum amino acids: ↑ phenylalanine	Restriction of phenylalanine Tetrahydrobiopterin trial to rule out deficiency as cause of PKU

Urea cycle disorders	Neonatal, infantile (partial enzyme deficiency)	Appear normal initially but quickly develop cerebral edema, lethargy, seizures, vomiting, hypothermia, coma; diffuse white matter changes on MRI	↑ serum ammonia; abnormal serum amino acids and urine organic acids	Protein restriction; dialysis to remove ammonia IV arginine chloride + sodium phenylacetate/sodium benzoate
<i>Organic acidemias</i> (maple syrup urine disease, propionic acidemia, glutaric aciduria type I, biotinidase deficiency)	Neonatal, infancy, childhood	Appear well at birth then vomiting, poor feeding, seizures, lethargy, coma	Urine organic acids, serum and urine amino acids, blood spot acylcarnitine profile, enzymatic analysis in fibroblasts; molecular analysis	Dietary restriction of precursor amino acids; replacement with deficient enzymes; compounds to dispose of toxic metabolites
Glutaric aciduria type I	Infancy	Acute encephalopathy, severe dystonia-dyskinesia, sudden dystonic spasms, seizures; MRI w/ cyst-like widening of sylvian fissures	↑ urinary glutaric acid	Protein restriction (low lysine and tryptophan), carnitine supplementation
Biotinidase deficiency	Neonatal, infancy, childhood	Seizures, hypotonia, dermatitis, developmental delay, ataxia, optic atrophy, hearing loss	↓ serum biotinidase	Biotin 5-40 mg/d
Peroxisomal disorders (X-ALD, AMN, Zellweger syndrome)	Neonatal, infancy, childhood	Seizures, hepatic disease, retinopathy, deafness, ataxia, spasticity	↑ plasma very long chain fatty acids	Symptomatic
Zellweger syndrome	Neonatal, infancy	Seizures, hepatic, cardiac, and renal disease, hypotonia, poor feeding, retinopathy, deafness; large fontanelles; chondrodyplasia punctata; polymicrogyria	↑ very long chain fatty acids Genetic testing: PEX1 gene	Symptomatic
Disorders of GABA metabolism		Refractory seizures, accelerated growth, hypotonia, lethargy, irritability	↑ GABA in serum and CSF	Symptomatic
GABA transaminase deficiency	Neonatal, infancy	Varies from mild mental retardation, speech delay, behavior problems to severe psychomotor retardation with refractory seizures	↑ GABA in urine Genetic testing: ALDH5A1 gene	Inconsistent results with Vigabatrin
Succinic semialdehyde dehydrogenase deficiency	Infancy, childhood	MRI: ↑ T2 signal in b/l globus pallidus, dentate and subthalamic nuclei		

(continued)

Table 2.2 (continued)

Disorder	Onset	Clinical presentation	Diagnosis	Treatment
<i>Mitochondrial disorders</i> (MELAS, MERRF, LS, NARP)	Infancy to adulthood	Hepatic dysfunction, lactic acidosis, deafness, myopathy; seizures MRI - stroke-like lesions that do not respect vascular territories (MELAS)	↑ CSF and plasma lactate MR spectroscopy - ↑ lactate peak; muscle biopsy	Mitochondrial cocktail (L-carnitine, coenzyme Q, riboflavin); avoid valproic acid
<i>Congenital disorders of glycosylation</i>	Infancy, childhood	Severe developmental delay, multiorgan involvement, hypotonia; inverted nipples	Isoelectric focusing of serum transferrin Genetic testing	Symptomatic
Others				
Glucose transporter 1 (GLUT1) deficiency	Neonatal, infancy	Refractory seizures, developmental delay, ataxia, paroxysmal dyskinesia, microcephaly	↓ CSF glucose, ↓ CSF/plasma glucose <0.5 w/normal or low lactate Genetic testing: SLC2A1 gene	Ketogenic diet
Creatine deficiency	Infantile	Seizures, mental retardation, language delay, autism, movement disorders	Urine and plasma guanidinoacetate and creatinine MR spectroscopy: ↓ creatine peak Genetic testing: GAMT, GATM, SLC6A8 genes	PO creatine monohydrate 5–20 g/d; arginine restriction, ornithine supplementation
Menkes disease	Infancy	Early focal status, then epileptic spasms, then myoclonic and multifocal epilepsy; “kinky hair,” hypopigmentation of the skin and hair, developmental regression MRI – cortical and cerebellar atrophy, subdural fluid collections	↓ serum copper and ceruloplasmin Genetic testing: ATP7A gene	Subcutaneous copper histidine supplementation

Abbreviations: X-ALD X-linked adrenoleukodystrophy, AMN adrenomyeloneuropathy, MELAS mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, MERRF myoclonic epilepsy with ragged red fibers, LS Leigh syndrome, NARP neurogenic muscle weakness, ataxia, and retinitis pigmentosa

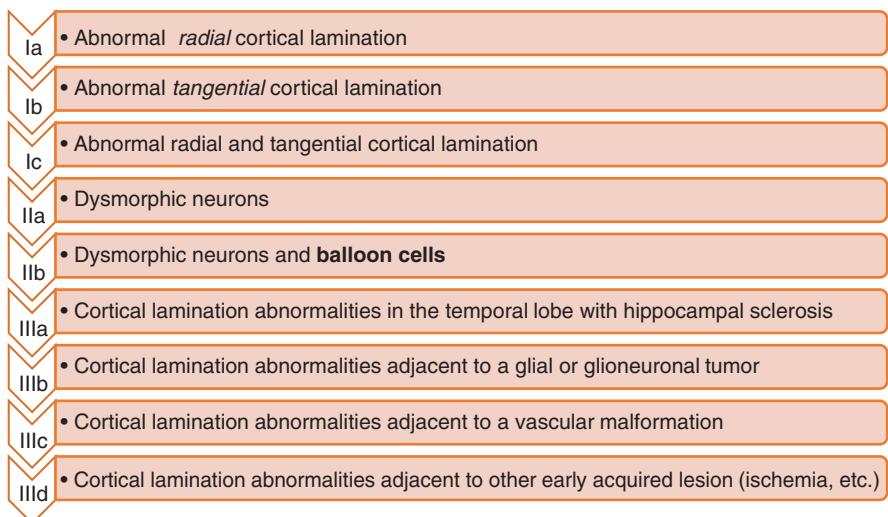


Fig. 2.3 ILAE classification system of focal cortical dysplasias [13]

- Surgical outcome [14]:
 - Sixty percent are seizure-free after FCD resection (~80% with a complete resection vs. ~20% with incomplete resection)
 - Incomplete resection typically occurs when FCD is located in eloquent cortex

Periventricular Heterotopia [15]

- Results from the failure of periventricular neurons to migrate
- Affects females > males
- MRI: isointense to gray matter on all sequences
 - Differentiate from subependymal nodules of tuberous sclerosis (Table 2.3)
- Familial periventricular heterotopia
 - Bilateral periventricular nodular heterotopia
 - FLNA gene (encodes filamin A)
 - X-linked dominant
 - Females of normal intelligence
 - Mutation is typically fatal for males; however, sporadic mutations in males may occur
 - ARFGEF2 gene [16]
 - Autosomal recessive
 - Severe developmental delay and microcephaly

Subcortical Band Heterotopia and Lissencephaly [15]

- Subcortical band heterotopia – band of gray matter separated from the cortex by a rim of white matter (“double cortex”)

Table 2.3 Periventricular heterotopia vs. subependymal nodules of tuberous sclerosis (TSC) [17]

Periventricular heterotopia	Subependymal nodules of TSC
Ovoid, smooth	Irregular, elongated
Isointense to gray matter	Iso/hypointense to white matter
No enhancement	Gadolinium enhancement
No calcification	Calcification on CT

- DCX gene mutation on X chromosome (encodes for doublecortin) leads to:
 - Subcortical band heterotopia in females
 - Lissencephaly in males
- Lissencephaly – “smooth brain” with varying severity
 - LIS1 on chromosome 17
 - Pachygryria – few, flat gyri
 - Agyria – absent gyri

Polymicrogyria

- Irregular cortical surface due to excessive, small gyri
- May be unilateral or bilateral
- Several syndromes with bilateral symmetric polymicrogyria of varying location have been described [18]

2.4.3.2 Hippocampal Sclerosis (HS)

- Often used interchangeably with mesial temporal sclerosis (MTS)
- MTS implies involvement of extrahippocampal tissue (amygdala, parahippocampal gyrus)
- Although there may be a history of prolonged febrile seizures, the association with HS is unclear [19, 20]
- HS is associated with good surgical outcome [21]
- MRI features of HS:
 - Increased T2/FLAIR signal
 - Hippocampal atrophy
 - Loss of internal architecture
- ILAE classification of HS [22]:
 - Type 1 – severe neuronal loss and gliosis predominantly in CA1 and CA4 regions
 - Type 2 – CA1 predominant neuronal loss and gliosis
 - Type 3 – CA4 predominant neuronal loss and gliosis

2.4.3.3 Tuberous Sclerosis Complex (TSC) [23]

- Autosomal dominant
- TSC1 gene encodes hamartin
- TSC2 gene encodes tuberin
- Approximately 85% have epilepsy
- Onset occurs within first few years of life
- Associated with epileptic spasms and focal seizures (\pm bilateral tonic clonic seizures)
- Epileptic spasms are more common with TSC2 mutation
- Vigabatrin is indicated for epileptic spasms due to tuberous sclerosis
 - Prognosis – Approximately 2/3 have refractory epilepsy

2.4.3.4 Epilepsy and Brain Tumors [24]

- Seizure is the initial presentation in 30–50% of patients with brain tumors
- The epileptogenesis of brain tumors is likely multifactorial and includes tumor type, morphological changes in the cortex adjacent to the tumor, and genetic factors
- Other potential confounders for seizures in these patients include:
 - CNS infection due to immunosuppression by chemotherapy
 - Medications (which may lower seizure threshold):
 - Chemotherapy (cisplatin, etoposide, vincristine, ifosfamide, interleukin 2)
 - Antibiotics (metronidazole, beta-lactams)
 - Antidepressants (bupropion, TCAs, SSRIs)
 - Neuroleptics (clozapine, phenothiazines, butyrophenones)
 - Radionecrosis as a result of radiation therapy
- Cortical location of the tumor is the biggest risk factor for the development of seizures
- Slow-growing tumors tend to be more epileptogenic
- Seizure frequency is highest with dysembroblastic neuroepithelial tumors (DNET) followed by gangliogliomas and low-grade astrocytomas
- Treatment:
 - AED prophylaxis in patients with brain tumors who have never had a seizure is NOT indicated
 - Potential drug-drug interactions should be considered when selecting an AED
 - Enzyme-inducing AEDs decrease the efficacy of corticosteroids and several chemotherapeutic agents and thus should be avoided

2.4.3.5 Vascular

- Hypoxic-ischemic injury – common cause of neonatal seizures
- Subarachnoid hemorrhage (SAH)
 - Risk of seizure after aneurysmal SAH ranges from 4%–27% [25]
 - Although there is lack of high quality evidence to support its use, short-term AED prophylaxis (3–7 days) is commonly used
 - Risk of developing epilepsy after SAH is about 7% at 12 months [26]
- Stroke [27]
 - Approximately 10% of patients with hemorrhagic stroke will have a seizure compared to 8% of patients with ischemic stroke
 - Biggest risk factor for seizure is cortical location
 - Only 2.5% will develop epilepsy after a stroke (ischemic or hemorrhagic)

2.4.3.6 Traumatic Brain Injury (TBI)

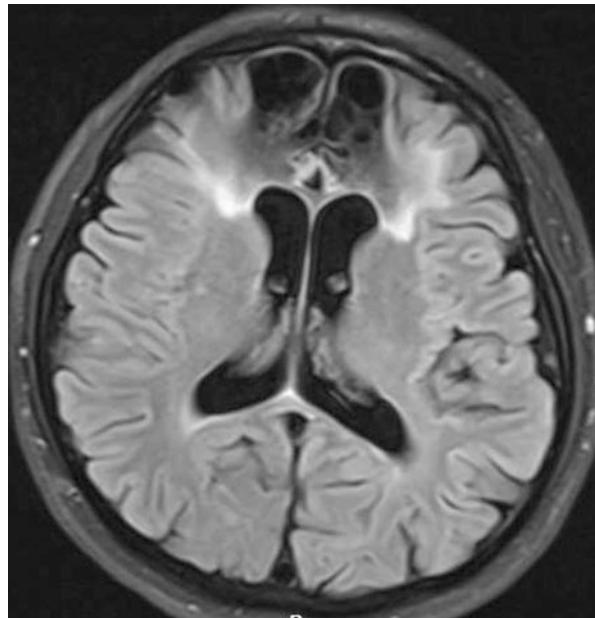
- Although heterogeneity exists among various studies analyzing post-traumatic seizures, TBI is commonly defined as [28]:
 - Mild – loss of consciousness (LOC) < 30 min and no skull fracture
 - Moderate – LOC > 30 min but <24 h, with or without skull fracture
 - Severe – LOC > 24 h, with contusion, hematoma, or skull fracture
- Post-traumatic seizures (PTSs) are seizures resulting from TBI:
 - Immediate PTSs – occurring <24 h after injury

- Clinical significance is unclear
- Early PTSs – occurring <1 week after injury:
 - Biggest risk factor is intracranial bleeding (Table 2.4)
- Late PTSs – occurring >1 week after injury:
 - Late PTSs constitute post-traumatic epilepsy
 - Most occur within the first year but can occur several years later
 - Biggest risk factor for late PTSs is early PTSs (Table 2.4)
- The relative risk of developing epilepsy after TBI (compared to the general population) increases with higher injury severity [29]:
 - Severe TBI confers a 29-fold increased risk (Fig. 2.4)
 - Moderate TBI = fourfold increased risk
 - Mild TBI = 1.5-fold increased risk
- Remission rates range from 25 to 40% [30]
- Those with frequent seizures within the first year are less likely to experience seizure remission
- AED prophylaxis after TBI [31]

Table 2.4 Risk factors for early and late post-traumatic seizures (PTSs) [30]

Early PTSs	Late PTSs
Acute intracranial bleeding	Early PTSs
Acute subdural hematoma (children)	Acute intracranial bleeding
Chronic alcoholism	Brain contusion
Higher injury severity, LOC or post-traumatic amnesia >30 min	Higher injury severity, LOC or post-traumatic amnesia >24 h
Younger age	Age > 65 at time of injury

Fig. 2.4 Axial FLAIR demonstrating bifrontal encephalomalacia in a 32 y/o male with post-traumatic epilepsy after a motor vehicle accident. (Image courtesy of Dr. Jack J. Lin)



- AAN guidelines recommend prophylaxis with phenytoin (beginning with an IV loading dose) after severe TBI \times 7 days to prevent early PTSs
- AED prophylaxis is not recommended after 7 days as it does not decrease risk of late PTSs

2.4.4 CNS Infections

2.4.4.1 Meningitis/Encephalitis

- Bacterial meningitis increases risk of developing epilepsy by 5-fold [32]:
 - Risk is greatest in the first 2 years after infection
 - Similar to TBI, early seizures increase the risk for late seizures
- Viral encephalitis increases risk of epilepsy by 16-fold [29]

2.4.4.2 Neurocysticercosis [33]

- Parasitic infection caused by the tapeworm, *Taenia solium*
- Acquired by ingestion of undercooked pork
- Common cause of seizures in developing countries (Latin America, Africa, India, China)
- Due to immigration, up to 10% of ED visits for seizures in the Southwestern USA are attributed to neurocysticercosis
- Most common initial presentation is a seizure and is usually associated with a cyst undergoing degeneration
- Epilepsy due to neurocysticercosis is typically associated with calcified granulomas
- Treatment:
 - Albendazole 400 mg BID for active cysts significantly reduces the number of seizures with generalization compared to placebo [34]

2.4.4.3 Cerebral Abscess [29]

- 30% will have seizures
 - Risk is greatest in first 5 years

2.4.5 Autoimmune Epilepsy [35]

- Early recognition of an autoimmune etiology to seizures is critical
- Treatment will require immunotherapy in addition to AEDs
- Early treatment with immunotherapy may improve seizure outcome:
 - In a study by Quek et al., the median time from seizure onset to starting immunotherapy was 4 months for responders and 22 months for non-responders ($p < 0.05$) [36]
- Early initiation of immunotherapy is an independent predictor of good outcome in anti-NMDAR encephalitis [37]
- Features suggestive of autoimmune epilepsy:
 - Onset with status epilepticus or several seizures
 - Onset after age of 30

- Signs of limbic encephalitis: cognitive decline, behavioral disturbance, temporal lobe seizures
- Early drug resistance
- MRI with ↑ T2/FLAIR signal changes or swelling in mesial temporal region or bilateral mesial temporal abnormalities
- History of an autoimmune disease
- Limbic and diffuse encephalitis is commonly associated with seizures
- Paraneoplastic limbic encephalitis precedes the diagnosis of a malignancy in up to 50%
- Antibodies (Table 2.5) should be checked in both serum and CSF
- Malignancy screening for limbic encephalitis:
 - Whole-body FDG-PET is more sensitive than CT
 - If negative, repeat PET/CT q6 months until 4 years of negative testing
- Treatment for autoimmune encephalitis:
 - Currently no evidence-based guidelines

Table 2.5 Antibodies associated with autoimmune epilepsies

Antibody	Clinical features (other than limbic encephalitis)	Neoplasm	CSF	MRI
Anti-VGKC antibodies				
LGI1	Faciobrachial dystonic seizures; SIADH, hyponatremia, REM sleep behavior disorder	Rare; thymoma, SCLC	Typically normal; mildly ↑ protein, oligoclonal bands	↑ T2 signal in mesial temporal lobes
Caspr2	Neuromyotonia or Morvan syndrome	Thymoma	Typically normal; mildly ↑ protein, oligoclonal bands	↑ T2 signal in mesial temporal lobes
Antibodies against a neuronal surface antigen [39]				
NMDAR [37]	Typically affects young women; psychosis, catatonia, orofacial dyskinesias, autonomic instability, hypoventilation, coma; EEG – extreme delta brush in 30%	Ovarian teratoma >90%; tumor is rare in men (lung, breast, testicular)	Lymphocytic pleocytosis	Abnormal in 1/3: ↑ T2 signal in cortical, subcortical, cerebellum, and/or brainstem
GABA-A	Typically affects males; median age 22; refractory status epilepticus or epilepsy partialis continua	Rare	Lymphocytic pleocytosis	Multifocal cortical, mesial temporal, basal ganglia, or brainstem changes

Table 2.5 (continued)

Antibody	Clinical features (other than limbic encephalitis)	Neoplasm	CSF	MRI
GABA-B	Median age 65; prominent seizures	SCLC or thymoma in 50%	Lymphocytic pleocytosis	↑ T2 signal in mesial temporal lobes
AMPA (GluR1 or GluR2 subunits)	Typically affects middle aged women (median age 60); prominent psychiatric symptoms	SCLC, breast, or thymoma in 70%	Lymphocytic pleocytosis, ↑ protein	↑ T2 signal in mesial temporal lobes
mGluR5 (also an onconeural antibody)	Ophelia syndrome = Hodgkin disease + LE; myoclonus	Hodgkin lymphoma	Lymphocytic pleocytosis, ↑ mononuclear cells	↑ T2 signal in mesial temporal lobes or pons
Onconeural antibodies				
Hu	Cerebellar degeneration, peripheral neuropathy or neuronopathy, autonomic dysfunction	SCLC, melanoma, breast, prostate	↑ protein in >60% ↑ WBCs in 50%	All with mesial temporal or diffuse changes
CV2-CRMP-5 [40]	May have widespread nervous system involvement; chorea, optic neuritis	Lung, thymoma	↑ protein ± pleocytosis	All with mesial temporal or diffuse changes
Ma2/Ta [41]	Limbic, diencephalic, and/or brainstem dysfunction; excessive daytime sleepiness, vertical gaze paresis, ophthalmoplegia	Testicular > lung	↑ protein ± pleocytosis	All with mesial temporal or diffuse changes
Amphiphysin	Stiff-person syndrome	Breast	↑ protein ± pleocytosis	All with mesial temporal or diffuse changes

- Removal of underlying neoplasm for paraneoplastic encephalitis; however, it does not guarantee neurologic improvement
- First-line treatment: IV steroids, IVIg, plasmapheresis, alone or in combination
- Second-line: Rituximab and cyclophosphamide were shown to be effective in patients with NMDAR encephalitis who did not respond to first-line treatment [37]

2.4.5.1 Seizures Associated with Autoimmune Diseases

- Multiple sclerosis
 - Patients with MS have a two- to threefold increased risk of seizures compared to age-matched controls

- Acute Demyelinating Encephalomyelitis (ADEM)
 - Seizures are seen in up to two-thirds of severe cases
- Primary CNS vasculitis
- Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT)
 - Approximately 2/3 will have seizures
- Systemic lupus erythematosus (SLE)
 - 15% of patients have seizures
 - Antiphospholipid antibodies confer a higher risk of seizures
 - Seizures tend to occur with flares
- Celiac disease
 - Cases of occipital lobe epilepsy and occipital calcifications have been reported in Southern Europe and South America
- Behçet disease
- Sarcoidosis
- Wegener granulomatosis

2.4.5.2 Rasmussen Encephalitis (RE)

- Triad of progressive cortical atrophy, refractory seizures, and progressive neurological impairment
- Thought to be related to T-cell-mediated inflammation
- GluR3 antibodies are neither sensitive nor specific
- Typically affects children (average age of onset is 6 years), although adult cases also exist
- Epilepsia partialis continua (EPC) is common
- Diagnosis [38]:
 - Requires all three criteria of Part A or 2/3 criteria of Part B:
 - Part A:
 - Clinical – focal seizures (\pm EPC) and unilateral cortical deficit(s)
 - EEG – unilateral hemispheric slowing \pm epileptiform activity and unilateral seizure onset
 - MRI – unilateral hemispheric focal cortical atrophy + at least one of the following:
 - Gray or white matter T2/FLAIR hyperintense signal
 - Hyperintense signal or atrophy of the ipsilateral caudate head
 - Part B:
 - Clinical – EPC or progressive unilateral cortical deficit(s)
 - MRI – progressive unilateral hemispheric focal cortical atrophy
 - Histopathology – T-cell-dominated encephalitis with activated microglial cells and reactive astrogliosis; numerous parenchymal macrophages, B cells or plasma cells, or viral inclusion bodies exclude the diagnosis of RE
- Treatment:
 - Hemispherectomy or hemispherotomy

- If high risk of postoperative functional deterioration: IVIg, plasmapheresis, steroids
- Rituximab or natalizumab

2.4.5.3 Refractory Status Epilepticus After a Febrile Illness

- Occur in previously healthy individuals
- Associated with high mortality
- No causative antibodies have been identified thus far
- FIREs (Febrile Infection-Related Epilepsy Syndrome)
- NORSE (New-Onset Refractory Status Epilepticus)
- AERRPS (Acute Encephalitis with Refractory Repetitive Partial Seizures)
 - Treatment – often respond better to immunotherapy and/or ketogenic diet

2.5 Diagnosis of Epilepsy

- As mentioned earlier, any of the following criteria can be used to diagnose epilepsy:
 - At least two unprovoked (or reflex) seizures occurring >24 h apart
 - One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
 - For instance, someone who experienced a first-time seizure and was found to have an epileptogenic lesion (i.e., FCD) thought to be the cause of the seizure qualifies for epilepsy
 - Diagnosis of an epilepsy syndrome
 - Although epilepsy is largely a clinical diagnosis, in some cases the EEG may be diagnostic of an epilepsy syndrome (i.e., 4–6 Hz polyspike and slow wave discharges in someone with history suggestive of JME)

2.6 Neuroimaging and Epilepsy [42]

- Neuroimaging is an essential part of the epilepsy workup and may assist with diagnosis, seizure etiology, prognosis, or guide further management/treatment

2.6.1 CT Imaging

- Mainly useful for the identification of acute blood (intracerebral hemorrhage, subarachnoid hemorrhage, subdural/epidural hematoma, etc.)
- CT may also detect subacute/chronic stroke, large tumors, and calcified neurocysticercosis

- According to the AAN recommendations, an emergency CT should be considered in patients presenting with seizure in the emergency department who have an abnormal neurologic examination, predisposing history, or focal seizure onset (Level B) [43]
- Other features that may warrant an urgent CT:
 - Recurrent seizures
 - Persistent altered mental status
 - Headache
 - Fever
 - Recent head trauma
 - Use of anticoagulation medication
 - History of malignancy, hydrocephalus, stroke, bleeding disorder, HIV, or immunosuppression

2.6.2 MRI

- All patients should have a 3-Tesla MRI
- Important part of presurgical evaluation
- Typical epilepsy protocol MRI studies include the following sequences:
 - Sagittal T1
 - Axial T1, T2, and FLAIR
 - Axial DWI (diffusion-weighted imaging)
 - Axial SWI (susceptibility-weighted imaging) or GRE (gradient-echo)
 - Coronal FLAIR
 - Coronal MPRAGE (magnetization-prepared rapid-acquisition gradient-echo)
 - Three-dimensional, high-resolution T1 sequence

2.6.2.1 Mesial Temporal Sclerosis (MTS)

- Mesial temporal lobe epilepsy is the most common surgically treatable epileptic syndrome
- MTS is the most common pathology associated with drug-resistant mesial temporal lobe epilepsy
- MRI features of MTS (Fig. 2.5):
 - Increased T2/FLAIR signal
 - Hippocampal atrophy – most specific for MTS
 - Loss of internal architecture

2.6.2.2 Focal Cortical Dysplasia (FCD) (Figs. 2.6 and 2.7)

- Causes refractory epilepsy in approximately 75%
- Patients with focal epilepsy and a non-lesional MRI are often suspected to have an undetected FCD
- MRI features of FCD type I:

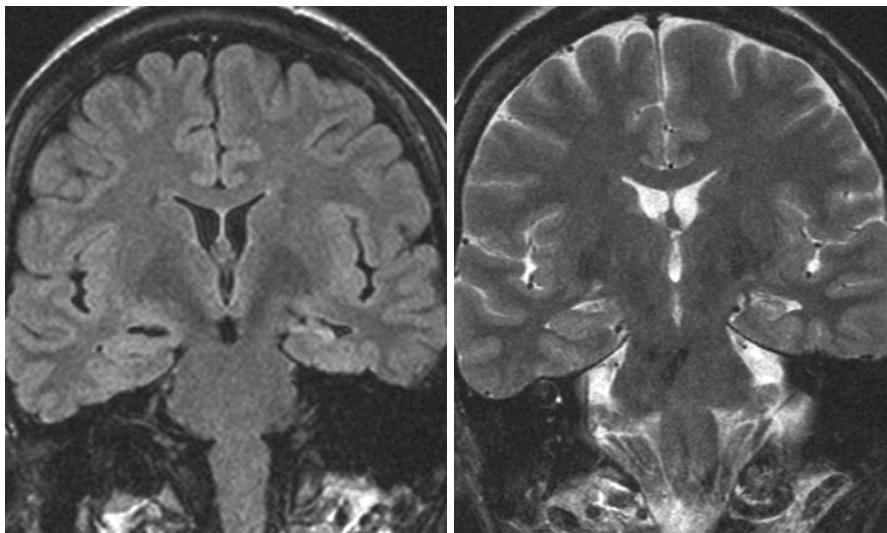


Fig. 2.5 Coronal FLAIR (left image) and T2 (right image) MRI images on a patient with left MTS. Note FLAIR signal changes and smaller hippocampal size on the left. (Image Courtesy of Dr. Anton Hasso)

- Thin cortex
- Blurring of the gray-white matter junction
- Subcortical white matter volume loss with ↑T2 and ↓T1 signal
- Abnormal sulcal or gyral patterns
- Lobar or hemispheric hypoplasia
- MRI abnormalities are more common in FCD type II and include:
 - Thick cortex
 - Blurring of the gray-white matter junction
 - Abnormal sulcal or gyral patterns
 - ↑T2/FLAIR signal in white matter underneath the FCD
 - Transmantle sign is seen in FCD type IIb:
 - Radially oriented T2 hyperintensity extending from the cortex to the ventricle

2.6.2.3 Brain Tumors

- Most common primary brain tumors associated with seizures: dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas, and diffuse low-grade gliomas
- Dysembryoplastic neuroepithelial tumors (DNETs) (Fig. 2.8):
 - Temporal > frontal cortex
 - Pseudocystic or multicystic “bubbly” appearance
 - Hypointense on T1, hyperintense on T2
 - No mass effect or edema
- Gangliogliomas:

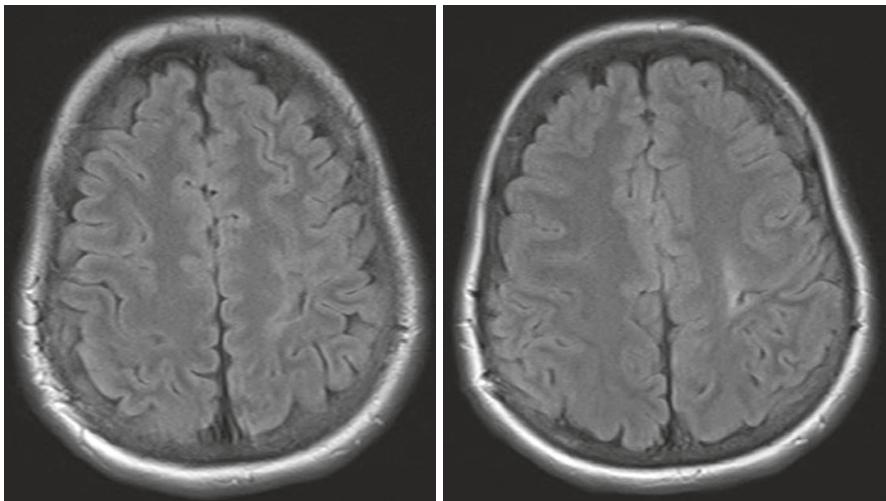


Fig. 2.6 Axial T2 FLAIR images of a 32-year-old woman with a history of drug-resistant epilepsy. Subtle asymmetric T2 hyperintensity with blurring of the gray-white differentiation and associated deep sulcus involving the left precentral gyrus suggests focal cortical dysplasia. (Image courtesy of Dr. Lilit Mnatsakanyan)

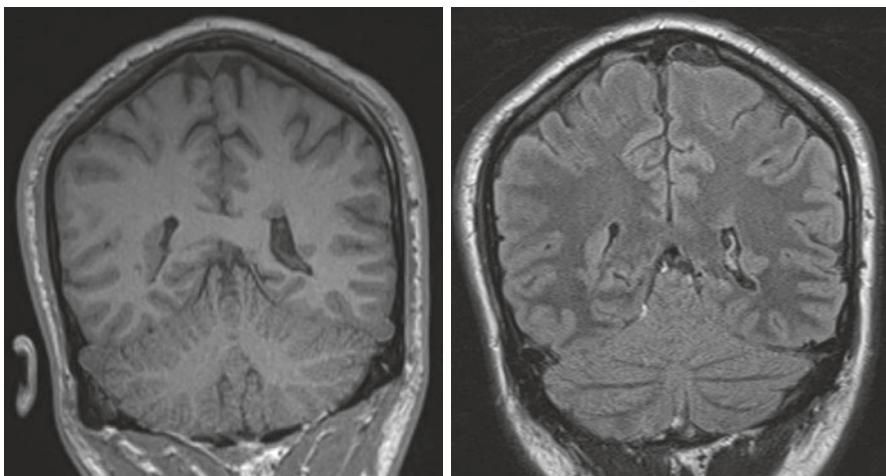


Fig. 2.7 Coronal T1 and T2 FLAIR images showing bilateral periventricular heterotopia in a 25-year-old man with drug-resistant epilepsy

- Temporal lobe
- Isointense to gray matter
- No mass effect
- Commonly has a cystic component
- Diffuse low-grade gliomas (grade II astrocytomas, oligoastrocytomas, oligodendrogiomas) (Fig. 2.9):

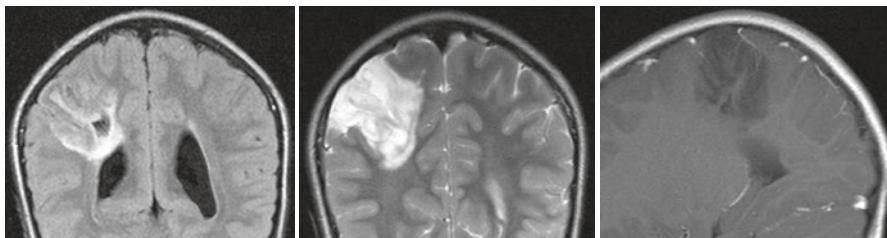


Fig. 2.8 MRI coronal FLAIR (left), coronal T2 (middle), and sagittal T1 post gadolinium (right) of a patient with epilepsy since age 5 and found to have a DNET. (Images courtesy of Dr. Anton Hasso)

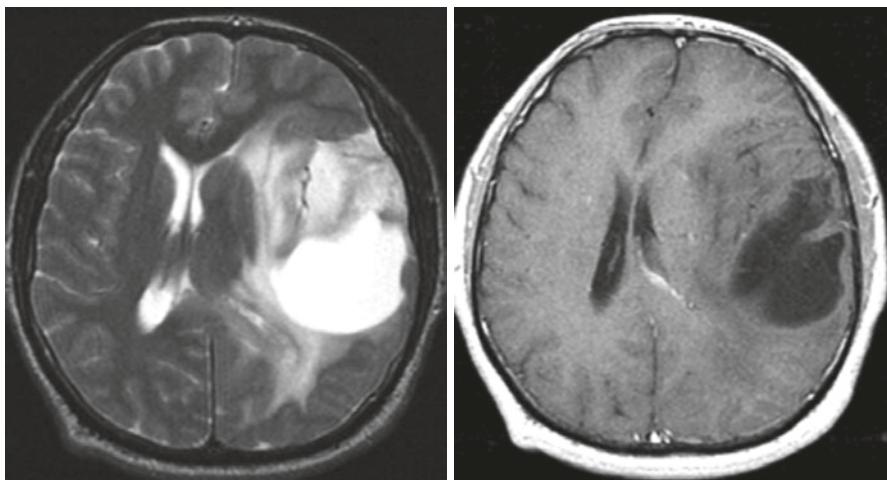


Fig. 2.9 MRI axial T2 and axial T1 post gadolinium in a 35-year-old with seizures, intermittent headaches, and speech difficulties representing a glioma. (Images courtesy of Dr. Anton Hasso)

- Hypointense on T1, hyperintense on T2
- May contain calcifications
- No mass effect or edema
- Typically do NOT enhance with gadolinium
- Meningiomas:
 - Important cause of seizures as resection is often curative [44]
 - However, new-onset seizures in patients without prior history of epilepsy have been described after meningioma resection [44]
 - MRI features:
 - Homogenous enhancement with gadolinium
 - Dural tail

2.6.2.4 Encephalomalacia

- Non-specific finding seen as a result of various insults
- Bifrontal or temporal pole involvement typically results from TBI

- Location in an arterial distribution is suggestive of a prior stroke
- Congenital strokes of all types are often associated with a porencephalic cyst (Fig. 2.10)

2.6.2.5 Vascular Malformations

- Cavernous hemangiomas (Cavernomas) (Fig. 2.11)
 - Most common vascular malformation associated with epilepsy
 - Seizures are thought to result from perilesional hemosiderin
 - “Popcorn” appearance
 - Resection is curative in approximately 75%
- Arteriovenous malformations (AVMs, Fig. 2.12)
 - Abnormal connection of arteries and veins without an intervening capillary bed
 - Tangle of flow voids on MRI
 - Sclerotic tissue adjacent or within the AVM will appear hyperintense on T2/FLAIR

2.6.2.6 CNS Infections

- Neurocysticercosis (Fig. 2.13)
 - MRI findings vary according to the stage of the parasite
 - Vesicular stage – Scolex; thin-walled cyst with fluid isointense to CSF
 - Colloidal vesicular stage – Ring-enhancing lesion with surrounding edema
 - Calcified nodule – better seen on CT; on MRI, appears hypointense on T1 and T2

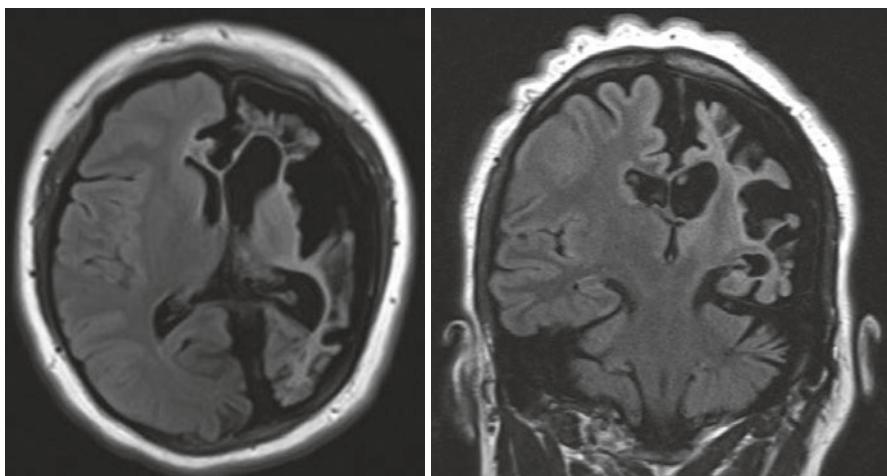


Fig. 2.10 MRI T1 axial (left) and coronal (right) images of a patient with drug-resistant focal epilepsy and history of congenital stroke. Note dilatation of the left lateral ventricle (ex-vacuo hydrocephalus) as a result of brain atrophy

Fig. 2.11 MRI coronal T2 image of a 30-year-old man with a history of drug-resistant focal seizures with impaired awareness. Note right anterior temporal cavernoma with hypointense rim

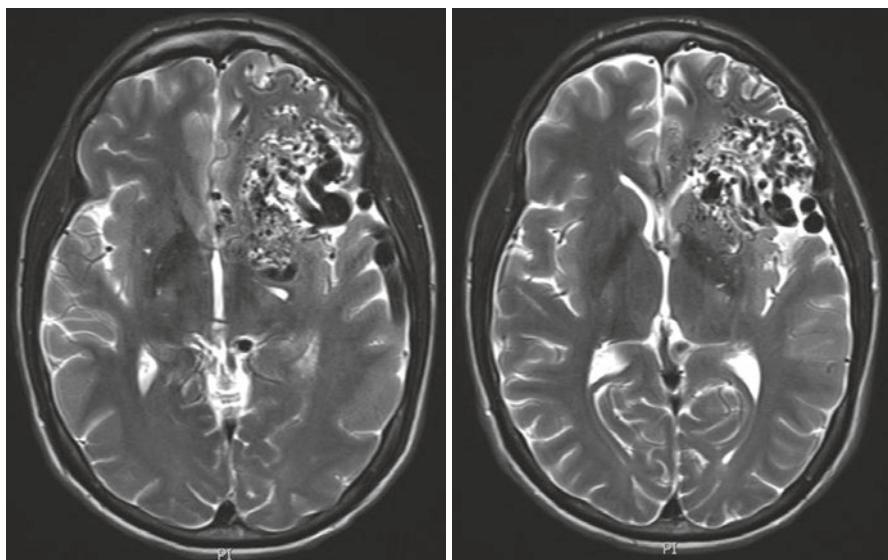
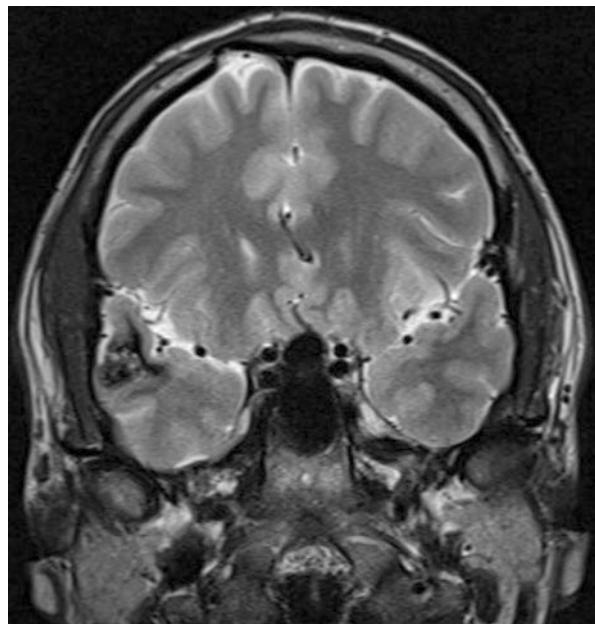


Fig. 2.12 MRI axial T2-weighted images in a 32-year-old man with focal epilepsy. Note the large left inferior frontal lobe arteriovenous malformation. Images courtesy of Dr. Lilit Mnatsakanyan

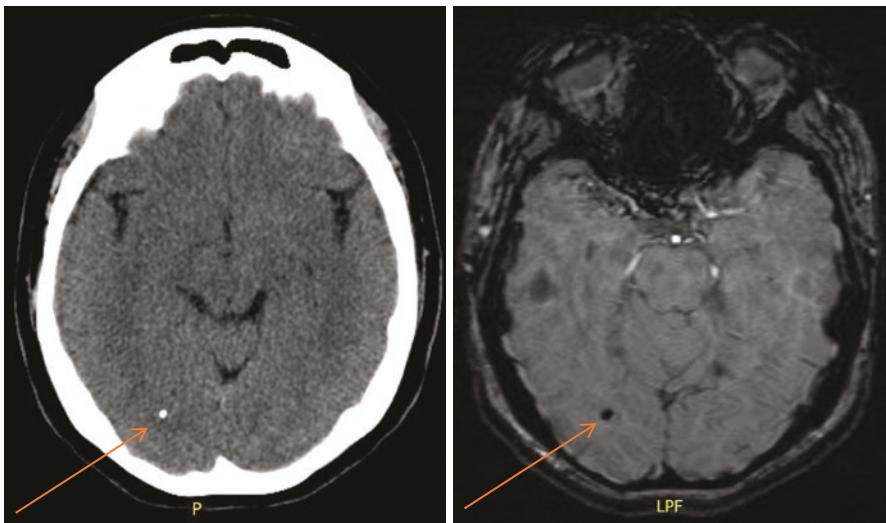


Fig. 2.13 CT head (left) and axial SWI MRI (right) images in a 36-year-old Hispanic woman showing a small calcification in the right occipital lobe likely representing sequela of remote neurocysticercosis

2.6.3 Other Imaging and Workup Prior to Epilepsy Surgery

- May identify an epileptogenic lesion or potential epileptogenic area, lateralize language and memory, and help predict surgical success
- Imaging factors associated with a better post-surgical outcome [45]:
 - Presence of mesial temporal sclerosis or tumor
 - Absence of focal cortical dysplasia or malformation of cortical development
 - Concordance of MRI and EEG

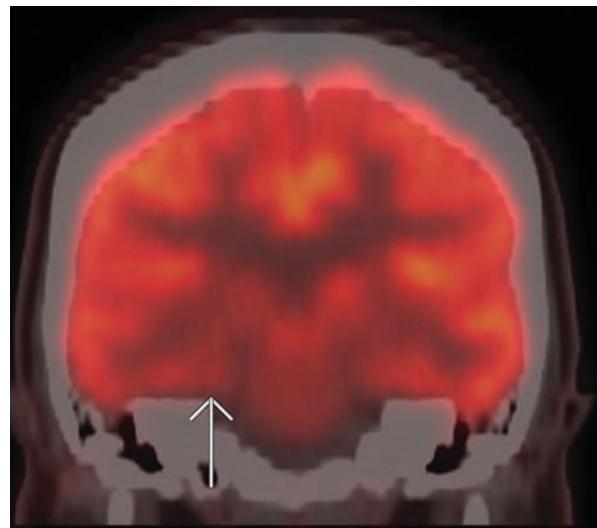
2.6.3.1 Positron Emission Tomography (PET)

- Most commonly utilizes FDG (18-Fluorodeoxyglucose), a radiolabeled glucose analogue, to measure the brain's metabolism of glucose
- Concomitant EEG is used to confirm an interictal study
- Interictal epileptogenic area is hypometabolic and usually larger than the epileptogenic zone
- Most reliable for temporal lobe epilepsy
- May demonstrate temporal hypometabolism in MRI negative hippocampal sclerosis (Fig. 2.14) [46]

2.6.3.2 Single-Photon Emission Computed Tomography (SPECT)

- Measures cerebral blood flow via a radiotracer
- Radiotracer is injected via an IV immediately after seizure onset
- Ictal activity is identified by region of increased cerebral perfusion

Fig. 2.14 Coronal PET-CT fused image of a 36-year-old woman with right mesial temporal lobe epilepsy showing hypometabolism in the right mesial temporal area



- Ictal SPECT is then compared to an interictal scan
- Successful localization improves with faster time to injection
- Localization of the epileptogenic zone may be improved by coregistering to MRI (Subtraction Ictal SPECT Coregistered to MRI or SISCOM) (Fig. 2.15)

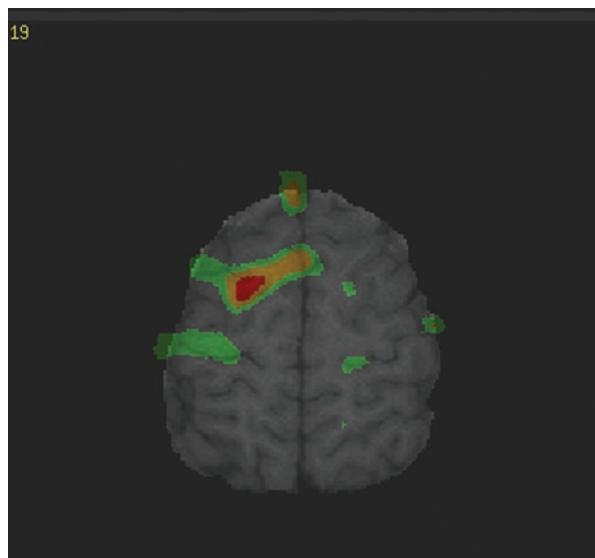
2.6.3.3 Wada Test (aka Intracarotid Amobarbital Procedure or IAP)

- Named after Dr. Juhn Wada
- Used for language and memory lateralization
- Injection of amobarbital into the internal carotid artery disrupts the ipsilateral hemisphere for 3–5 min
- EEG is used to confirm unilateral hemispheric suppression
- Patient is given language tasks, and if able to perform, language is lateralized to the hemisphere contralateral to the injection
- If the patient becomes aphasic after the injection, language is ipsilateral to the injection
- Memory is similarly tested by showing the patient several different items or pictures and then assessing their ability to recall items after the effect of amobarbital dissipates

2.6.3.4 Functional MRI (fMRI)

- Localizes functional areas by measuring changes in blood oxygen levels in response to various tasks
- Used for language >> memory lateralization
- May be used to localize sensorimotor cortex; however, mapping via direct cortical stimulation remains gold standard

Fig. 2.15 Subtraction Ictal SPECT Coregistered to MRI (SISCOM) in an 8-year-old boy with right frontal lobe epilepsy. Pathology after resection showed focal cortical dysplasia



2.7 Sleep and Epilepsy

- Sleep and epilepsy are reciprocally related, with each impacting the other
- Sleep effects epilepsy in several ways:
 - Cerebral hypersynchrony occurs in NREM sleep [47]
 - Both generalized and focal epileptiform discharges increase with increasing depth of NREM sleep
 - Sleep-related seizures most commonly occur during stage II sleep
 - REM sleep diminishes epileptic activity
 - Sleep deprivation also increases the yield of epileptiform discharges and precipitates seizures
 - The sleep wake cycle influences seizures and epileptiform discharges in various epilepsy syndromes [47]:
 - Seizures occur primarily upon awakening in:
 - Juvenile myoclonic epilepsy
 - Epilepsy with generalized tonic-clonic seizures on awakening
 - Epileptic spasms
 - Seizures occur primarily during sleep in:
 - Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
 - Benign childhood epilepsy with centrotemporal spikes (BECTS)
 - Tonic seizures of Lennox-Gastaut syndrome
 - Electrical status epilepticus in sleep (ESES) occurs when generalized spike-wave discharges occupy 85% or more of non-REM sleep and is seen in:
 - Continuous spikes and waves during sleep (CSWS) [48]:
 - Presents around the age of 5 with nocturnal focal motor seizures

- Progresses to an epileptic encephalopathy
 - Develop multiple seizure types including absence and atonic seizures
- Landau-Kleffner syndrome [49]:
 - Acquired epileptic aphasia
 - Language regression peaks around the age of 5–7 and begins with verbal auditory agnosia
 - Seizures occur in 70%
- Epilepsy has both direct and indirect effects on sleep:
 - Excessive daytime sleepiness (EDS), insomnia, and poor sleep quality are common in patients with epilepsy
 - EDS, defined as an Epworth Sleepiness Scale score ≥ 10 , is more common in epilepsy patients [50]
 - The number or type of AEDs, sleep-related seizures, seizure frequency, and type of epilepsy (focal vs. generalized) are not significant predictors of EDS
 - REM sleep is reduced by up to 50% on nights during which there is a nocturnal seizure [47]
 - Diurnal seizures reduce both REM and NREM sleep, the night after a seizure [47]
 - AEDs have various effects on slow wave sleep (SWS) and REM
- Obstructive sleep apnea (OSA) co-occurs with epilepsy:
 - OSA is a common disorder that affects approximately 24% of men and 9% of women [51]
 - The prevalence of OSA is higher in patients with epilepsy; approximately 33% of adults with epilepsy have OSA [52, 53]
 - OSA exacerbates seizures in elderly patients with epilepsy [54]
 - Several retrospective studies have shown that treatment of OSA with CPAP improves seizure control [55–59]
 - One study concluded that the improvement was independent of epilepsy type or severity [55]
 - A randomized pilot trial comparing therapeutic to sham CPAP showed a nonsignificant reduction in seizures with therapeutic CPAP but was under-powered [60]

2.8 Sudden Unexpected Death in Epilepsy (SUDEP) [61]

- Definitions [62]:
 - Definite SUDEP – Sudden, unexpected, witnessed or unwitnessed, nontraumatic, and non-drowning death that occurs in benign circumstances in an individual with epilepsy, with or without evidence for a seizure, and excludes documented status epilepticus, in which postmortem examination does not reveal a cause of death
 - Definite SUDEP plus – Death satisfying criteria for definite SUDEP, if a comitant condition other than epilepsy is identified before or after death, if the death might have been due to the combined effect of both conditions, and if

- autopsy or direct observations or recording of the terminal event did not prove the concomitant condition to be the cause of death
- Probable SUDEP or probable SUDEP plus – criteria as above, but without autopsy
 - According to the American Academy of Neurology/American Epilepsy Society Practice Guideline Summary [63]:
 - Clinicians *should* inform parents/guardians that in 1 year, SUDEP affects ~1 in 4500 children with epilepsy
 - Clinicians *should* inform adult patients that in 1 year, SUDEP affects ~1 in 1000 adults with epilepsy
 - For patients who continue to experience GTC seizures, clinicians *should* continue to actively manage therapies to reduce seizures and SUDEP risk
 - Clinicians *should* inform patients that seizure freedom, particularly from GTC seizures, is strongly associated with decreased SUDEP risk
 - For patients with frequent GTC seizures and nocturnal seizures, clinicians *may* advise, if permitted by their individualized epilepsy and psychosocial circumstances, to use nocturnal supervision or other nocturnal precautions, such as the use of a remote listening device, to reduce SUDEP risk
 - The major risk factor for SUDEP is the presence and frequency of GTC seizures [63]
 - There is a low level of evidence that other factors may alter SUDEP risk [63]:
 - Nocturnal seizures (\uparrow risk)
 - LTG use in women (\uparrow risk)
 - Never treated with an AED (\uparrow risk)
 - Number of AEDs used overall (\uparrow risk)
 - Extratemporal epilepsy (\uparrow risk)
 - Intellectual disability (\uparrow risk)
 - Male sex (\uparrow risk)
 - Anxiolytic drug use (\uparrow risk)
 - Heart rate variability (NOT associated with \uparrow risk)
 - Any specific AED (none associated specifically with \uparrow risk)
 - Most common in young adults (ages 20–45)
 - Usually follows a GTC seizure and occurs most often during sleep hours (04:00–08:00) with the person typically found in a prone position
 - Mechanism of SUDEP is not completely understood:
 - Likely results from a combination of postictal activation of sympathetic and parasympathetic systems, respiratory dysfunction, arousal failure, non-tachyarrhythmic cardiac dysfunction, and brainstem dysfunction
 - In the MORTEMUS study [64], the typical sequence of events was immediate postictal tachypnea, \pm transient sinus tachycardia followed by non-tachyarrhythmic (bradycardia, bigeminy, or irregular rhythm) cardiac dysfunction, then apnea, and finally asystole
 - Prevention of SUDEP:
 - Educate patients and caregivers about SUDEP
 - Modifiable risk factors:
 - Medication compliance
 - Sleepy hygiene and avoidance of sleep deprivation

- Minimizing alcohol consumption
- Postictal stimulation or oxygen administration may prevent PGES [65]
- Suggested, but unproven interventions to prevent SUDEP:
 - Rapid seizure recognition
 - Reposition patient from prone to lateral
 - Ensure nasopharynx and airway are unobstructed
 - Stimulation (tactile or auditory)
 - Suction and administer oxygen
 - Resuscitation
- Important to inform family and caregivers that rapid identification of seizures and resuscitation does not guarantee prevention of SUDEP

2.9 Driving and Epilepsy

- Each state has specific driving laws for people with epilepsy or other disorders with lapses of consciousness
- Certain states require the physician/surgeon to report such patients
- In most states, people with epilepsy may be eligible to drive if they have been seizure-free for 3–6 months

2.9.1 Commercial Driving [66]

- Section 391.41(b)(8) of Federal Motor Carrier Safety Regulations prohibits an individual with epilepsy from operating a commercial motor vehicle in interstate commerce
- People with epilepsy who have been seizure free and off antiseizure medication for 10 years may qualify to drive
- Patients may apply for an exemption to drive under certain conditions:
 - Epilepsy diagnosis: seizure-free for 8 years, on or off AEDs; if taking AEDs, medications must be stable for 2 years
 - Single unprovoked seizure: seizure-free for 4 years, on or off AEDs; if taking AEDs, medications must be stable for 2 years
 - Single-provoked seizure: provoking factor will be considered

2.9.2 Aircraft Pilots [67]

- People with epilepsy or history of an unexplained disturbance of consciousness are prohibited from operating an aircraft
- Certification may be possible if there is an identifiable cause and recurrence of loss of consciousness is unlikely
- In rare instances, the FAA may grant authorization for people who have outgrown an age-dependent epilepsy and are seizure-free for years off antiseizure medications

Take-Home Points

- In the 2017 ILAE Seizure Classification, seizures are named by onset (focal vs. generalized vs. unknown)
 - Simple partial seizures → focal aware seizure
 - Complex partial seizure → focal seizure with impaired awareness
 - Secondary generalized tonic-clonic seizure → focal to bilateral tonic-clonic seizure
- Ohtahara syndrome (EIEE) is characterized by tonic spasms with a continuous suppression-burst pattern on EEG
- Early myoclonic encephalopathy is characterized by myoclonic seizures with EEG showing a suppression-burst predominantly during *sleep*
- Suspect CDKL5 mutation in an infant with tonic seizures within the first 3 months with Rett-like features
- Gene mutation in Rett syndrome is MECP2
- Consider Unverricht-Lundborg disease in a patient from Finland with progressive myoclonic epilepsy
- Suspect sialidosis in a patient with PME and burning extremity pain
- Suspect neuronal ceroid lipofuscinosis in a patient with PME, vision loss, and rapidly progressive dementia
- Alpers syndrome (POLG1) often presents with convulsive status epilepticus; may see rhythmic high amplitude delta with superimposed polyspikes on EEG
- High α-amino adipic semialdehyde is seen in pyridoxine-dependent seizures and folinic acid-responsive seizures
- Suspect a urea cycle disorder in a neonate or infant that quickly develops cerebral edema and has hyperammonemia
- Elevated plasma very long chain fatty acids are seen in peroxisomal disorders (X-ALD, AMN, Zellweger syndrome)
- Suspect Zellweger syndrome in a neonate or infant with large fontanels, chondrodyplasia punctata, and polymicrogyria
- DCX gene mutation leads to subcortical band heterotopia (females) and lissencephaly (males)
- MRI features of MTS include increased T2/FLAIR signal, hippocampal atrophy, and loss of internal architecture
- Hippocampal sclerosis (HS) type 1 is characterized by severe neuronal loss and gliosis in CA1 and CA4 regions
- HS type 2 is characterized by CA1 predominant neuronal loss and gliosis
- HS type 3 is characterized by CA4 predominant neuronal loss and gliosis
- Slow-growing tumors tend to be more epileptogenic (DNET, ganglioglioma, low-grade astrocytoma)
- Features suggestive of autoimmune epilepsy:
 - Onset with status epilepticus or several seizures
 - Onset after age of 30

- Signs of limbic encephalitis (cognitive decline, behavioral disturbance, temporal lobe seizures)
- Early drug resistance
- ↑ T2/FLAIR signal changes or swelling in mesial temporal region or B/L mesial temporal abnormalities
- History of an autoimmune disease
- Rasmussen encephalitis (RE) is a triad of progressive unilateral cortical atrophy, refractory seizures, and progressive neurological impairment
- Suspect anti-NMDAR encephalitis in a young woman with psychosis, seizures, catatonia, and orofacial dyskinesias
- Suspect anti-AMPA (GluR1 or GluR2 subunits) in an elderly woman with new onset epilepsy and psychiatric symptoms
- Suspect anti-mGluR5 in a patient with limbic encephalitis and Hodgkin lymphoma
- Poorly controlled GTC seizures (primary or secondary) is the biggest risk factor for SUDEP

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Treatment of Seizures

3

3.1 Choosing Seizure Medications

- In order to choose an appropriate antiepileptic drug (AED), several factors must be considered
- Identifying the type of epilepsy (focal vs. generalized) is typically the first step
 - Narrow spectrum AEDs are indicated for focal epilepsies and may exacerbate genetic generalized epilepsies
- For patients with drug-resistant epilepsy, several factors must be taken into consideration when selecting a combination of AEDs (rational polytherapy):
 - Mechanism of action
 - Choosing AED regimens with different mechanisms of action may be more effective and could avoid compounding adverse effects
 - Safety and tolerability
 - Pharmacokinetics
 - Potential treatment of other comorbidities

3.2 Antiepileptic Drugs (AEDs) [1]

- Mechanism of Epileptic Seizures (Fig. 3.1)
 - Too little inhibition
 - Ionic: outward K⁺ and inward Cl⁻ currents
 - Neurotransmitter: GABA
 - Too much excitation
 - Ionic: Inward Na⁺ and Ca⁺⁺ currents
 - Neurotransmitter: Glutamate aspartate
 - When the factors that enhance the excitatory postsynaptic potential (EPSP) work stronger than those that enhance the inhibitory postsynaptic potential (IPSP), seizure happens (Fig. 3.1)
- AEDs act to decrease excitation or increase inhibition of the brain



Fig. 3.1 Seizure control is achieved by balance between the factors that influence the excitatory postsynaptic potential (EPSP) and those that influence inhibitory postsynaptic potential (IPSP)

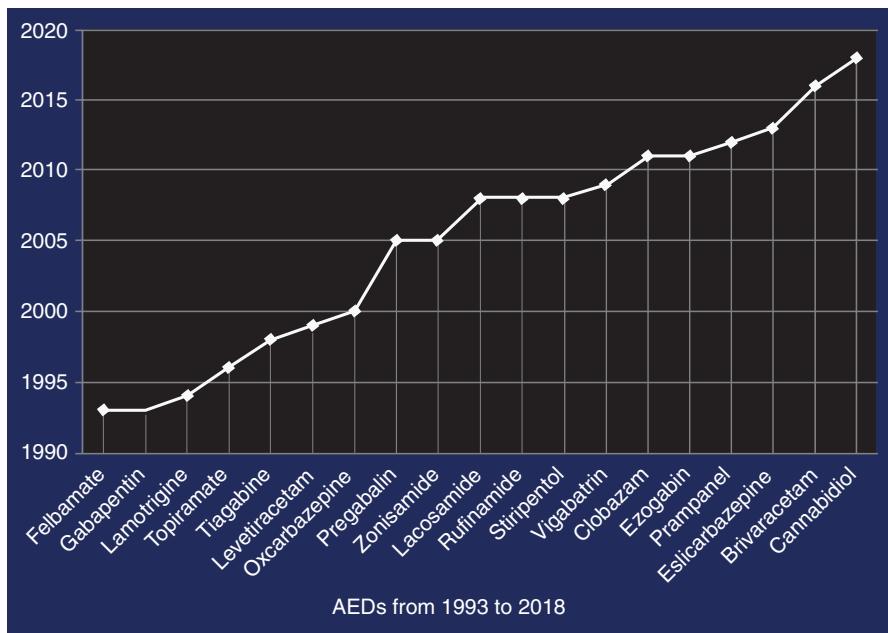


Fig. 3.2 Timeline of approval of new antiepileptic drugs (AEDs) between 1993 and 2018. Stiripentol used for Dravet syndrome is not commercially available in the USA and has orphan drug designation status

- Enhancing inhibitory neurotransmitters
- Inhibiting neuroexcitatory transmitters
- Acting at specific receptors in the brain
- There have been many new AEDs approved by the FDA since the early 1990s (Fig. 3.2)
- Mechanisms of antiepileptic drugs
 - There are at least eight mechanisms of action identified for AEDs which are summarized in Table 3.1
- Blocking voltage-gated sodium channels

AED	Na ⁺ channel blockage	binds α-2-δ subunit of VGCC	T-type Ca ²⁺ current blockage	GABA augmentation	Glutamate/AMPA inhibition	Carbonic anhydrase inhibition	SV2A binding	K ⁺ channel opener
Benzodiazepines								
Brivaracetam								
Carbamazepine	+							
Esketamine	+							
Ethosuximide		+						
Ezogabine								
Felbamate	+							
Gabapentin		+						
Jacobsenamide	+ ^a							
Lamotrigine	+							
Levetiracetam							+	
Oxcarbazepine	+							
Phenobarbital	+							
Phenytoin	+							
Pirampanel								
Pregabalin		+						
Rufinamide	+							
Stiripentol					+ ^{c,g}			
Tiagabine					+ ^d			
Topiramate	+				+ ^f			
Valproic acid	+ ^b				+			
Vigabatrin					+ ^e			
Zonisamide	+				+			

^aEnhances slow inactivation of Na channels
^bValproic acid at high concentration has Na⁺ channel blocking effect
^cDirect effect on GABA_A receptors

^dAntagonizing GABA reuptake
^eInterfering with breakdown of GABA

^fSite of GABA receptor action unknown

^gOrphan drug designation in US for Dravet syndrome

^bDiscontinued by manufacturer

- Blocking low threshold T-type Ca^{2+} currents
- Binding alpha-2-delta subunit of voltage-gated Ca channel (VGCC)
- Augmenting GABA inhibition
- Inhibiting glutamate/AMPA excitation
- Carbonic anhydrase inhibitors
- Synaptic vesicle protein 2A binding
- Potassium channel opening

3.2.1 When to Start Seizure Medication?

- In a study by Hauser and colleagues, 208 patients were followed after a first unprovoked seizure for a mean duration of 4 years [2]:
 - Seizures recurred in 64 patients
 - If no EEG or CT abnormalities:
 - Recurrence risk at 1 year: 14%
 - Recurrence risk at 3 years: 29%
 - Recurrence risk at 5 years: 34%
 - That means if we do not start seizure medication, there is a 66% chance that the patient will not have another unprovoked seizure
 - There is rationale to *start medication after a first seizure when:*
 - There is previous neurologic insult (risk increased 2.5 times)
 - A sibling has epilepsy
 - Generalized spike and wave/epileptiform abnormality on EEG
 - Acute symptomatic seizure (abnormal neuroimaging)

3.2.2 Broad-Spectrum AEDs Used in Generalized Epilepsy

- Benzodiazepines
- Felbamate
- Lamotrigine (may worsen myoclonic seizures)
- Levetiracetam
- Perampanel
- Rufinamide (Lennox-Gastaut Syndrome)
- Topiramate
- Valproic acid
- Zonisamide

3.2.3 AEDs Used for Focal Onset Epilepsy

- *All of the broad-spectrum AEDs plus:*
 - Carbamazepine
 - Eslicarbazepine

- Ezogabine
- Gabapentin
- Lacosamide
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pregabalin
- Tiagabine

3.2.4 AEDs Requiring Bloodwork/Therapeutic Drug Monitoring (TDM)

- Carbamazepine
 - CBC, Na⁺, TDM
- Lamotrigine
 - TDM (pregnancy, OCP)
 - Idiosyncratic reactions
- Oxcarbazepine/Eslicarbazepine
 - CBC, Na⁺
- Phenytoin
 - CBC, LFTs, TDM
- Topamax, Zonegran
 - Metabolic acidosis, TDM
- Valproic Acid/Felbamate
 - LFTs, CBC, TDM
 - Reticulocyte count for felbamate

3.2.5 AEDs with Serious Adverse Reactions

- Some AEDs may cause serious life-threatening adverse reactions (Table 3.2)
- There is an FDA warning for all AEDs regarding worsening depression and suicidal ideation
- *Perampanel* has a *black box warning* for severe psychiatric and behavioral reaction
- *Felbamate* has a *black box warning* for aplastic anemia and hepatic failure
- *Valproic acid* has a *black box warning* for hepatotoxicity (especially in mitochondrial disease), fetal risk of congenital malformation, and pancreatitis
- *Carbamazepine* has a *black box warning* for serious dermatologic reaction in people with HLA-B*1502 allele, aplastic anemia, and agranulocytosis

- *Phenytoin* has a *black box warning* for cardiovascular risk with rapid infusion
- *Lamotrigine* has a *black box warning* for serious rash including Stevens-Johnson syndrome (SJS)
- *Vigabatrin* has a *black box warning* for risk of permanent visual loss

3.2.6 AEDs with IV Formulation

- Benzodiazepines
- Brivaracetam
- Carbamazepine
- Depacon
- Lacosamide
- Levetiracetam
- Phenobarbital
- Phenytoin/Fosphenytoin

3.2.7 AEDs: Metabolic and Elimination Pathways

Hepatic

- Carbamazepine
- Clonazepam
- Ethosuximide
- Lamotrigine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Tiagabine
- Topiramate
- Valproate
- Zonisamide

Table 3.2 AEDs with life-threatening adverse reactions

Hepatic failure/ AHS/hematological	Status epilepticus	Pancreatic failure	Renal failure	Anhidrosis	Congestive heart failure
Carbamazepine	Rufinamide	Gabapentin	Ethosuximide	Topiramate	Pregabalin
Eslicarbazepine	Tiagabine	Valproic acid	Gabapentin	Zonisamide	
Ethosuximide			Pregabalin		
Felbamate					
Lamotrigine					
Oxcarbazepine					
Phenobarbital					
Phenytoin					
Valproic acid					

AHS – acute hypersensitivity reaction

Renal

- Gabapentin
- Lacosamide
- Levetiracetam
- Pregabalin
- Rufinamide
- Vigabatrin

3.2.8 Individual AED Summaries**Brivaracetam [3]**

- Indications – FDA approved as adjunctive therapy for focal onset seizures in adolescents and adults 16 years of age and over
- Mechanism of action – highly selective SV2A ligand resulting in ↓ neurotransmitter release
- Pharmacokinetics – hepatic and extrahepatic hydrolysis
- Half-life – 9 h
- Adverse effects – somnolence, dizziness, fatigue, headache

Carbamazepine (CBZ)

- Indications – focal or GTC seizures; trigeminal neuralgia, mood stabilization (also used in bipolar disorder)
- Mechanism of action – Na^+ channel inhibitor, prolongs the fast inactivate state, ↓ high-frequency neuronal firing
- Pharmacokinetics – P450 enzyme inducer; hepatic metabolism; *auto-induction* occurs over the initial 2–4 weeks resulting in lower levels and shorter $\frac{1}{2}$ life
- Half-life – variable due to auto-induction; initially 25–65 h and 12–17 h with multiple doses
- Recommended therapeutic range – 4–12 mg/L
- Adverse effects – most are related to the active metabolite carbamazepine-10,11-epoxide; headache, dizziness, nausea, fatigue; hyponatremia; diplopia, blurred vision, nystagmus, tremor, and unsteadiness may occur with ↑ levels; aplastic anemia (~1 in 200,000), SJS, toxic epidermal necrolysis, and hypersensitivity syndrome (hepatic and renal dysfunction, fever, rash, eosinophilia, lymphadenopathy); with chronic use: decreased bone density and anemia
- Other – ↑ risk of SJS and toxic epidermal necrolysis in Asians with HLA-B1502 allele

Clobazam (CLB)

- Indications – generalized seizures
- Mechanism of action – GABA-A agonist; ↑ frequency of Cl^- channel opening
- Pharmacokinetics – hepatic metabolism; converted to *N*-desmethylclobazam (active metabolite)
- Half-life – 71–82 h (*N*-desmethylclobazam)

- Adverse effects – sedation, drowsiness (less likely than other benzodiazepines)
- Other – only 1,5-benzodiazepine (position of nitrogen); others are 1,4-benzodiazepines

Clonazepam (CLZ)

- Indications – generalized seizures
- Mechanism of action – GABA-A agonist; ↑ frequency of Cl⁻ channel opening
- Pharmacokinetics – hepatic metabolism; converted to inactive metabolite
- Half-life – 20–50 h
- Adverse effects – sedation, drowsiness (improves over time)
- Other – tolerance may develop

Eslicarbazepine Acetate (ESL)

- Converted into S-licarbazepine, the monohydroxy derivative of oxcarbazepine, and active metabolite
- Indications – focal seizures
- Mechanism of action – Na⁺ channel inhibitor
- Pharmacokinetics – hepatic metabolism; >50% is excreted in urine unchanged; weak inhibitor of CYP 2C19 (↑ PHT level at high doses) and weak inducer of CYP 3A4 (↓ effectiveness of OCPs at high doses)
- Half-life – 13–20 h (once daily dosing)
- Adverse effects – dose-related dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremors; hyponatremia in 1% of patients on 800 mg and 1.5% of patients on 1200 mg dose may have Na⁺ below 125 mEq/L

Ethosuximide (ESM)

- Indications – drug of choice for generalized absence seizures
- Mechanism of action – blocks T-type calcium channels
- Pharmacokinetics – hepatic metabolism
- Half-life – 30–60 h
- Recommended therapeutic range – 40–100 mg/L
- Adverse effects – dose-related GI upset, N/V/D, abdominal discomfort, anorexia, insomnia, drowsiness, and ataxia; headache, depression, psychosis, rash (including SJS), rare aplastic anemia, and autoimmune thyroiditis

Ezogabine (Retigabine): Discontinued by Manufacturer in 2017

- Indications – focal seizures
- Mechanism of action – K⁺ channel opener
- Pharmacokinetics – hepatic metabolism; ↑ clearance of lamotrigine
- Half-life – 7–11 h
- Adverse effects – bluish pigmentation of the retina, skin, and nails may occur with long-term use; blurred vision, tremor, confusion, dizziness, fatigue, and drowsiness, nausea

Felbamate (FBM)

- Indications – focal seizures and generalized seizures (Lennox-Gastaut syndrome)
- Mechanism of action – NMDA receptor antagonist, GABA enhancement, and Na⁺ channel inhibitor
- Pharmacokinetics – hepatic metabolism; CYP 2C19, 1A2 inhibitor (\uparrow levels of PHB, PHT, VPA, carbamazepine epoxide, warfarin); weak CYP 3A4 inducer (\downarrow CBZ level and OCP effectiveness)
- Half-life – 20–23 h
- Recommended therapeutic range – 40–100 ug/mL
- Adverse effects – GI upset, N/V, anorexia (ameliorated by administering with food) weight loss, insomnia, irritability; aplastic anemia (estimated risk of 1 in 5000–8000 patients); hepatic failure (estimated risk of 1 in 26,000–54,000 patients)
- Other – \uparrow risk of aplastic anemia in postpubertal females with autoimmune disease [4]; check CBC and LFTs prior to initiation of felbamate and then q2 weeks \times 6 months; both aplastic anemia and hepatic failure are unlikely to occur after 1 year

3.2.8.1 Gabapentin (GBP)

- Indications – adjunctive therapy for focal seizures; peripheral neuropathy, postherpetic neuralgia; restless legs syndrome (GBP encarbil)
- Mechanism of action – binds to the alpha-2-delta subunit of voltage-gated calcium channels, decreasing calcium entry and neurotransmitter release under hyperexcitable conditions
- Pharmacokinetics – eliminated unchanged in urine
- Half-life – 5–7 h
- Adverse effects – drowsiness, weight gain, peripheral edema, dizziness, ataxia, myoclonus
- Other – bioavailability decreases with increasing doses due to saturable transport system from the gut to the bloodstream

3.2.8.2 Lacosamide (LCM)

- Indications – focal seizures
- Mechanism of action – Na⁺ channel inhibitor that enhances *slow* inactivation; binds to CRMP-2 [5]
- Pharmacokinetics – hepatic metabolism; 40% is excreted in the urine unchanged
- Half-life – 13 h
- Adverse effects – PR prolongation; dose-dependent dizziness, fatigue, sedation, headache, N/V

3.2.8.3 Lamotrigine (LTG)

- Indications – focal seizures, generalized tonic-clonic seizures, Lennox-Gastaut syndrome, bipolar I disorder
- Mechanism of action – Na⁺ channel inhibitor; likely has other mechanisms given its broad-spectrum efficacy

- Pharmacokinetics – hepatic metabolism; clearance is significantly increased during pregnancy
- Half-life – 24 h (monotherapy), > 48 h with valproic acid, 13–14 h with an enzyme-inducing AED
- Recommended therapeutic range – 2–20 mg/L
- Adverse effects – dose-related insomnia, headache, dizziness, unsteadiness, tremor, blurred vision, diplopia, N/V, rash including SJS and toxic epidermal necrolysis (risk is ↑ with fast titration and co-administration with VPA), hypersensitivity syndrome
- Other – slow titration is required to ↓ risk of rash; may have a synergistic effect with VPA [6]

3.2.8.4 Levetiracetam (LEV)

- Indications – focal seizures, GTC seizures, generalized myoclonic seizures
- Mechanism of action – binds to SV2A (synaptic vesicle protein) resulting in ↓ neurotransmitter release under hyperexcitable conditions
- Pharmacokinetics – renally cleared; 66% is excreted in the urine unchanged
- Half-life – 6–8 h
- Adverse effects – irritability, depression, somnolence, fatigue, dizziness

3.2.8.5 Oxcarbazepine (OXC)

- Converted into licarbazepine, the monohydroxy derivative and active metabolite
- Indications – focal seizures
- Mechanism of action – Na⁺ channel inhibitor, ↓ high-frequency neuronal firing
- Pharmacokinetics – hepatic metabolism; weak inhibitor of CYP 2C19 (↑ PHT level at high doses), weak inducer of CYP 3A4 (↓ effectiveness of OCPs at high doses)
- Half-life – 8–10 h for licarbazepine
- Recommended therapeutic range – 15–35 mg/L (monohydroxy derivative)
- Adverse effects – higher risk of hyponatremia compared to CBZ (especially in elderly and with use of a diuretic), headache, drowsiness, fatigue, rash; diplopia, blurred vision, ataxia, and N/V may occur with ↑ levels
- Other – equally effective as CBZ with better tolerability; 25% cross-reactivity with CBZ

3.2.8.6 Perampanel (PER)

- Indications – focal seizures and GTC seizures
- Mechanism of action – noncompetitive AMPA antagonist
- Pharmacokinetics – hepatic metabolism; ↑ clearance of lamotrigine
- Half-life = 105 h (once daily dosing)
- Adverse effects – aggression and hostility (seen in up to 20%), headache, ataxia, dizziness, drowsiness, depression, nausea, weight gain, blurred vision
- Other – PER is effective as add-on therapy for treatment-resistant adult focal epilepsy (Level A evidence) [5]

3.2.8.7 Phenobarbital (PB)

- Indications – focal or GTC seizures
- Mechanism of action – GABA-A agonist; prolongs Cl⁻ channel opening
- Pharmacokinetics – P450 enzyme inducer; hepatic metabolism; ~25% is excreted in urine unchanged
- Half-life – 80–100 h
- Recommended therapeutic range – 15–40 mg/L
- Adverse effects – sedation, lethargy, depression; with chronic use: Dupuytren's contractures, decreased bone density
- Pregnancy – teratogenic: cardiac malformations, decreased cognitive abilities

3.2.8.8 Phenytoin (PHT)

- Indications – focal or GTC seizures
- Mechanism of action – Na⁺ channel inhibitor; prolongs the fast inactivate state, ↓ high-frequency neuronal firing
- Pharmacokinetics – P450 enzyme inducer; hepatic metabolism; *nonlinear kinetics* (after a certain concentration, increase in the dose results in a disproportionate rise in serum level)
- Half-life = 7–42 h
- Recommended therapeutic range = 10–20 mg/L
- Adverse effects – rash including rare SJS and toxic epidermal necrolysis, hypersensitivity syndrome (hepatic and renal dysfunction, fever, rash, eosinophilia, lymphadenopathy), ataxia, nystagmus, diplopia; with chronic use: cerebellar atrophy, gingival hyperplasia, hirsutism, peripheral neuropathy, decreased bone density, anemia
 - IV administration may cause hypotension, arrhythmias, phlebitis, purple glove syndrome, paresthesia
- Other – highly protein bound resulting in drug-drug interactions. Phenytoin free fraction increases with renal/hepatic failure, low protein states, pregnancy, and co-administration of other highly protein bound drugs. Check protein-free level in those circumstances (therapeutic concentration – 1–2 mg/L)

3.2.8.9 Pregabalin (PGB)

- Indications – adjunctive therapy for focal seizures; postherpetic neuralgia; neuropathic pain
- Mechanism of action – binds to the alpha-2-delta subunit of voltage-gated calcium channels, decreasing calcium entry and neurotransmitter release under hyperexcitable conditions
- Pharmacokinetics – eliminated unchanged in urine
- Half-life – 6 h
- Adverse effects – dizziness, drowsiness, weight gain, peripheral edema, myoclonus
- Other – PGB-IR is effective as add-on therapy for treatment-resistant adult focal epilepsy (Level A evidence) [5]

3.2.8.10 Primidone (PRM)

- Converted into phenobarbital and phenylethylmalonamide (PEMA)
- Indications – focal or GTC seizures; essential tremor
- Mechanism of action – GABA-A agonist; prolongs Cl⁻ channel opening
- Pharmacokinetics – P450 enzyme inducer; hepatic metabolism; ~25–50% is excreted in urine unchanged
- Half-life – 10–15 h (monotherapy); ~6–8 h with enzyme inducers
- Adverse effects – same as phenobarbital, but also causes an acute toxic reaction of dizziness, N/V, ataxia, drowsiness

3.2.8.11 Rufinamide (RUF)

- Indications – adjunctive treatment for Lennox-Gastaut syndrome (Level A evidence) [5]
- Mechanism of action – Na⁺ channel inhibitor, likely has other mechanisms given its broad-spectrum efficacy
- Pharmacokinetics – hepatic metabolism (hydrolysis); levels are significantly elevated by co-administration with VPA; weak inducer of CYP 3A4 (↓ CBZ level and effectiveness of OCPs at high doses); weak inhibitor of CYP 2E1, weak inducer of UDP-GT (uridine diphosphate glucuronyltransferase)
- Half-life – 6–10 h
- Adverse effects – *QT shortening*; headache, dizziness, drowsiness, N/V
- Other – bioavailability increases with food

3.2.8.12 Tiagabine (TGB)

- Indications – focal seizures
- Mechanism of action – GABA reuptake inhibitor
- Pharmacokinetics – hepatic metabolism
- Half-life – 7–9 h (monotherapy), 2–5 h with an enzyme-inducing AED
- Adverse effects – tremor, nervousness, depression, emotional lability, dizziness, fatigue
- Other – dose-related encephalopathy or *nonconvulsive status epilepticus* may occur even without a history of epilepsy

3.2.8.13 Topiramate (TPM)

- Indications – focal seizures, generalized tonic-clonic seizures, Lennox-Gastaut syndrome; migraine prophylaxis, off-label for bipolar disorder
- Mechanism of action – AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid)/kainate receptor antagonist, Na channel inhibitor, augmentation of GABA
- Pharmacokinetics – minimal hepatic metabolism; 70% is eliminated in the urine unchanged; weak inhibitor of CYP 2C19 (↑ PHT level at high doses), weak inducer of CYP 3A4 (↓ CBZ level & effectiveness of OCPs at high doses)
- Half-life – 21 h
- Adverse effects – cognitive slowing, word-finding problems, acute myopia, *secondary angle-closure glaucoma*, paresthesia, nephrolithiasis (occurs in <2%),

weight loss, drowsiness, fatigue, depression; hyperammonemia when co-administered with VPA, oligohydrosis, metabolic acidosis, hyperthermia

- Other – ↑ risk of birth defects, especially oral clefts

3.2.8.14 Valproic Acid (VPA)

- Indications – broad-spectrum; focal and generalized seizures (including myoclonic and absence); migraines, bipolar disorder
- Mechanism of action – Na channel inhibitor, blocks T-type calcium channels, GABA potentiation
- Pharmacokinetics – P450 inhibitor; hepatic metabolism
- Half-life – 13–16 h; 9 h in the presence of enzyme-inducing AEDs
- Recommended therapeutic range – 50–100 mg/L
- Adverse effects – GI upset, anorexia, N/V (ameliorated with extended-release preparation), thrombocytopenia, alopecia, weight gain, polycystic ovaries in women, peripheral edema, tremor, drowsiness, confusion; rare life-threatening pancreatitis and hepatotoxicity (↑ risk with polytherapy and young age; avoid if <3 years old)
- Pregnancy – ↑ risk of dose-related teratogenicity (major congenital malformations) as well as ↓ verbal IQ and autism in offspring
- Other – highly protein bound; co-administration with phenytoin will result in ↑ free levels due to competition for protein binding; may have a synergistic effect with LTG [6]

3.2.8.15 Vigabatrin (VGB)

- Indications – epileptic spasms associated with tuberous sclerosis; focal seizures
- Mechanism of action – irreversible GABA transaminase inhibitor
- Pharmacokinetics – renally cleared; weak inducer of CYP 2C19 (↓ PHT level at high doses)
- Half-life – 10.5 h (5–6 h in children)
- Adverse effects – permanent bilateral concentric visual field constriction in up to 30–40% (↑ risk with ↑ dose and longer duration of treatment); drowsiness, fatigue, irritability, psychosis, depression
- Other – use is limited by risk of permanent visual impairment

3.2.8.16 Zonisamide (ZNS)

- Indications – FDA approved as adjunctive therapy for focal seizures; however, it is considered a broad-spectrum AED
- Mechanism of action – Na⁺ channel inhibitor, blocks T-type calcium channels, weak carbonic anhydrase inhibitor
- Pharmacokinetics – hepatic metabolism
- Half-life – 60 h (once daily dosing)
- Recommended therapeutic range – 10–40 mg/L
- Adverse effects – nephrolithiasis (up to 4% of patients) dizziness, sedation, weight loss, anorexia, irritability, fatigue, nausea, cognitive slowing (high doses), oligohydrosis, metabolic acidosis, hyperthermia; rare depression, psychosis, rash including SJS and toxic epidermal necrolysis

3.2.9 Definition and Treatment of Status Epilepticus (SE)

- SE is a neurological emergency with mortality estimates of 7.6%–39%; mortality rate is lower in children (<15 y/o) ~ 3% [7]
- The incidence of generalized convulsive SE is about 6.2 per 100,000 [7]
- Until recently, generalized convulsive status epilepticus (in people over the age of 5) was defined as a continuous seizure lasting ≥5 min or ≥2 seizures without an intervening return to baseline [8]
- The ILAE revised the definition of status epilepticus to be “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It is a condition that can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.” [9]
- The operational dimensions (time t_1 and t_2) are variable and depend on the type of status epilepticus (Table 3.3)
 - Time (t_1) indicates the time after which a seizure is likely to continue and therefore when treatment should be initiated
 - Time (t_2) indicates the time of continuous seizure activity beyond which long-term sequelae may occur
- The ILAE also proposed a diagnostic classification of SE with four axes [9]
 - Semiology
 - With prominent motor symptoms
 - Convulsive SE – further subdivided into generalized, focal onset to bilateral convulsive SE or unknown
 - Myoclonic SE – with or without coma
 - Focal motor SE – epilepsia partialis continua (EPC), etc.
 - Tonic SE
 - Hyperkinetic SE
 - Without prominent motor symptoms (nonconvulsive SE or NCSE)
 - NCSE with coma
 - NCSE without coma – further subdivided into generalized (typical/atypical/myoclonic absence status), focal, or unknown
 - Etiology
 - Known (symptomatic) – toxic/metabolic, structural, infectious, inflammatory, or genetic
 - Unknown (cryptogenic)
 - EEG correlates – the following are used to describe the electrographic patterns:
 - Location – generalized, lateralized, bilateral independent, multifocal

Table 3.3 Time that emergency treatment of status epilepticus should be initiated (t_1) and when long-term consequences may occur (t_2) [9]

Type of status epilepticus	Time t_1	Time t_2
Tonic-clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min	Unknown

- Name of the pattern – spike/sharp and wave plus subtypes, periodic discharges, rhythmic delta activity
- Morphology
- Time-related features – onset (sudden vs. gradual), dynamics (evolving, fluctuating, or static), frequency, duration, etc.
- Modulation – stimulus-induced vs. spontaneous
- Effect of medication on EEG
- Age
 - Neonatal (<30 days)
 - Infancy (1 month to 2 years)
 - Childhood (>2–12 years)
 - Adolescence and adulthood (>12–59 years)
 - Elderly (≥ 60 years)

3.2.9.1 Subtypes of SE

- *Established SE* – status epilepticus that persists despite appropriate treatment with benzodiazepines
- *Refractory SE* – status epilepticus that continues despite appropriate treatment with first-line (benzodiazepines) and second-line (IV AEDs) medications
- *Superrefractory SE* – “status epilepticus that continues 24 h or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia” [10]

3.2.9.2 Nonconvulsive Status Epilepticus (NCSE)

- NCSE requires a high index of suspicion as there may no, or only subtle, motor phenomena
- EEG is required for diagnosis and should be considered in any patient with an unexplained disturbance of consciousness, especially those with acute structural brain lesions (intracranial hematoma, trauma, tumor, etc.) [11]
- The prevalence of NCSE varies across studies due to variations in patient population and scenarios during which EEGs were obtained
 - Claassen et al. showed that 10% of patients who underwent continuous EEG monitoring for evaluation of unexplained decreased level of consciousness or to rule out subclinical seizures were found to have NCSE [12]
 - Towne et al. demonstrated that 8% of comatose patients were found to have NCSE [13]. Of note, the majority (42%) of the patients in that study who had NCSE had hypoxia/anoxia as the underlying etiology [13]
- NCSE may persist after convulsive SE is controlled
 - In one study, 48% of patients had persistent electrographic seizures, and 14% were found to have NCSE after convulsions stopped [14]

3.2.9.3 Diagnosis of NCSE

- The Salzburg Criteria, which were developed by a panel of experts at the fourth London-Innsbruck Colloquium on Status Epilepticus in 2013, are highly accurate (sensitivity 97.7%, specificity 89.6%, positive predictive value 84%, negative predictive value 98.6%) in diagnosing NCSE [15]

Salzburg Criteria for Diagnosis of NCSE [16, 17]

- Without history of epileptic encephalopathy
 - Epileptiform discharges (EDs) >2.5 Hz (>25 EDs per 10s epoch)
 - EDs \leq 2.5 Hz or rhythmic delta/theta activity >0.5 Hz *and* 1 of the following:
 - EEG *and* clinical improvement after IV AED
 - Subtle clinical ictal phenomena during the above EEG patterns
 - Spatiotemporal evolution
 - Incrementing onset (\uparrow in voltage and change in frequency), or evolution in pattern (change in frequency $>$ 1 Hz or change in location), or decrementing termination (voltage or frequency)
- History of epileptic encephalopathy
 - \uparrow in prominence or frequency of the above features compared to baseline *with* observable change in clinical state
 - EEG *and* clinical improvement after IV AED
- Possible NCSE
 - EEG improvement without clinical improvement
 - Fluctuation without definite evolution

3.2.9.4 Treatment of NCSE

- It is unclear whether NCSE in humans causes neuronal damage as seen in convulsive SE and in animal models of limbic SE [18, 19]
- Typical absence SE [20]
 - IV lorazepam 4 mg or diazepam 10 mg; may repeat dose after 10 min if seizures persist
 - IV valproic acid 25–45 mg/kg bolus or IV phenobarbital 20 mg/kg bolus
- Atypical absence SE [20]
 - Same treatment as absence SE, but may not respond to benzodiazepines and therefore may require additional VPA or PB
- Focal NCSE with impaired awareness [20, 21]
 - Trial of first-line therapy, and if necessary, second-line therapy as used in convulsive SE (see below)
 - IV anesthetics may be used if refractory NCSE develops
 - However, anesthetics should be used with caution as the treatment may be more harmful than continued nonconvulsive seizure activity and since focal NCSE typically has a favorable outcome without permanent neurological or neuropsychological sequelae
- An aggressive approach may be warranted for NCSE in coma [18]
 - Trial of IV AEDs after excluding drug intoxication
 - With intoxications, AEDs may cause further detrimental sedation and should be used cautiously
 - Coma with generalized epileptiform discharges is less ominous with intoxications, and return to baseline is possible
 - Due to the risks of AEDs including potentially harmful sedation, AEDs should only be continued if they result in BOTH electrographic and clinical improvement

- The role of anesthesia to achieve burst suppression in refractory NCSE is questionable as continuous epileptiform discharges may have minimal to no harm on the brain

3.2.9.5 Treatment of Convulsive Status Epilepticus

- Appropriate treatment of SE (Fig. 3.3) should be initiated immediately and reduces both morbidity and mortality [22]
- Always check ABCs (airway, breathing, circulation) first
- Be prepared to intubate as respiratory dysfunction and/or depression may occur as a result of SE or treatment
- The most common treatment-related adverse events include hypotension, respiratory depression, and cardiac rhythm disturbance
- Continuous EEG monitoring is necessary
- First-line treatment – Benzodiazepines
 - IM midazolam, IV lorazepam, and IV diazepam are established as effective [23]
- Second-line treatment – IV AEDs
 - No class I evidence to support one AED over another [23]
- Third-line treatment
 - No clear evidence to guide therapy
 - Treatment options include anesthetic doses of propofol, midazolam, pentobarbital, or thiopental with titration to burst suppression or repeating second-line treatment [23]
 - Two high-dose, non-GABAergic AEDs should be continued [10]
 - Options include levetiracetam, lacosamide, topiramate, and pregabalin
 - After a minimum of 12 h of seizure control, the infusion may be slowly titrated down over another 12 h

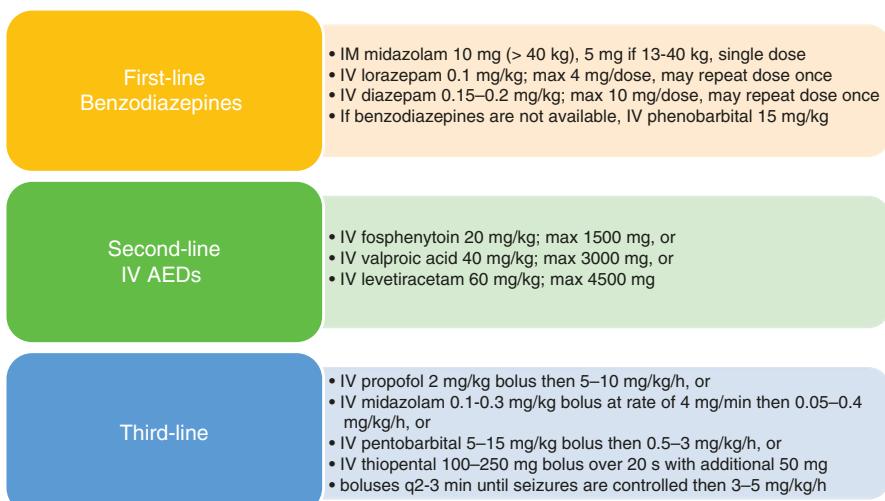


Fig. 3.3 Treatment of convulsive SE

- If seizures recur during this period, the infusion should be titrated back to burst suppression for another 12 h
- Longer durations of anesthesia (typically 24–48 h, up to 5 days) should be tried if status again recurs with weaning [10]
- Compared to first-line therapy, second-line therapy is less effective, and third-line therapy is even less effective
- With prolonged seizures, there is a decrease in the number of activated GABA-A receptors, while the number of NMDA receptors increase, which may in part explain the decreased effectiveness of third-line therapy [24]

3.2.9.6 Super-refractory Status Epilepticus

- No randomized controlled trials to guide treatment
- Some evidence to support the use of ketamine, a noncompetitive NMDA receptor antagonist, in refractory and superrefractory SE [10, 24]
 - IV ketamine 1–3 mg/kg bolus followed by continuous infusion of 0.6–10 mg/kg/h (titrated to burst suppression)
 - Unlike other anesthetics, ketamine does not cause cardiorespiratory depression or hypotension
- Other treatment options are based on very limited evidence [10]
 - No evidence to guide which to try first or to support one therapy over another
 - IV magnesium 2–6 g/h for a goal serum level of 3.5 mmol/l
 - No major risks although PR prolongation and hypotension may occur
 - May enhance respiratory depression if co-administered with benzodiazepines or barbiturates
 - Caution if co-administered with calcium channel blockers or digoxin
 - Immunological therapy
 - Based on possibility of an autoimmune/immunological etiology (i.e., anti-NMDAR encephalitis) as well as the possibility that inflammation results in epileptogenesis
 - Recommended in patients without a history of epilepsy or identified etiology
 - High-dose steroids (1 g/day in adults) × 3 days followed by 1 mg/kg/d × 1 week, then continued if there is a response
 - IVIg 0.4 g/kg/d × 5 days
 - Plasmapheresis
 - Ketogenic diet
 - Contraindicated with pyruvate carboxylase and β -oxidation deficiencies
 - Hypothermia
 - Target temperatures between 32 °C and 35 °C and continued in the first instance for 24–48 h
 - Emergency neurosurgery
 - Can be considered if a lesion is identified as the etiology of SE
- IV pyridoxine 180–300 mg/d can be tried in young children
 - Small risk of anaphylaxis with Pabrinex®

3.2.9.7 Prognosis of SE

- Outcome after SE depends on etiology, age, and depth of coma at presentation [7, 25]
- In refractory and superrefractory SE, approximately half result in either death or a severe neurological deficit (35% and 13%, respectively), while 1/3 recover to baseline [10]
- Epidemiology-based mortality score in SE (EMSE) can be used to predict poor outcome (death in hospital) [26] and 30-day morbidity [27]
 - Based on four parameters which are scored based on published mortality rates; for example, stroke as the etiology of SE is given a score of 26 points which is derived from a study which reported a mortality rate of 25.6% for stroke
 - Etiology – only 1 etiology is scored
 - SE resulting from alcohol abuse or low AED levels is associated with a relatively good prognosis [7, 26]
 - Anoxia portends the worst prognosis [7, 26]
 - Age – ↑ age is assigned more points
 - Comorbidity – sum of each morbidity score
 - EEG – only the worst EEG pattern is scored
 - Spontaneous burst suppression – 60 points
 - After status ictal discharges (ASIDs), LPDs, or GPDs – 40
 - No ASIDs, LPDs, or GPDs – 0
 - EMSE score ≥ 64 is associated with a poor outcome
 - In the prediction of death, the negative predictive value (NPV) of EMSE-64 ranges from 97.5% to 100%, while the positive predictive value (PPV) is only 59.8–68.8% [26, 27]
 - EMSE score < 64 predicts a high likelihood of survival
 - In the prediction of clinical worsening at 30 days post-SE, as measured by modified Rankin Scale (mRS), the PPV of EMSE-64 is 87.8%, while the NPV is 71.3% [27]

3.2.10 Treatment of Specific Epilepsy Syndromes

- Specific therapies are indicated for various syndromes as discussed in detail below and summarized in Table 3.4

3.2.10.1 Epileptic Spasms/West Syndrome

- May still be referred to as infantile spasms during that age
- Etiology is identified in >70% [28]
 - Malformations of cortical development
 - Hypoxic-ischemic encephalopathy
 - CNS infection
 - Genetic
 - Metabolic
 - Neurocutaneous syndromes

Table 3.4 Treatment of epilepsy syndromes

Syndrome	Treatment
Metabolic disorders	See Chap. 2, Table 2.2
Dravet syndrome [45] (SMEI)	First-line: clobazam, valproic acid Other: CBD, topiramate, levetiracetam, ketogenic diet, VNS
Epileptic spasms (infantile spasms)	First-line: ACTH Second-line: VGB
Lennox-Gastaut syndrome	Broad-spectrum AEDs Drop attacks: felbamate, LTG, topiramate, rufinamide, corpus callosotomy, add-on CBD Other: VNS, ketogenic diet
Childhood absence epilepsy	First-line: ethosuximide Other: VPA is equally effective but causes ↑ attentional deficits; LTG is less effective
Juvenile absence epilepsy	Broad-spectrum AEDs ± ethosuximide
Juvenile myoclonic epilepsy	First-line: VPA (except in women of childbearing age) LTG or levetiracetam for young women Other: broad-spectrum AEDs

SMEI Severe Myoclonic Epilepsy of Infancy

- Onset is typically between 4 and 8 months
- Spasms consist of brief flexion (less commonly extension) of the neck, trunk, and/or extremities
- Typically occur in clusters upon awakening
- EEG
 - Hypsarrhythmia [29] – chaotic background with multifocal, very high amplitude spikes, and slow waves
 - Variations known as modified hypsarrhythmia also exist [30]
 - Electrodecrement immediately follows each spasm
- West syndrome
 - Triad of epileptic spasms, hypsarrhythmia, and intellectual disability
- Often evolves into Lennox-Gastaut syndrome
- Treatment
 - Should be started immediately as earlier treatment may improve long-term cognitive outcomes [31]
 - High-dose ACTH is generally considered first-line treatment, but there is insufficient evidence to recommend the optimum dosage and duration of treatment [32]
 - Low-dose ACTH should be considered as an alternative to high-dose ACTH [31]
 - Vigabatrin (VGB) may also be used in the treatment of infantile spasms in patients with and without tuberous sclerosis complex (TSC) [31, 32]
 - Serial ophthalmological exams are required due to potential retinal toxicity
 - ACTH may be preferred over VGB in infants with cryptogenic infantile spasms as it may improve developmental outcome [31]

3.2.10.2 Lennox-Gastaut Syndrome (LGS) [33]

- Severe epileptic encephalopathy characterized by triad of multiple seizure types (*tonic*, atonic, atypical absence; less frequently myoclonic, focal, or GTC), slow spike and wave (2–2.5 Hz) complexes, and cognitive dysfunction
- Onset occurs prior to 8 years of age (peak 3–5 years)
- Etiology can be symptomatic (70%) or cryptogenic (30%)
- Often develops after infantile spasms/West syndrome
- Generalized paroxysmal fast activity (≥ 10 Hz) lasting a few seconds is commonly seen during slow wave sleep
- Treatment
 - Seizures are drug-resistant and require a combination of broad-spectrum AEDs
 - Epidiolex (cannabidiol) [CBD] oral solution is FDA approved for the treatment of seizures associated with LGS and Dravet syndrome, in patients 2 years of age and older
 - CBD is effective in treatment of drop seizures [34]
 - Low-dose benzodiazepines can be effective against all seizure types
 - Clobazam may be preferred (lower sedative effect)
 - Felbamate, lamotrigine, topiramate, and rufinamide are effective against drop attacks
 - Other options to consider:
 - Corpus callosotomy for drop attacks
 - Vagus nerve stimulation (VNS) reduces all seizure types including atonic seizures
 - Ketogenic diet

3.2.10.3 Childhood Absence Epilepsy (CAE) [35]

- Onset 4–8 years of age (peak 6 years)
- Multiple (dozens to 100s) daily absence seizures in otherwise normal children
- Absence seizures consist of behavioral arrest, staring, impaired awareness, \pm eyelid fluttering and upward eye deviation; oral automatisms may also occur
 - Duration is usually <10 s
- EEG
 - Generalized 3 Hz spike and wave discharges
 - Discharges are elicited by hyperventilation in 95%
 - Occipital intermittent rhythmic delta activity (OIRDA) is seen in up to 70% and may be notched in appearance
- Treatment [36, 37]
 - Ethosuximide (first-line)
 - VPA is equally as effective as ethosuximide but causes \uparrow attentional deficits; LTG is less effective

3.2.10.4 Juvenile Absence Epilepsy [35]

- Onset 10–17 years of age (peak 10–12 years) [38]
- Absence seizures are less frequent than in CAE
- Infrequent GTC seizures may occur upon awakening

- Mild myoclonic jerks occur in approximately 20%
- EEG
 - Generalized 3–4 Hz spike and wave discharges
 - Discharges are activated by hyperventilation
- Treatment
 - Broad-spectrum AEDs ± ethosuximide

3.2.10.5 Juvenile Myoclonic Epilepsy (JME) [35]

- Onset 12–18 years of age
- Seizures typically occur upon awakening and are triggered by alcohol, sleep deprivation, and fatigue
- Myoclonic seizures predominantly involve the upper extremities
 - Ask about early morning clumsiness which could represent myoclonic seizures
- GTC seizures usually occur 2–3 years after onset of myoclonic seizures
 - Myoclonic seizures may occur right before GTC seizures
- Absence seizures are infrequent and occur in approximately 1/3
 - May go unnoticed by the patient
- EEG
 - Generalized 4–6 Hz polyspike and wave discharges (maximal in the fronto-central head regions)
 - Medium to high amplitude 10–16 Hz polyspikes followed by 1–3 Hz slow waves are seen ictally (myoclonic seizure) and interictally
 - Focal EEG abnormalities are seen in approximately 20–50% and could be mistaken for focal epilepsy [39]
 - Focal slowing
 - Focal spikes or sharp waves
 - Spikes, spike and slow waves, or slow waves preceding generalized discharges
 - Amplitude asymmetry of generalized discharges
 - Focal discharges of similar morphology without associated focal slowing likely represent fragments of generalized discharges [35]
 - Photosensitivity is seen in approximately 40%
 - Seizures or discharges may be triggered by flashes of light including photic stimulation
 - Hyperventilation may also elicit discharges
- Treatment [40]
 - VPA is the most effective and results in complete seizure control in about 80% [41–43]
 - Due to its teratogenicity, VPA should not be used as first-line treatment in women of childbearing age
 - First-line therapy in young women include levetiracetam and lamotrigine
 - Clonazepam may be used in conjunction with LTG for myoclonic seizures
 - Combination therapy should be considered after failure of two AEDs
 - Combination therapy with VPA (even in young women) should be considered if both levetiracetam and lamotrigine are ineffective

- Lamotrigine and VPA may have a synergistic effect [6] but also ↑ risk of teratogenicity
- Prognosis [44]
 - The majority are controlled with appropriate AEDs
 - 1/6 are drug-resistant
 - High rate of relapse with AED withdrawal
 - 17% remain seizure free after discontinuing AEDs
 - 75% have one or more major unfavorable social outcomes (depression, unemployment, failure to complete high school, unplanned pregnancy, living alone)

Other Key Points

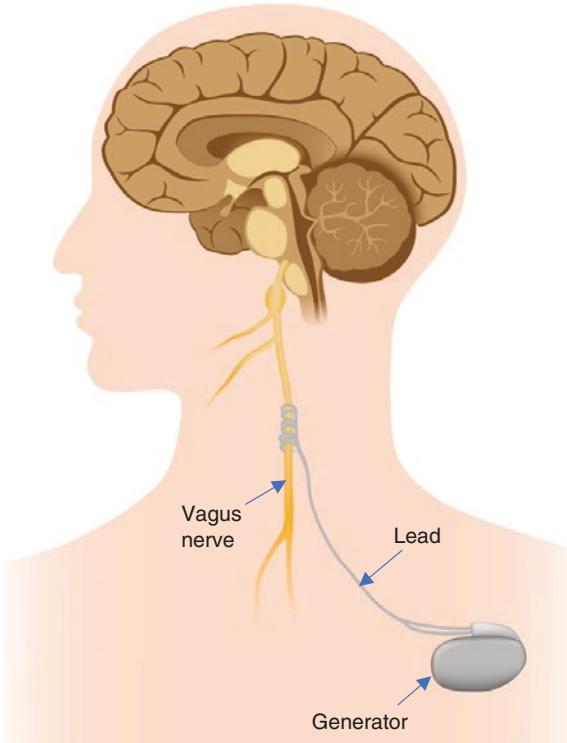
- Avoid VPA in mitochondrial disorders and in patients with POLG1 mutations due to ↑ risk of hepatotoxicity
- LTG may exacerbate myoclonic seizures
- Na channel inhibitors are contraindicated in SCN1A-related epilepsy (Dravet syndrome)
 - Na channel inhibitors are first-line treatment in SCN2A-related epileptic encephalopathies [46]

3.3 Stimulation Devices

3.3.1 Vagus Nerve Stimulation (VNS)

- FDA approved as an adjunctive therapy for drug-resistant focal onset epilepsy in adults and children 4 years of age and over
 - Also effective for generalized epilepsies [47, 48]
- FDA approved as adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments
- Small pulse generator (Fig. 3.4) is placed subcutaneously in the left chest with a lead attached to the left vagus nerve
- Vagus nerve is stimulated with electrical pulses at regular intervals
 - Additional stimulation can be provided by swiping the magnet over the generator
 - Patients should be advised to swipe the magnet during seizure auras as it may result in seizure termination [49]
- The mechanism of action of VNS is unknown, but hypotheses include:
 - Activation of the nucleus tractus solitarius and locus ceruleus causes release of norepinephrine and GABA which inhibit seizures [50]
 - Increasing the seizure threshold by inducing cerebral blood flow changes in various epileptogenic structures (most consistently the thalamus) [50]
 - Induction of EEG changes by an unclear mechanism [50]
- VNS efficacy increases over time [51, 52]

Fig. 3.4 Vagus nerve stimulation (VNS). Pulse generator is placed subcutaneously in the left chest with a lead attached to the left vagus nerve



- Elliot et al. [53] reported mean seizure reduction at:
 - 6 months = 35.7%
 - 1 year = 52.1%
 - 2 years = 58.3%
 - 4 years = 60.4%
 - 6 years = 65.7%
 - 8 years = 75.5%
 - 10 years = 75.5%
- VNS may also decrease seizure duration and the postictal period [47]
- Adverse effects typically ↓ over time
 - Hoarseness
 - Cough
 - Dyspnea
 - Paresthesia
- Programmable stimulation parameters – initial programming can be done as soon as 2 weeks post-op
- Dosing guidelines are available at <https://us.livanova.cyberonics.com/health-care-professionals/resources/product-training>
 - Normal mode
 - Output current – start with 0.25 mA and ↑ by 0.25 mA increments

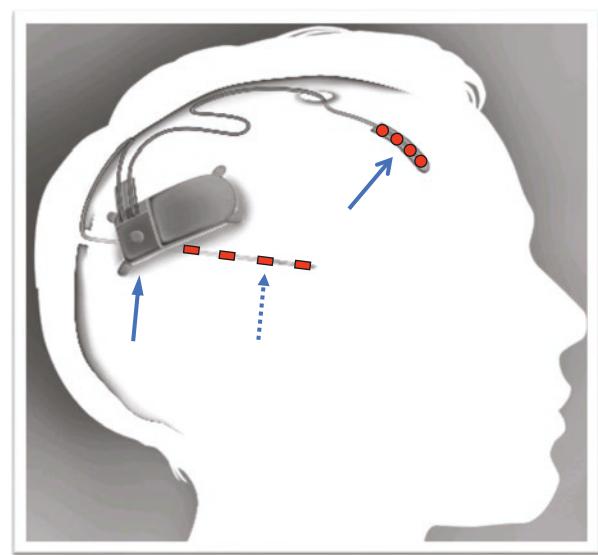
- Multiple increases may be made in one visit based on patient tolerability
- Follow-up visits q1–2 weeks are suggested until output is at the therapeutic range
- Normal mode therapeutic range = 1.5–2.25 mA [54, 55]
- Frequency – start with 30 Hz
- Pulse width – duration of a single pulse of stimulation; start with 500 μ s
- On time – start with 30 s
- Off time – start with 5 min
 - Duty cycle = (on time + 4 s)/(on time + off time)
 - Can ↑ q3–6 months based on response
- Magnet mode – start with:
 - Output current = 0.5 mA (normal mode + 0.25 mA)
 - On time = 60 s
 - Pulse width = 500 μ s
- Autostim mode
 - Currently only available for AspireSR Model 106
 - 64% of all generalized seizures and 71% of focal onset seizures are associated with ictal tachycardia or significant ↑ in HR [56]
 - Automatically delivers stimulation when rapid ↑ in HR is detected
 - Baseline HR is established over 5-min periods
 - Detection occurs when foreground HR exceeds background by specified threshold (20%–70%)
 - Start with:
 - Threshold = 40%
 - Output current = 0.375 mA (normal mode + 0.125 mA)
 - On time = 60 s
 - Pulse width = 500 μ s
- Options to mitigate side effects:
 - Pulse width – ↓ to 250 μ s
 - Signal frequency – ↓ to 25 or 20 Hz
 - Output – ↓ by 0.25 mA; ↓ by 0.125 mA for AspireSR

3.3.2 Responsive Neurostimulation (RNS)

- FDA approved as an adjunctive therapy for drug-resistant focal onset epilepsy in adults 18 years of age or older with two or fewer epileptogenic foci
- Pediatric indication is pending
- Closed-loop system that continuously records electrocorticographic (ECoG) activity and provides responsive electrical stimulation when physician specified epileptiform patterns are detected
- Programmable neurostimulator is cranially implanted and connected to one or two depth or subdural cortical strip leads (each containing four electrodes) which are placed at the predetermined seizure foci (Fig. 3.5)

Fig. 3.5 RNS® system.

The neurostimulator (solid arrow) is connected to a depth lead (dashed arrow) and a cortical strip lead (open arrowhead)



- Up to four leads (any combination of depth/subdural) may be placed, but only two can be connected to the neurostimulator
 - Ability to connect four leads is pending
- Patient holds a wand over the neurostimulator to upload data to the NeuroPace Programmer (laptop)
 - Only 6 min of ECoG can be stored
 - Patients should upload data daily to minimize overwriting
- Physicians can access the RNS data via a secure website, PDMS (Patient Data Management System)
- ECoGs are typically stored in 90 s durations (60 s before detection and 30 s after) and includes:
 - Scheduled ECoG storage – ECoG recordings are automatically stored at set times of the day
 - Magnet swipe – patients swipe to mark a seizure
 - Saturation and long episodes (LE) – patterns that are *suggestive* of electrographic seizures
 - Parameters are set by the physician
 - Saturation = high amplitude ECoG
 - Long episode = sustained epileptiform activity greater than a specified duration
- Stimulation parameters with typical initial settings:
 - Frequency = 200 Hz
 - Pulse Width = 160 μ s
 - Burst duration = 100 ms
 - Current = 1.0 mA

- Stimulation montages:
 - Bipolar – electrode to electrode
 - Monopolar – lead to lead or lead to can
 - Creates wider current spread
- Effective in mesial temporal lobe epilepsy (mTLE), neocortical TLE, and extra-temporal epilepsy [57, 58]
- Median % seizure reduction by location:
 - mTLE = 70%
 - Temporal neocortical = 58%
 - Frontal & parietal = 70%
 - Multilobar = 51%
- Sustained long-term efficacy [59, 60]
 - Median seizure reduction:
 - 1 year = 44%
 - 2 years = 53%
 - 6 years = 65.7%
- RNS also improves quality of life [60, 61]
- Adverse events [60, 61]
 - Post-op implant site pain – 9.9%
 - Headache – 10.5%
 - Dysesthesia – 6.3%
 - Implant site infection – 9.4%
 - ↑ in focal seizures with impaired awareness – 7.8%

3.3.3 Deep Brain Stimulation (DBS)

- FDA approved for the treatment of drug-resistant (failed ≥3 AEDs), focal onset epilepsy in adults 18 years of age and older
- Bilateral DBS electrodes are implanted in the anterior nucleus of the thalamus (Fig. 3.6)
- Bilateral stimulation of the anterior nucleus of the thalamus was shown to be effective in reducing seizures (SANTE or Stimulation of the Anterior Nuclei of Thalamus for Epilepsy trial) [62]
- The anterior nucleus projects to frontal and temporal lobe structures commonly involved in seizures and inhibits chemically induced seizures in rat models [62]
- The mechanism of DBS in epilepsy is unknown
- Median seizure reduction: [62, 63]
 - 1 year = 41%
 - 2 years = 56%
 - 3 years = 53%
 - 4 years = 66%
 - 5 years = 69%
- Other benefits of DBS include decreased seizure severity, improvement in quality of life (QOL), and improvement in several neuropsychological measures (attention, executive function, depression, anxiety, mood disturbance, subjective cognitive function) [63]

Fig. 3.6 Deep brain stimulation (DBS). DBS neurostimulator is implanted subcutaneously in the chest with electrodes implanted in the bilateral anterior nucleus of the thalamus



- 73% of subjects were satisfied with the therapy 5 years after implantation [63]
- Device-related adverse events: [63]
 - Implant site pain (23.6%)
 - Paresthesias at the stimulator implant site (22.7%)
 - Implant site infection (12.7%)
 - Discomfort (9.1%)
 - Sensory disturbance (8.2%)
 - Memory impairment (7.3%)

3.4 Diet Therapy

3.4.1 Ketogenic Diet (KD)

- Typical KD = 3:1 or 4:1 ratio of fat: carbohydrates + protein
- Fasting is optional (typical duration is 24–48 h)
 - May lead to faster seizure reduction, but seizure control at 3 months is the same for fasting and non-fasting [64]
 - Weight loss, hypoglycemia, and acidosis are more common with fasting [64]
- Two approaches to diet initiation:
 - Constant ratio (3:1 or 4:1) with daily ↑ in calories until full calorie meals are tolerated
 - Start with full calories but ↑ ratio daily (1:1, 2:1, 3:1, 4:1)
- Low carbohydrate multivitamins with minerals, calcium, and Vitamin D supplementation are recommended [65]
- Oral citrates (Polycitra K) may prevent nephrolithiasis [65]
- Indications for the KD [65]
 - GLUT-1 deficiency
 - Pyruvate dehydrogenase deficiency (PDHD)
 - Drug-resistant epilepsy
- KD is also very effective for [65, 66]:
 - Dravet syndrome
 - Lennox-Gastaut syndrome

- Doose syndrome
- Epileptic spasms
- Tuberous sclerosis complex
- Contraindications [65]
 - Pyruvate carboxylase deficiency
 - Carnitine deficiencies
 - β -oxidation defects
 - Porphyria
- Efficacy of KD
 - 75% of children respond within the first 2 weeks [67]
 - Children (ages 2–16):
 - 47.7% median seizure reduction after 3 months [68]
 - 38% have >50% seizure reduction and 7% have >90% seizure reduction at 3 months [68]
 - Adolescents (ages 12–18) and adults:
 - ~50% have >50% seizure reduction and 13% become seizure free [69]
 - KD may have a synergistic effect with zonisamide [70]
 - Monitor for acidosis if co-administered with topiramate or zonisamide
- Challenges of KD
 - Compliance – restrictive diet that may be difficult to maintain
 - 45% of children quit the KD within the first year (~30% because the diet was too restrictive) [71]
 - 51% of adults quit the KD before the study was completed (duration ranged from 3–26 months) [66]
 - Children require admission to hospital for a few days at diet initiation
 - Risk of hypoglycemia
- KD is not recommended beyond 2–3 years due to potential long-term complications [72]:
 - Hyperlipidemia
 - ↑ in triglycerides and cholesterol and ↓ in high-density lipoprotein (HDL) are reversible and not significant after 24 months
 - Low risk of pancreatitis 2/2 hypertriglyceridemia
 - Growth alterations
 - Nephrolithiasis
 - Vitamin, mineral, and electrolyte deficiencies
 - Osteopenia, which may occur despite vitamin D supplementation
- Most common adverse effects [68]
 - Constipation
 - ↓ energy
 - Vomiting
 - Diarrhea
 - Abdominal pain
- Discontinuation of the KD [65]
 - If ineffective, consider discontinuing the KD after 3 months
 - If seizures paradoxically worsen for more than a few days, KD should be discontinued immediately

- In children with >50% seizure reduction, KD is typically discontinued after 2 years (exceptions: GLUT-1, PDHD)
- 80% of children who became seizure free as a result of the KD will remain seizure free after KD discontinuation [73]
 - Seizure recurrence risk is ↑ in those with epileptiform EEGs, structural abnormalities, and TSC
- Wean gradually over 2–3 months
 - ↓ the ratio gradually from 4:1 to 3:1 to 2:1 then ↑ calories and fluids
 - High carbohydrate foods can be introduced once urinary ketosis resolves

3.4.2 Modified Atkins Diet (MAD)

- Limits carbohydrates to 10–20 g/day [66]
- Achieves ketosis without restricting fluids, calories, or protein
- Efficacy of MAD
 - Similar to KD: approximately 50% experience >50% seizure reduction, and 13% become seizure free [74]
 - Median time to seizure reduction is 2 weeks [75]
- Compliance is the major challenge of MAD
 - Only 55% of children continued the MAD >6 months [72]
 - 42% of adults quit the MAD before the study was completed (duration ranged from 3–26 months) [66]
- Adverse effects
 - ↑ in total cholesterol and low-density lipoprotein over the first 3 months but tend to normalize by 1 year [66]
 - Fatigue
 - Hair loss
 - GI upset

3.5 Epilepsy Surgery

- Approximately 40% of people with epilepsy will continue to have seizures despite treatment with AEDs [76, 77]
- The seriousness of drug-resistant epilepsy (DRE), defined as failure of adequate trials of two appropriately chosen and tolerated antiepileptic drugs used in combination or in monotherapy [78], is underrecognized, and consequently less than 1% of people with DRE are referred to an epilepsy center [77]
- DRE is associated with developmental delay in children and hinders the development of interpersonal and vocational skills leading to lifelong disability [75]
- Other negative consequences of DRE include psychological distress, memory problems, and an increased mortality rate 5–10 times that of the general population [77]

- There is an average delay of more than 20 years before referral to an epilepsy center which is often too late to prevent many of these consequences [79]
- The American Academy of Neurology recommends timely referral of all patients with DRE to a Level 3 or 4 epilepsy center [80]

3.5.1 Presurgical Evaluation

- The presurgical evaluation includes a number of different procedures and tests which are used in conjunction to identify the type of epilepsy (generalized vs. focal vs. multifocal) and to determine the seizure onset zone (SOZ)
- Several cortical areas are important to understand in the epilepsy surgery evaluation: [81]
 - Epileptogenic zone – area that generates epileptic seizures and which removal of, or disconnection from, is required for seizure freedom
 - Seizure onset zone – where clinical seizures originate
 - Irritative zone – area that generates interictal epileptiform discharges
 - Symptomatogenic zone – area that produces ictal symptoms
 - Functional deficit zone – interictal, functionally abnormal area
 - Eloquent cortex – area necessary for defined cortical functions
- The objective is to determine the best treatment option (resection, laser ablation, RNS, VNS, etc.)

3.5.1.1 Video-EEG Monitoring

- AKA Phase I monitoring (scalp or extracranial EEG)
- Goals of Phase I monitoring:
 - Confirm epilepsy diagnosis and determine the type of epilepsy (generalized vs. focal vs. multifocal)
 - One study showed an overall misdiagnosis rate for patients referred to an epilepsy clinic to be 26.1% [82]
 - In another study whereby either neurologists trained in epilepsy or epileptologists had referred patients believed to have DRE for video-EEG monitoring, 18.5% were found to have PNES [83]
 - Misclassification of epilepsy type (focal instead of generalized or vice versa) occurred in 2.4% [83]
 - Seizure characterization
 - Closed circuit video with time-locked EEG allows for simultaneous analysis of behavior and EEG
 - Determine seizure semiology (may differ from the description provided by the patient or witness) which can help with lateralization (Table 3.5)
 - Determine the temporal relationship between the electrographic and clinical onset
 - Clinical onset before electrographic onset may represent a propagated pattern

Table 3.5 Ictal and postictal lateralizing signs [81, 84]

Sign	Lateralization
Sensory aura	Contralateral somatosensory cortex
Hemifield visual aura	Contralateral visual cortex and adjacent areas
Complex visual aura	Right temporal
Head/eye version	Contralateral premotor cortex, frontal eye fields
Clonic activity	Contralateral primary motor and premotor cortex
Tonic activity	Contralateral SMA, possibly also premotor cortex, anterior cingulate and subcortical
“Figure-of-4 sign”	Contralateral (to extended arm) SMA or prefrontal
Motor automatisms with contralateral dystonic posturing [85]	Ipsilateral to automatisms
Automatisms with preserved awareness	Non-dominant
Ictal spitting	Non-dominant
Ictal vomiting	Non-dominant temporal lobe
Ictal urinary urge	Non-dominant temporal lobe
Ictal (unilateral) eye blinking	Ipsilateral
Ictal speech	Non-dominant
Ictal aphasia	Dominant language areas
Ictal drinking	Non-dominant
Postictal weakness	Contralateral primary motor and premotor
Postictal nosewiping	Ipsilateral

- Localization of the seizure onset zone(s)
 - If seizure localization or lateralization is not possible, Phase II (intracranial) monitoring may be indicated

3.5.1.2 Neuroimaging

MRI

- 3-Tesla with epilepsy protocol, which typically includes the following sequences:
 - Sagittal T1
 - Axial T1, T2, and FLAIR
 - Axial DWI (diffusion-weighted imaging)
 - Axial SWI (susceptibility-weighted imaging) or GRE (gradient-echo)
 - Coronal FLAIR
 - Coronal MPRAGE (magnetization-prepared rapid-acquisition gradient-echo)
 - 3-dimensional, high-resolution T1 sequence
- Used to identify potential epileptogenic lesions
- If the lesion is co-localized to the SOZ as determined by EEG, the patient may be a skip candidate (resection without Phase II monitoring) (Fig. 3.7)
- If Phase II monitoring is necessary, the lesion should be covered to determine if it is epileptogenic and, if so, if it is concordant with the SOZ

Positron Emission Tomography (PET) Scan

- Used to identify potential epileptogenic areas
- FDG (18-fluorodeoxyglucose) PET is most commonly used
- Most reliable for temporal lobe epilepsy

Fig. 3.7 Coronal FLAIR T2 image of a 39 y/o gentleman with right Mesial Temporal Sclerosis (MTS) and drug-resistant Temporal Lobe Epilepsy (TLE)



- FDG-PET is not helpful in patients with large lesions, tuberous sclerosis, or history of prior resection [86]
- Interictal epileptogenic area will be hypometabolic (Figs. 3.8 and 3.9)
- Hypometabolic area is usually larger than the epileptogenic zone
- FDG-PET has high sensitivity and specificity and is associated with an excellent surgical outcome for MRI-negative TLE and FCD Type II [87]
- In MRI-negative epilepsy where intracranial EEG (iEEG) is used to identify the SOZ, the sensitivity and specificity of FDG-PET are 39.5% and 53.3%, respectively [87]
- In MRI-negative epilepsy where Engel class I outcome defined the SOZ, the sensitivity and specificity of FDG-PET are 59% and 79%, respectively [87]
- The accuracy of PET for identifying the SOZ is low in extratemporal epilepsy [87]
- Coregistration with MRI is more sensitive than either test alone
 - ↑ detection of FCD by 35–40% [87]

Ictal and Interictal Single-Photon Emission Computed Tomography (SPECT) [88]

- Challenging study that requires trained medical personnel and precise timing to work
- Best results are seen in focal seizures with impaired awareness
- Secondarily generalized seizures may show multiple areas of hyperperfusion
- May be helpful in patients with tuberous sclerosis or history of prior resection [86]
- IV radiotracer is injected immediately after seizure onset
- Faster radiotracer injection decreases the chance of catching seizure propagation

Fig. 3.8 Axial PET showing right temporal hypometabolism in a 39 y/o gentleman with right Mesial Temporal Sclerosis (MTS) and drug-resistant Temporal Lobe Epilepsy (TLE)



Fig. 3.9 MRI/PET fusion images showing right lateral temporal hypoperfusion in a 45-year-old man with right temporal lobe epilepsy

- Tracer takes ~30 s to reach the brain
- Ictal activity is identified by region of hyperperfusion
- Postictal hypoperfusion occurs ~1–2 min after a temporal lobe seizure ends
- To be of any localizing value, extratemporal lobe seizures should continue \geq 10–15 s after injection
- Subtraction ictal SPECT coregistered to MRI (SISCOM) improves localization of the area of hyperperfusion
- SISCOM may detect FCD not seen on MRI
- Pitfalls:
 - May be capturing seizure propagation
 - Ictal hyperperfusion does not exclude possibility of multifocal epilepsy

Wada Test (Aka Intracarotid Amobarbital Procedure or IAP)

- Used to lateralize temporal lobe dysfunction
- Used for language and memory lateralization
- Amobarbital injection disrupts the ipsilateral hemisphere for 3–5 min
- Important to predict and avoid potential deficits after temporal lobe resection
- Higher Wada memory score asymmetry correlates with better surgical outcome [89, 90]

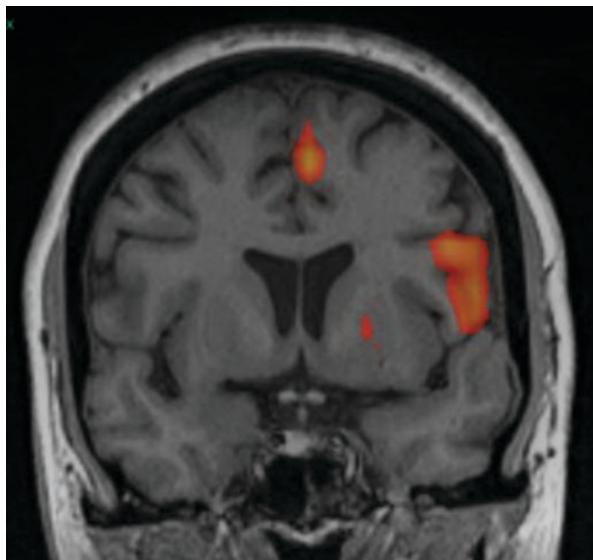
Functional MRI (fMRI)

- Noninvasive method to determine language lateralization
- Important to predict and avoid potential deficits after temporal lobe resection
- According to the 2017 AAN practice guideline summary on the use of fMRI in the presurgical evaluation of epilepsy [91]:
 - fMRI may be considered an option for lateralizing language in place of IAP
 - Language lateralization is concordant with IAP in 87% of mesial temporal cases and 81% of extratemporal (Fig. 3.10)
 - fMRI may be considered an option for lateralizing memory in place of IAP in patients with mTLE but is of unclear utility in other epilepsy types
 - fMRI may be considered to predict language deficits after ATL resection
 - fMRI of verbal memory or language encoding should be considered for predicting verbal memory outcome in patients undergoing evaluation for left mTLE surgery
 - fMRI using nonverbal memory encoding may be considered for predicting visuospatial memory outcomes
 - fMRI could be an alternative to IAP memory testing for predicting verbal memory outcome

Magnetoencephalography (MEG)

- Both electrical potentials and magnetic fields are generated by neuronal activity
- Magnetic fields are produced by intracellular currents of apical dendrites and can be recorded from the scalp with MEG [92]

Fig. 3.10 fMRI in a 46-year-old woman as a part of her presurgical workup. Two language/speech tasks (word- and verb-generation) were performed by the patient during the fMRI, and their activation maps are presented. The largest areas of activation are mostly found in the inferior frontal lobe of the left hemisphere (Broca's area) for this patient. Other notable area of activation is the left SMA (supplementary motor area)



- An advantage of MEG for source localization is that magnetic fields are minimally affected by intervening structures between the brain and scalp [92]
- Most accurate in the detection of sources that are tangentially oriented to the scalp (frontal or parietal neocortical areas) [87, 92]
- MEG is not sensitive for the detection of deep or radially oriented foci (bottom of sulcus or top of gyri) [87, 92]
- Tightly clustered spikes are associated with a favorable surgical outcome [87] (Fig. 3.11)
- MEG can also be coregistered with MRI (magnetic source imaging or MSI) (Fig. 3.11)
- Uses of MEG/MSI:
 - Identify potential epileptic foci when MRI is non-lesional
 - Sensitivity of MSI for detection of focal spikes ranges from 35% to 90% [87]
 - Guide placement of intracranial electrodes
 - The SOZ as determined by iEEG is colocalized to the center of spiking areas on MSI in 81–100% [87]
 - Identify which MRI lesions may be epileptogenic and/or perilesional epileptogenic areas
 - Localization of epileptogenic region in postsurgical patients being considered for repeat resection [92]

Diffusion Tensor Imaging (DTI) [93]

- Measures diffusion of water and its preferred orientation (fractional anisotropy) to identify white matter tracts (Fig. 3.12)

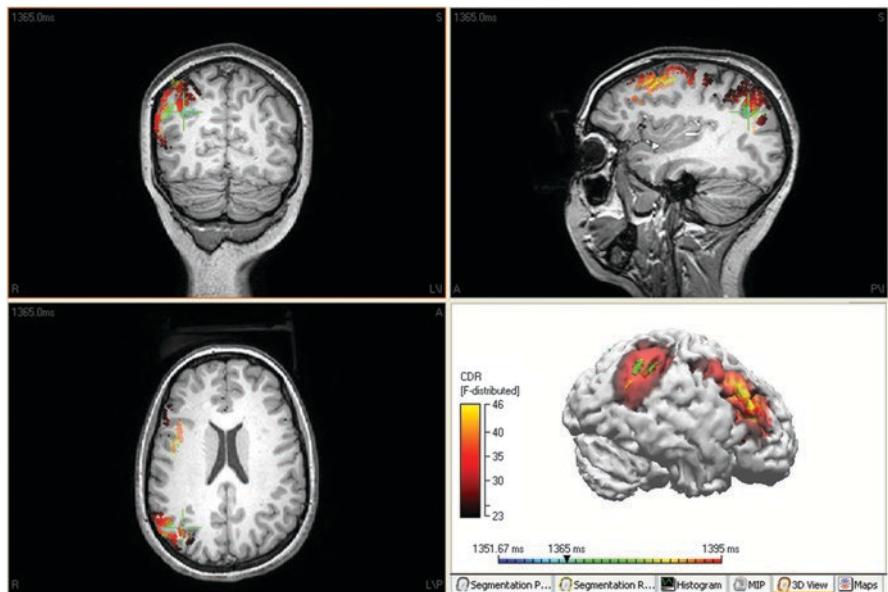


Fig. 3.11 Standardized low resolution brain electromagnetic tomography identifying spike cluster in a presurgical epilepsy patient. Localization with the single equivalent current dipole gave a right lateral frontal localization for the right frontal spikes and a right parietal location at the onset of the bursts

- May be used in surgical planning to avoid deficits caused by disruption of critical white matter tracts (Meyer's loop, arcuate fasciculus, etc.)

Neuropsychological Assessment

- Various neuropsychological tests (Table 3.6) are used for the following purposes:
 - Predict potential risks and outcomes of surgical resection
 - Identify relative strengths and weaknesses in various domains:
 - General cognitive functioning/IQ
 - Attention/executive functions
 - Language
 - Memory (verbal and nonverbal) and learning
 - Visuospatial/visuoperceptual/constructional
 - Motor
 - Mood
 - Quality of life
 - Weaknesses (areas of dysfunction) can assist with lateralization/localization of the epileptogenic zone

General Cognitive Functioning/IQ

- Assessment of general capacity

Fig. 3.12 DTI image in a 46-year-old woman with drug-resistant epilepsy as a part of her presurgical work up

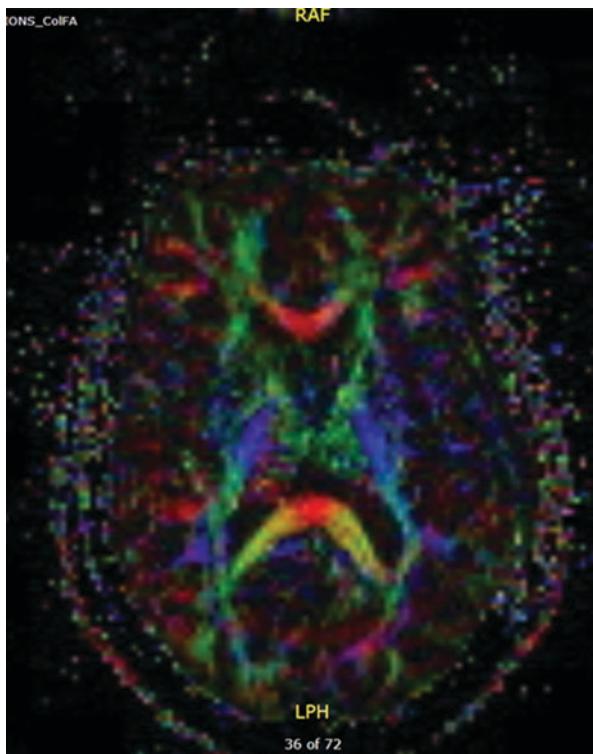


Table 3.6 Common neuropsychological tests

Domain	Test
Attention and executive function	
Attention	Trail making test, parts A and B Test of variables of attention Conners' continuous performance tests
Working memory	Digit span backward Auditory consonant trigrams Sentence memory
Set-shifting	Wisconsin card sorting test Trail making test
Inhibition	Stroop color word test
Planning	Tower of London Rey-Osterrieth complex figure test
Visuoperceptual/ constructional	
	Judgment of line orientation test Rey-Osterrieth complex figure test – copy trial Beery-Buktenica development test of visual-motor integration Hooper test of visual organization
Fine motor	
	Grooved pegboard test Purdue pegboard test
Academic achievement	
	Woodcock Johnson II tests of achievement Wechsler individual achievement test

- IQ is an independent predictor of seizure outcome (lower IQ = ↓ probability of seizure freedom) [94]
- Intellectual disability (IQ < 70) is not a contraindication to epilepsy surgery with worthwhile improvement possible
 - 54% of patients with an IQ of 50–69 and baseline seizure frequency > 100/month had >75% seizure reduction (37% Engel Class I after 2 years) [94]
 - 22% with IQ < 50 were seizure-free (Engel Class I) [94]
- Test of intelligence = Wechsler Abbreviated Scale of Intelligence

Language

- Tests of language analyze five different domains (Table 3.7)
- Approximately 25% of right-handed patients with epilepsy have atypical dominance (right or bilateral)
 - More common with earlier onset of epilepsy and early insults (i.e., perinatal stroke)
- Word-finding problems are common in TLE and may be attributed to hippocampal dysfunction
- Naming is a function of the left temporal lobe [95]
- Approximately 30–50% of patients will experience significant word-finding difficulties after left ATL resection [96]
- Predictors of postoperative word-finding difficulty [96]:
 - Extensive resection of lateral temporal cortex
 - Non-lesional MRI
 - Better presurgical naming ability
 - Later age at seizure onset

Table 3.7 Language tests

Domain	Test
Verbal fluency	Delis-Kaplan executive function system (DKEFS)-verbal fluency Controlled oral word association test (COWA)
Naming	Boston naming test (BNT) Expressive one-word picture vocabulary test
Receptive vocabulary	Peabody picture vocabulary test Receptive one-word picture vocabulary test
Comprehension	Clinical evaluation of language fundamentals Concepts and following directions
Phonological skills	Comprehensive test of phonological processing

Table 3.8 Visual and verbal memory tests

Domain	Test
Visual	Rey-Osterrieth complex figure test recall Wechsler memory scale: visual reproduction, design memory Brief visual spatial memory test Children's memory scale: dot locations, faces
Verbal	Rey auditory verbal learning test California verbal learning test Wechsler memory scale: logical memory, verbal paired associates Children's memory scale: stories, word pairs

Memory

- Chronic TLE is associated with progressive memory impairment [97]
- Seizure freedom may result in memory improvement [97]
- Verbal memory is typically a function of the left temporal lobe [97]
- Nonverbal or visual memory is more variable but typically associated with right TLE [98]
- Preoperative tests are used to establish potential risk and prognosis after surgery (Table 3.8)
- Approximately 25% of patients with TLE who undergo ATL resection will experience a significant postoperative decline in verbal learning [99]
- Risk of decline in verbal memory is twice as high for left ATL compared to right (44% vs. 20%) [98]
- The biggest risk factor for a decline in verbal learning is a higher level of preoperative verbal learning [99]
- Risk of postoperative visual memory decline is ~20–25% in both left and right TLE [98]

Mood/Quality of Life

- Depression, anxiety, and decreased quality of life (QOL) is common in people with epilepsy
- Up to 50% of people with epilepsy report depression and/or anxiety [100]
- Depression in epilepsy is likely multifactorial [100]
 - “Learned helplessness” and attributional style – pessimism about why someone experiences unpredictable and uncontrollable adverse events (seizures) is significantly associated with depression [101]
 - Psychosocial factors (quality of life, adjustment to epilepsy, perceived stigma, life stressors, employment, etc.)
 - Seizure type – depression is more common with focal seizures with impaired awareness and TLE
 - Effects of AEDs – any AED can cause depression, but link is strongest with barbiturates
- People with epilepsy are also more likely to report serious psychological distress (feeling depressed, worthless, nervous, restless, hopeless) even after controlling for demographics and other comorbidities [102]
- Treatment of depression in epilepsy [100]
 - First-line – SSRIs (i.e., citalopram)
 - AEDs with mood-stabilizing properties (may be inadequate as an antidepressant): VPA, CBZ, LTG, GBP
- Predict outcome after surgery
 - Postsurgical seizure freedom is a reliable predictor of psychiatric improvement [100]
- Tests of mood/QOL:
 - Beck Depression Inventory
 - Beck Anxiety Inventory
 - Adaptive Behavior Assessment System
 - Minnesota Multiphasic Personality Inventory
 - Quality of life in Epilepsy-31

3.5.2 Surgical Diagnostic Procedures

3.5.2.1 Subdural and Depth Electrode Phase II Monitoring

- Should be considered when the presurgical workup failed to adequately localize the SOZ
- Subdural grids and strips (Fig. 3.13)
 - Used when the suspected SOZ is neocortical
- Depth electrodes or stereotactic EEG (SEEG) (Fig. 3.14)
 - Used when the suspected SOZ is deep (i.e., mTLE, orbitofrontal, anterior cingulate, etc.)
 - Typically placed with robotic assistance
 - Risk of hemorrhage is ~1% [103]
- May need a combination of subdural grids/strips and SEEG

3.5.2.2 Cortical Stimulation and Brain Mapping

- Used to identify eloquent cortex (sensorimotor/language) in order to delineate the extent of surgical resection
- Can be done intraoperatively via direct cortical stimulation or bedside (requires subdural grids and/or strips)
- Load with AED prior to mapping to minimize risk of causing seizures
- Cold saline can be used intraoperatively to abort seizures caused by direct cortical stimulation
- Extraoperative (bedside) mapping
 - Electrical stimulation is applied to a single electrode with an adjacent electrode used as reference
 - Stimulation intensity is gradually increased to a threshold (typically 12–15 mA) or until a behavioral response is observed
 - EEG is monitored for seizures or afterdischarges

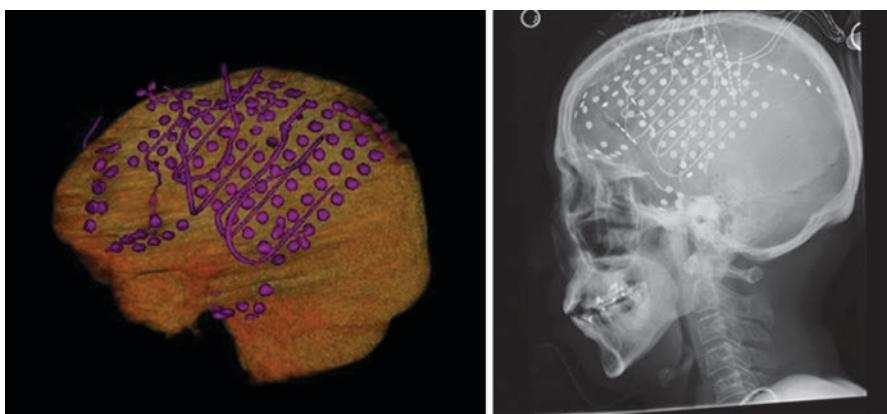
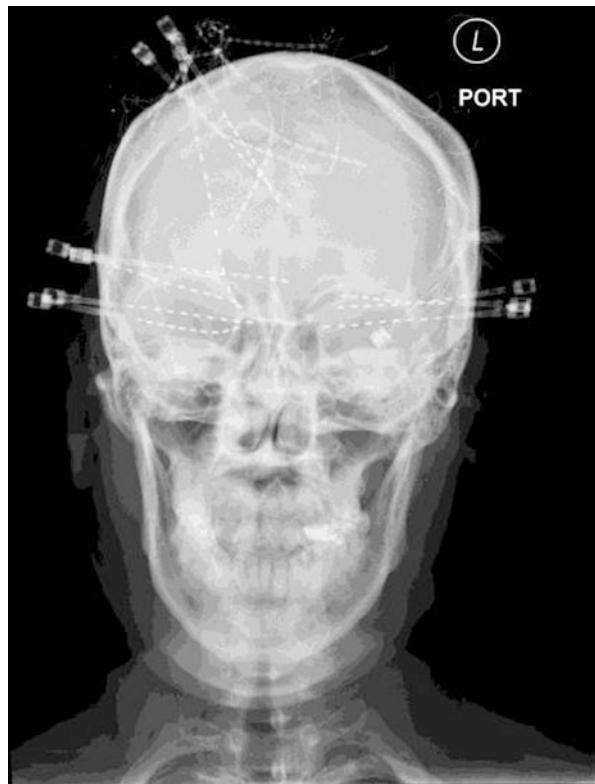


Fig. 3.13 Left lateral frontal subdural grid and several subdural strips in basal temporal, orbitofrontal, and parieto-occipital regions in a 42-year-old man with drug-resistant epilepsy being evaluated for surgery

Fig. 3.14 Robotic-assisted stereotactic placement of bilateral depth electrodes for stereo electroencephalography (SEEG) in a 36-year-old lady with a history of drug-resistant epilepsy



- Afterdischarges are rhythmic epileptiform discharges that may lead to a seizure even if the stimulated cortical region does not produce spontaneous seizures [104]

3.5.3 Surgical Treatment Procedures

3.5.3.1 Surgical Resection

- Surgical resection is the gold standard treatment for drug-resistant temporal lobe epilepsy [105, 106]
- In the seminal randomized, controlled trial (RCT) comparing ATL resection to medical management, 64% of patients who underwent resection were free of seizures impairing awareness after 1 year compared to 8% in the medical group [105]
- The Early Randomized Surgical Epilepsy Trial (ERSET) compared early TLE surgery (within 2 years of failing two AEDs) to medical management [106]
 - During year 2 of follow-up, 11/15 patients in the surgical group were seizure free compared to 0/23 patients in the medical group [106]
- The following structures are typically removed in a standard anterior temporal lobe (ATL) resection [103]:

- 4.5 cm (dominant temporal lobe) or 6.5 cm (non-dominant temporal lobe) of neocortex as measured from the temporal pole
- Amygdala
- Hippocampus
- Parahippocampus
- Uncus
- Fusiform gyrus
- Selective amygdalohippocampectomy (SAH) was developed in hopes of reducing neurocognitive side effects, although this is controversial
 - Studies have demonstrated no benefit with SAH compared to ATL in terms of verbal memory [107, 108] or IQ [109]
 - SAH is less likely to achieve seizure freedom compared to ATL [109, 110]
- Epilepsy surgery outcome scales:
 - Engel classification (Fig. 3.15)
 - ILAE classification (Fig. 3.16)
- Surgical resection is less successful for extratemporal epilepsy [111]:
 - Frontal lobe epilepsy: 45.1% seizure-free
 - Parietal-occipital epilepsy: 46% seizure-free
- Lesional epilepsy (LE), as determined by MRI *or* pathology, is significantly more likely than non-lesional (NL) to result in seizure freedom (Engel class I) [112]
 - LE defined by MRI *or* pathology: 68% (LE) vs. 43% (NL)
 - LE defined by MRI: 70% LE vs. 46% NL
 - TLE: 75% LE vs. 51% NL
 - Extratemporal: 60% LE vs. 35% NL

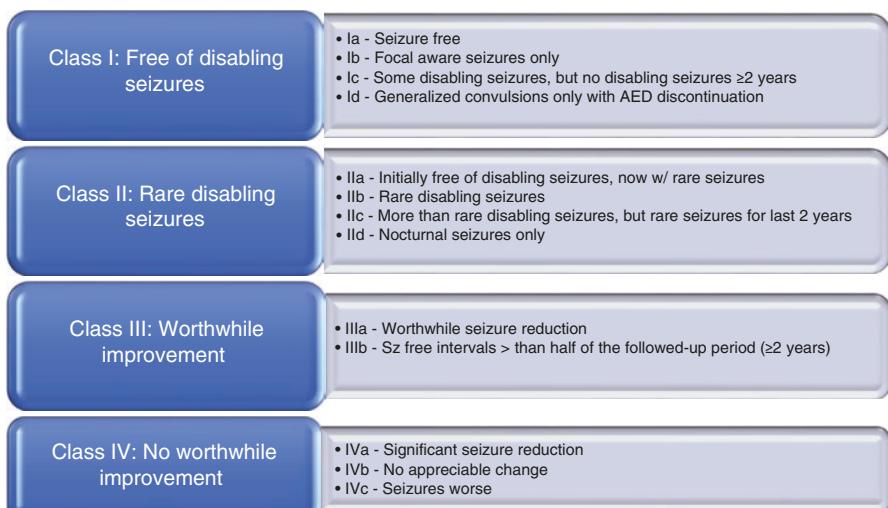


Fig. 3.15 Engel classification of postoperative seizure outcome [114]

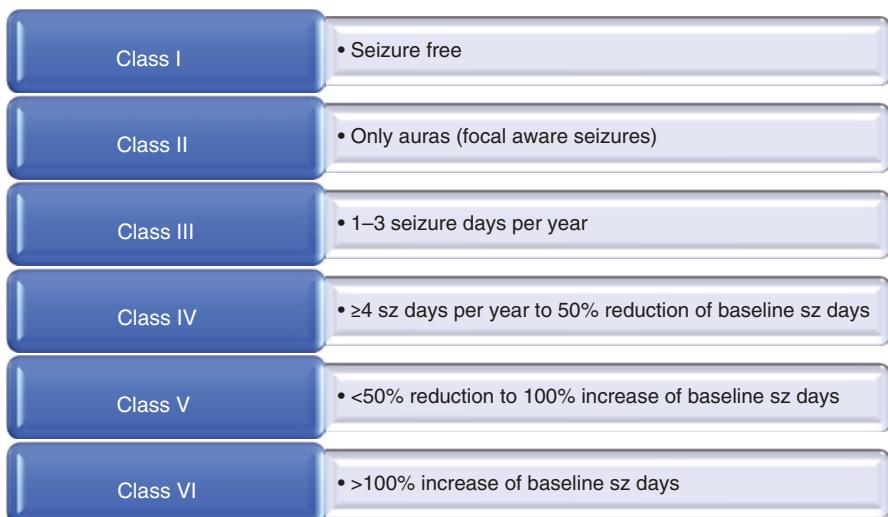


Fig. 3.16 ILAE classification of postoperative seizure outcome [115]

- Long-term outcome [113] of surgical resection
 - 5-year seizure-free rates (excluding focal aware seizures):
 - 55% for ATL resection
 - Significant difference in seizure freedom based on the surgical pathology
 - 57% for hippocampal sclerosis
 - 63% for dysembryoplastic neuroepithelial tumor (DNET)
 - FCD, other malformations, and no abnormality had significantly earlier relapses compared to hippocampal sclerosis
 - 56% for temporal lesionectomy
 - 40% for extratemporal lesionectomy
 - 64% for hemispherectomy
 - 10-year seizure-free rates (excluding focal aware seizures):
 - 49% for ATL resection
 - 56% for temporal lesionectomy
 - 31% for extratemporal lesionectomy

3.5.3.2 Disconnection and Other Surgical Options

Corpus Callosotomy

- Palliative procedure aimed to prevent interhemispheric spread of epileptic activity
- Total is more likely than an anterior two-thirds corpus callosotomy to result in a worthwhile (Engel Class I or II) seizure reduction (88.2% vs. 58.6%) [116]
- Most effective for drop attacks (tonic, atonic) [117]
- Also effective for tonic, atonic, GTC, and absence seizures; patients with Lennox-Gastaut syndrome [117, 118]
- Favorable prognostic factors [117]:
 - Seizure type (drop attacks, GTC seizures, atypical absences)

- Younger age at the time of surgery
- Slow spike-wave activity on ictal and interictal EEG
- ↓ synchrony of postoperative discharges
- Transient disconnection syndrome is more likely with total compared to anterior two-thirds corpus callosotomy (12.5% vs. 0%) [119]
- Postsurgical neurologic deficits are estimated to occur in ~13% and tend to resolve [119]:
 - Alien limb
 - Mutism
 - Paresis
 - Ataxia
 - Apraxia
 - Agraphia
- Disconnection syndrome [120] is more common in patients with LGS or severe intellectual disability and typically resolves by 6 weeks [116]
 - SMA syndrome (contralateral leg weakness, incontinence, ↓ spontaneous speech)
 - Alien hand syndrome
 - Dichotic listening suppression
 - Hemispatial neglect
 - Alexia without agraphia

Multiple Subpial Transection [121]

- Technique used when the epileptogenic zone involves eloquent cortex
- Horizontal intracortical fibers are severed at intervals of 5 mm, sparing vertical fibers and the cortex
- Due to lack of well-controlled trials, there is lack of evidence to support or refute its use

Functional Hemispherectomy/Hemispherotomy

- The use of anatomic hemispherectomy (AH) fell out of favor due to delayed complications including obstructive hydrocephalus, superficial hemosiderosis, and intracranial hematoma
- The AH was modified to avoid late complications by leaving the frontal and/or occipital poles but disconnecting them (functional hemispherectomy) [122]
- Functional hemispherotomy achieves complete disconnection from the pathologic hemisphere via [123]:
 - Disconnection of the corticothalamic tract
 - Disconnection of the orbito-fronto-hypothalamic tract
 - Total corpus callosotomy
 - Resection of the medial temporal structures
- Hemispherectomy/hemispherotomy is typically performed in patients with drug-resistant epilepsy with an extensive unilateral epileptogenic zone and corresponding hemiparesis [123]:
 - Rasmussen encephalitis
 - Hemimegalencephaly

- Sturge-Weber syndrome
- Hemiconvulsion-hemiplegia-epilepsy syndrome
- Cortical dysplasia
- Congenital porencephaly
- Perinatal stroke
- Hemispheric surgery for drug-resistant epilepsy results in a seizure-free rate of 73% [124]

MR-Guided Laser Interstitial Thermal Therapy (MRgLITT)

- AKA laser ablation
- Stereotactic procedure that uses a laser catheter to ablate tissue using real-time visualization with MRI thermometry
- Option for epileptogenic foci in eloquent areas or that are deep and challenging to access surgically (i.e., hypothalamic hamartoma, etc.)
- Epilepsy indications for MRgLITT [125]
 - mTLE
 - Hypothalamic hamartoma
 - Periventricular nodular heterotopia
 - Focal cortical dysplasia
 - Tuberous sclerosis
 - Tumor
- Lower to comparable chance of seizure freedom compared to ATL
 - One small study reported 8/15 (53%) patients were free of seizures impairing consciousness after 6 months, 4/11 (36.4%) after 1 year, and 3/5 (60%) after 2 years [126]
 - 3/4 patients who failed LITT were seizure free after ATL [126]
 - In another study, 15/23 (65%) pts with mTLE were seizure-free after 1 year [127]
- Advantages compared to anterior temporal lobectomy (ATL)
 - Minimally invasive
 - ↓ risk of infection
 - Shorter recovery time (most are discharged on same day of the procedure)
 - Better neurocognitive outcome
 - One study showed that 0/19 patients who underwent MRI-guided stereotactic laser amygdalohippocampectomy for TLE experienced a decline in naming or recognition functions, whereas 32/39 who had an open resection had a decline in one or more measures [128]
- Adverse effects
 - Visual field deficits occur in 5%–29% [129]
 - Complete postoperative homonymous hemianopsia may be related to injury to the lateral geniculate nucleus (LGN) [129]
 - Small choroidal fissure allows spread of heat from hippocampal body to LGN [129]
 - ↓ in verbal memory may be seen in patients with mTLE who undergo dominant LITT [127]

Take-Home Points

- Narrow spectrum AEDs may worsen generalized seizures
- Broad-spectrum AEDs treat ALL types of seizures and include valproic acid, levetiracetam, lamotrigine (may worsen myoclonic sz), topiramate, zonisamide, felbamate, rufinamide, and benzodiazepines
- CYP450 inducers will decrease the levels of other AEDs and include carbamazepine, primidone, phenobarbital, and phenytoin
- Valproic acid is the main CYP450 inhibitor and will increase the level of other AEDs
- Carbamazepine undergoes *auto-induction* in the initial 2–4 weeks which results in lower levels and shorter $\frac{1}{2}$ life
- Asians with HLA-B1502 allele have a high risk of carbamazepine associated SJS and toxic epidermal necrolysis
- Lacosamide is a Na channel inhibitor that enhances *slow* inactivation
- Lacosamide is associated with PR prolongation
- The risk of aplastic anemia with felbamate is ~1 in 5000–8000 patients and is highest in postpubertal females with autoimmune disease
- Epidiolex (cannabidiol) [CBD] oral solution is FDA approved for the treatment of seizures associated with LGS and Dravet syndrome, in patients 2 years of age and older
- The ILAE revised the definition of status epilepticus to be “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It is a condition that can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”
- Treatment for convulsive status epilepticus consists of benzodiazepines (first-line), IV AEDs (second-line) and anesthetic doses of propofol, midazolam, pentobarbital, or thiopental (third-line)
- West syndrome consists of a triad of epileptic spasms, hypsarrhythmia, and intellectual disability
- Lennox-Gastaut syndrome consists of a triad of multiple seizure types (*tonic*, atonic, atypical absence > myoclonic, focal, or GTC), slow spike and wave (2–2.5 Hz) complexes, and cognitive dysfunction
- E ethosuximide is the treatment of choice for absence seizures
- VPA is the most effective treatment for JME
- VNS is FDA approved as an adjunctive therapy for drug-resistant *focal* onset epilepsy in adults and children 4 years of age and over; VNS is also effective for generalized epilepsies
- RNS is FDA approved as an adjunctive therapy for drug-resistant *focal* onset epilepsy in adults 18 years of age or older with two or fewer epileptogenic foci

- DBS is FDA approved for the treatment of drug-resistant (failed ≥3 AEDs), focal onset epilepsy in adults 18 years of age and older
- Ketogenic diet (KD) is the treatment of choice for GLUT-1 deficiency and pyruvate *dehydrogenase* deficiency
- KD is contraindicated in pyruvate *carboxylase* deficiency, carnitine deficiencies, β -oxidation defects, and porphyria

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Women with Epilepsy

4

4.1 Definition of Catamenial Epilepsy

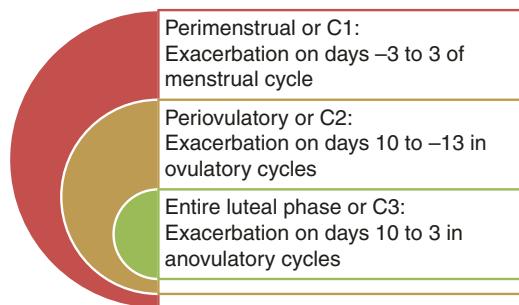
- Women with epilepsy (WWE) who experience cyclic exacerbation of their seizures at certain times of menstrual cycles related to fluctuations in sex hormones [1, 2]
- Derived from the Greek word katamenios, meaning “monthly [3]”
- About 1/3 of women with epilepsy have catamenial epilepsy (CE)

4.2 Patterns of Catamenial Epilepsy

Three patterns are described by Herzog and colleagues (Fig. 4.1) [4, 5]:

- Perimenstrual or C1: exacerbation on days –3 to 3 of menstrual cycle
- Periovulatory or C2: exacerbation on days 10 to –13 in ovulatory cycles
- Entire luteal phase or C3: exacerbation on days 10 to 3 in anovulatory cycles

Fig. 4.1 Three patterns of catamenial epilepsy. Described by Herzog, A.G., et al. Day 1 is the first day of the menstrual bleed and day –14 is the day of ovulation



4.3 Diagnosis of Catamenial Epilepsy

- Use seizure diaries and simultaneous charting of the time of ovulation (by basal body temperature method or ovulation kits) and menstruation for three cycles
 - If the majority of seizures (twofold or higher) occur during one of the above periods, a diagnosis of CE is made [5]
-

4.4 Mechanism of Catamenial Epilepsy

- Estrogen and progesterone have neuroactive properties
- Estrogen and progesterone alter neuronal excitability and seizure susceptibility by their effect on brain structures
- As a rule, estrogen is proconvulsant and progesterone anticonvulsant
 - Estradiol may potentiate seizures by increasing excitatory synapses in the hippocampus [6]
 - Progesterone's reduced metabolite, allopregnanolone, is a potent positive allosteric modulator of GABA_A neurotransmission [7]
 - Epilepsy Birth Control Registry (EBCR) data showed a relative risk for seizure increase 4.5 times higher in women taking hormonal combined contraception compared with non-hormonal contraception [8]
- In animal models of epilepsy:
 - Withdrawal of progesterone, mimicking premenstrual state, enhanced neuronal excitability and seizures [9]
 - Estrogen compounds significantly increased seizure frequency and severity [10]

4.5 Brain Regulation of Sex Hormones

- The brain regulates sex hormones via hypothalamic-pituitary-ovarian (HPO) axis (Fig. 4.2)
 - The hypothalamus produces gonadotropin-releasing hormone (GnRH)
 - GnRH stimulates anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
 - FSH makes ovarian follicle to grow and produce estrogen during follicular phase
 - Estrogen has negative feedback on FSH production and positive feedback on GnRH resulting in surge in LH
 - LH surge causes ovulation and corpus luteum formation which produces progesterone
 - Progesterone inhibits LH, FSH, and GnRH production
 - In the absence of pregnancy, corpus luteum regresses, and progesterone and estrogen drop resulting in menstruation

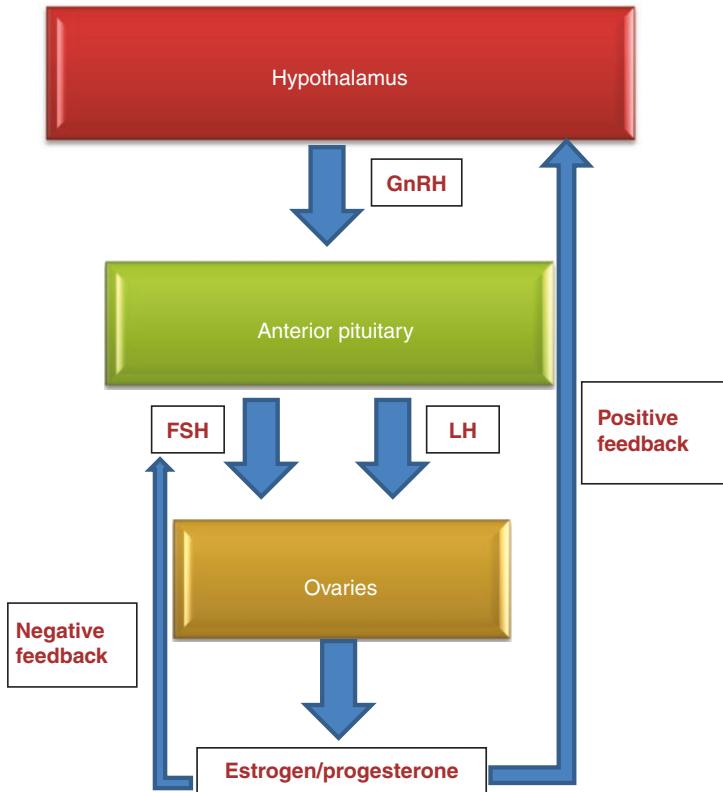


Fig. 4.2 Brain regulation of sex hormones through hypothalamic-ovarian-pituitary (HPO) axis

4.6 Reproductive Effects of Seizures

- Seizures can disrupt normal activity of brain structures, including the limbic system, amygdala, hypothalamus, and pituitary gland [11]
- The amygdala, which has close association with temporal lobe epilepsy, has reciprocal connections with the hypothalamus
 - Seizures originating from the amygdala can disrupt the GnRH-producing cells in the hypothalamus resulting in abnormal LH and FSH levels and therefore abnormal level of sex hormones and sexual dysfunction
- Menstrual disorders are estimated to occur in one-third of women with epilepsy as compared to 12–14% of women in the general population [12]
- Polycystic ovary disease (PCOS) occurs in 4–7% of women of reproductive age in the general population but in 10–25% of women with epilepsy [13, 14]
 - PCOS is characterized by:

- Enlarged ovaries with multiple small cysts
- Hypervascularized, androgen-secreting stroma
- Signs of androgen excess (hirsutism, alopecia, acne), obesity, and menstrual cycle disturbance (oligomenorrhea or amenorrhea)

4.7 Reproductive Effects of Seizure Medications

- Hepatic enzyme-inducing antiepileptic drugs (AEDs) such as phenytoin (PHT), carbamazepine (CBZ), and phenobarbital (PB) can lower concentration of the endogenous sex hormones [5]
- Valproic acid (VPA) is also known to cause endocrine side effects
 - Up to 45% of women treated with VPA have menstrual disorders and of those 90% showed PCOS and/or hyperandrogenism [15, 16]
 - VPA effects is more prominent in women younger than 26 years of age
- To date, no clinically significant endocrine effects are found associated with lamotrigine (LTG) or levetiracetam (LEV) [17]
- LEV can reduce basal estrogen secretion from ovarian follicles, but it does not affect the gonadotropin-stimulated estrogen secretion [18]

4.8 Treatment of Catamenial Epilepsy

- No FDA-approved treatment for CE
- *Progesterone lozenges/natural progesterone for C1 pattern*
- For the C1 type, consider using progesterone lozenges 200 mg three times daily around the days of seizure exacerbation or days 14–28 of the cycle [19]
- *Synthetic progestin*
- Consider oral daily synthetic progestin or IU devices with progestin versus depot medroxyprogesterone acetate (DMPA) at a dose of 150 mg every 3 months
- Reductions in seizure frequency of up to 39% over a 1-year period have been reported [20]
- *Acetazolamide*
- At 250 mg twice daily or 500 mg twice daily to be used around the 7–10 days of seizure exacerbation as determined by the seizure diary
- *Clobazam*
- 20–30 mg divided twice a day or one dose at night for 10 days, 2 days prior, and throughout the identified seizure exacerbation dates [21, 22]
- *Small increase in baseline AED*
- About 2 days prior to the identified period of seizure exacerbation for up to 10 days. Be cautious about phenytoin, carbamazepine, or other medications with higher risk for toxicity

4.9 Contraception in Women with Epilepsy

- The oral contraceptive failure rate is 1% in healthy women but 3–6% in the population of WWE [23–25]
- Contraceptive failure is the cause of one in four unplanned pregnancies
- Hepatic enzyme-inducing AEDs (EIAEDs) can lower progestin component of oral contraceptives and also cause failure of levonorgestrel subdermal implants [26, 27] through cytochrome P450 3A4 induction
- EIAEDs may reduce the efficacy of DMPA injections
 - It is common practice to administer the injections every 10 weeks in women using EIAEDs

4.10 Interactions of AEDs and Hormonal Contraception

- Some seizure medications may cause failure of hormonal contraception. Figure 4.3 summarizes the current knowledge of AEDs and hormonal contraceptives interaction

4.11 Pregnancy in Women with Epilepsy

- 24,000 WWE in the USA become pregnant every year

AEDs associated with contraceptive failure (EIAEDs)	AEDs with weak effect on contraceptive failure	AEDs with no known effect on contraceptive failure
<ul style="list-style-type: none">CarbamazepineClobazamEslicarbazepineOxcarbazepinePhenobarbitalPhenytoinPrimidoneRufinamide	<ul style="list-style-type: none">FelbamatePerampanelTopiramate	<ul style="list-style-type: none">ClonazepamEthosuximideGabapentinLacosamideLamotrigineLevetiracetam[†]PregabalinRetigabine/ezogabineTiagabineValproate*VigabatrinZonisamide

Fig. 4.3 Known interactions between AEDs and hormonal contraception. *Decreased free testosterone concentrations in men and increased androgen concentrations in women taking valproate. [†]Increased testosterone concentrations reported in men on levetiracetam

- In the majority of WWE, seizure frequency remains the same during pregnancy
- In 20–25% of WWE, there is increased seizure frequency during pregnancy
- Having a seizure disorder that was active in the year prior to pregnancy and in early pregnancy appears to be the best predictor of seizure recurrence during pregnancy [28]
- There is better seizure control during pregnancy in women with CE compared with WWE in general [29]
- The reasons for seizure recurrence during pregnancy are:
 - Reduced plasma concentration of AEDs and changes in AED metabolism (most common reason)
 - Increased renal clearance
 - Altered hepatic absorption
 - Increased plasma volume of distribution
 - Hepatic enzyme induction by steroid hormones
 - Lowering or stopping seizure medications
 - Hormonal fluctuations and higher estrogen to progesterone ratio especially in week 8–16 of pregnancy
 - Sleep deprivation
 - Psychosocial stress
- Lamotrigine clearance during pregnancy is 2–3 times higher than before pregnancy
- Estrogen enhances lamotrigine metabolism through hepatic glucuronidation during pregnancy [30]
- Zonisamide serum concentration may fall by over 40% during pregnancy [31]
- The plasma concentration of the active form of OXC declines by 36% to 50% in the late stages of pregnancy [32, 33]
- The American Academy of Neurology (AAN) practice guidelines suggest checking AED levels at baseline before conception and monthly thereafter [34]
- Dose adjustment should be considered to maintain an effective and stable level throughout pregnancy at least for WWE who are on LTG, OXC, LEV, CBZ, and PHT [34]

4.11.1 Pregnancy and Perinatal Counseling

4.11.1.1 Risks to the Fetus Due to Maternal Seizure Recurrence

- Epileptic seizures during pregnancy are independently associated with increased risk for adverse outcome of pregnancies in WWE. These include babies small for gestational age (SGA), low birth weight (LBW), and preterm deliveries [35]
- The risk associated with seizures may be related to fetal hypoxia, acidosis, decreased blood flow to the placenta, deceleration of fetal heart rate, and trauma as a result of maternal fall
- Frequent maternal tonic-clonic seizures during pregnancy were associated with lower verbal IQ in offspring of WWE [36]

- To avoid these harmful effects of convulsive seizures on the fetus, all efforts should be made to control seizures during pregnancy
- The benefits of using AEDs during pregnancy may outweigh the potential teratogenic side effects

4.11.1.2 Risk of Birth Defects or Fetal Death Due to AEDs

- The rate of major congenital malformation (MCM) is 2.2% in healthy women in the general population, 2.8% in children of untreated WWE, and 6.1% in children of WWE treated with AEDs (pooled analysis of 26 studies [37])
- Polytherapy results in higher rate of fetal malformation in the range of 6.8% compared with monotherapy with a risk of 4%
- The risk appears to be dose dependent and increased with higher doses of VPA (>700 mg/day), CBZ (>400 mg/day), PB (>150 mg/day), and LTG (>300 mg/day) as opposed to lower doses
- There are multiple ongoing pregnancy registries in the world which collect data on women taking AEDs during their pregnancy
- The North American AED Pregnancy Registry (NAAPR) published in its winter 2016 newsletter reported the following risk of fetal MCM for 11 AEDs (Fig. 4.4)
- According to NAAPR data, AEDs increase the risk for premature delivery and SGA [38]
- The most important risk factor for intrauterine death (spontaneous abortion and stillbirth combined) is maternal exposure to AED polytherapy and a parent with history of MCM [39]

4.11.1.3 Neurodevelopment and Fetal AED Exposure

- Fetal VPA exposure was associated with lower IQ and reduced cognitive abilities across a range of domains in offspring of WWE at 6 years of age in a dose-dependent manner NEAD study [40]
- The adjusted mean IQ score of children exposed to high-dose (more than 800 mg/day) VPA was significantly lower than that of controls by 9.7 points
- The predictors of low IQ in children of WWE were exposure to VPA, low maternal IQ, multiple convulsive seizures during pregnancy, and polytherapy [41]
- Other antiepileptic drugs, including CBZ, LTG, and PHT exposure, were not associated with lower IQ in children
- NAAPR investigators found specific deficits in socialization and motor function and a relative weakness in communication among children exposed to VPA [42]

4.11.1.4 Folic Acid Supplementation

- Folic acid during gestation is involved in nucleic acid and amino acid synthesis, cell division, DNA methylation, and tissue growth
- Some AEDs, such as VPA, CBZ, PB, PHT, and primidone (PRM), alter folic acid metabolism and may decrease folic acid levels in the blood

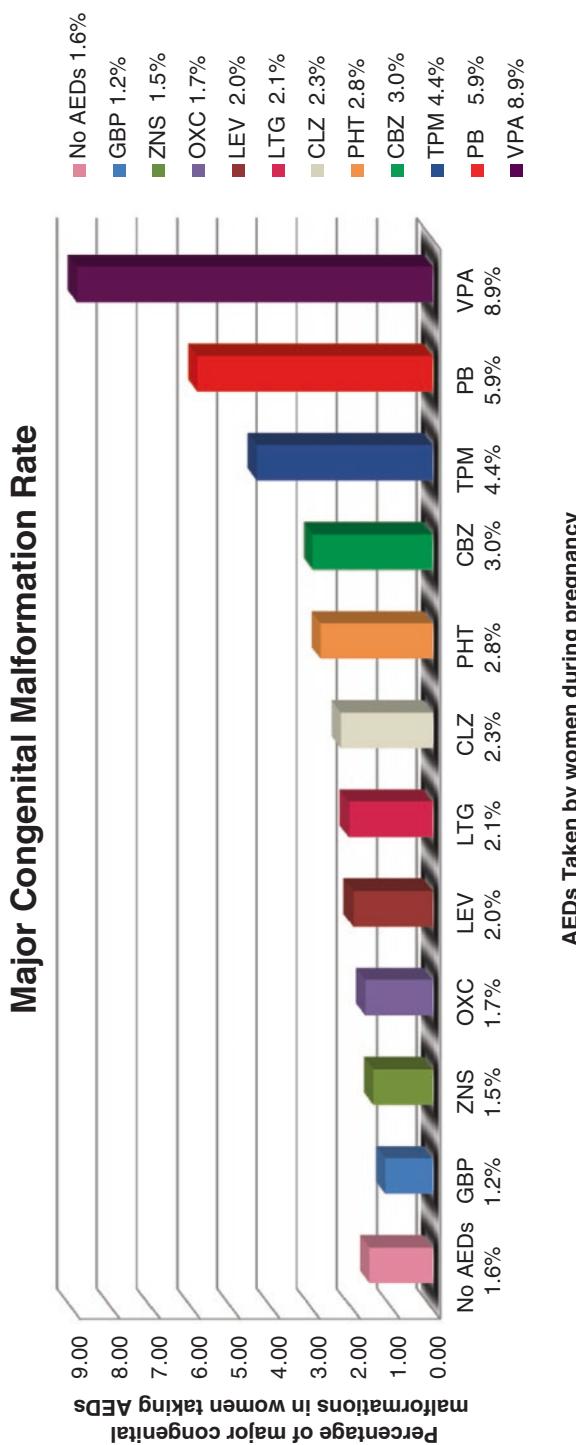


Fig. 4.4 Risk of major congenital malformation in women taking an AED as monotherapy during pregnancy compared with women taking no AEDs based on the data provided by the North American Antiepileptic Drug Pregnancy Registry (NAAPR 1997–2005). AED antiepileptic drug, GBP gabapentin, ZNS zonisamide, OXC oxcarbazepine, LEV levetiracetam, LTG lamotrigine, CLZ clonazepam, PHT phenytoin, CBZ carbamazepine, TPM topiramate, PB phenobarbital, VPA valproic acid

- Periconceptional folate supplementation has a positive association with better neurodevelopmental outcome and lower rate of autism spectrum disorder in general population [43]
- Folic acid supplementation is associated with higher IQ in children exposed to AEDs in utero [44]
- The US Public Health Service, Centers for Disease Control and Prevention, and American Academy of Neurology (AAN) recommend a dose of 0.4 mg per day of folate to be taken by all women of childbearing age to prevent neural tube defect [45]
- 5 mg of folic acid daily in women without epilepsy renders 85% protection against neural tube defects (systematic review [46])
- Study of 2302 mother-child pairs in Spain suggested that a high dosage of folate more than 1 mg/day may be associated with an increased risk of SGA at birth and lower levels of cognitive development in children 4–5 years of age [47]
- Common practice is using 1 mg folic acid daily in WWE of childbearing age
- A higher-dose folic acid of 4–5 mg daily may be considered in women taking VPA, CBZ, PB, PHT, and PRM

4.11.1.5 Breastfeeding

- All AEDs can pass into the breast milk to a certain degree, but the amount transferred is much less than the amount transmitted through the placenta to the fetus
- For barbiturates and benzodiazepines, the risk-benefit ratio for breastfeeding should be evaluated more carefully because of the reports of sedation, lethargy, weight loss, and higher drug levels in the child than in the mother
- Current practice is that breastfeeding is encouraged in women with epilepsy who took AEDs during pregnancy. The benefits may outweigh the risks
- In the NEAD study, breastfed children exposed to AEDs exhibited higher IQ and enhanced verbal abilities compared with AED exposed children who were not breastfed [40]

4.12 Perimenopause and Menopause

- Perimenopause is characterized by decreased ovarian progesterone secretion, leading to increased anovulatory menstrual cycles
- Early in perimenopause, estrogen secretion remains high, creating an excitatory environment and contributing to seizure exacerbation
- When menopause is achieved, due to diminished levels of FSH and hypogonadal state, seizures may stabilize
- Two-thirds of women experiencing early signs of menstrual changes report seizure exacerbation [48]

4.13 Bone Health

- Persons with epilepsy have a risk for fracture that is 2–6 times higher than that of the general population due to altered bone metabolism, decreased bone density, and propensity to fall as a result of seizure or AED-induced loss of balance [49–51]
- Risk factors for bone loss:
 - Epilepsy and AEDs
 - Female gender
 - Postmenopausal status
 - Sedentary lifestyle
 - Smoking
 - Excessive alcohol intake
 - Inadequate sun exposure
 - Certain endocrine conditions
- AEDs are known to alter bone metabolism
- The CYP450 enzyme-inducing AEDs (EIAEDs) such as PHT, PB, and PRM are most consistently associated with low bone mineral density and bone disorders [49]
- The data regarding the effect of VPA, CBZ, OXC, LTG, GBP, VGB, LEV, and TPM on bone metabolism and bone density are limited and show conflicting results
- Monitoring of calcium and vitamin D metabolites is important in patients who take AEDs
- Based on the Society for Endocrinology guidelines, 25-hydroxyvitamin D concentrations should be above 30 ng/mL
- To raise the vitamin D blood levels consistently above 30 ng/ml may require at least 1500–2000 IU/d of vitamin D
- Dual energy X-ray absorptiometry (DEXA) scan should be performed periodically to monitor BMD
- If osteopenia or osteoporosis is detected, consideration should be given to starting bisphosphonates or other therapeutic agents, increasing calcium and vitamin D supplementation, and/or replacing EIAEDs

Take-Home Points

- About 1/3 of women with epilepsy have catamenial epilepsy
- Women with CE have worsening of their seizures at certain times during their menstrual cycle associated with their hormonal fluctuation
- Estrogens are proconvulsant and progesterone is anticonvulsant
- Menstrual disorders are common in WWE
- The oral contraceptive failure rate is 3–6% in the population of WWE
- There is complex and at times bidirectional interactions between AEDs and hormonal contraception
- Intrauterine devices are safe and effective and method of choice for contraception in women with epilepsy

- Pregnancy has no effect or a protective effect on seizure frequency in the majority of WWE
- The best predictor of seizure recurrence during pregnancy is active seizure disorder the year prior to pregnancy
- Women with CE have better seizure control during pregnancy compared with WWE in general
- Prenatal counseling for WWE should include the need to stay on seizure medication, attempting monotherapy, and selecting medications with more favorable side effect profile
- Checking AED levels at baseline before conception and monthly thereafter is recommended by AAN guidelines
- Exposure to valproate in utero may adversely affect child IQ and contribute to autistic traits
- Current practice is that breastfeeding is encouraged in WWE who took AEDs during pregnancy
- Some AEDs can adversely affect bone health and calcium metabolism
- Early in menopause, seizures may worsen due to temporary increased estrogen to progesterone ratio. After menopause is established, women with CE may experience improvement in seizures

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Part II

EEG



Overview of EEG, Electrode Placement, and Montages

5

5.1 EEG Activity

- EEG records electrical activity of the brain neurons
- The electrical activity recorded by EEG is the postsynaptic potentials generated by cortical neurons
- Postsynaptic potentials are the alternation between the excitatory postsynaptic potential (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in apical dendrites of neurons
- Rhythmic activity recorded on EEG is the synchronized activity alternating between EPSPs and IPSPs. It arises from interaction between the cerebral cortex and thalami
- EEG activity is mainly generated by pyramidal cell postsynaptic potentials
- EEG records the difference in voltage between two brain locations plotted over time
- Rhythmic bursting EEG activity is generated in the nucleus reticularis of thalamus

5.2 EEG Recording

- Disc electrodes are conductors attached to the scalp and connected to the EEG recording instrument
- The amplitude and morphology of the electrical current produced by cortical generator cells is modified by brain tissue, CSF, skull, and scalp forming a volume conductor
- The standard set of electrodes in adults consists of 21 recording and 1 ground electrode
- The international 10–20 system is used for electrode placement [1] (Fig. 5.1)
- Odd numbers refer to the left-sided electrodes and even numbers to the right. For example, F3 is the left frontal electrode, and F4 is the right frontal

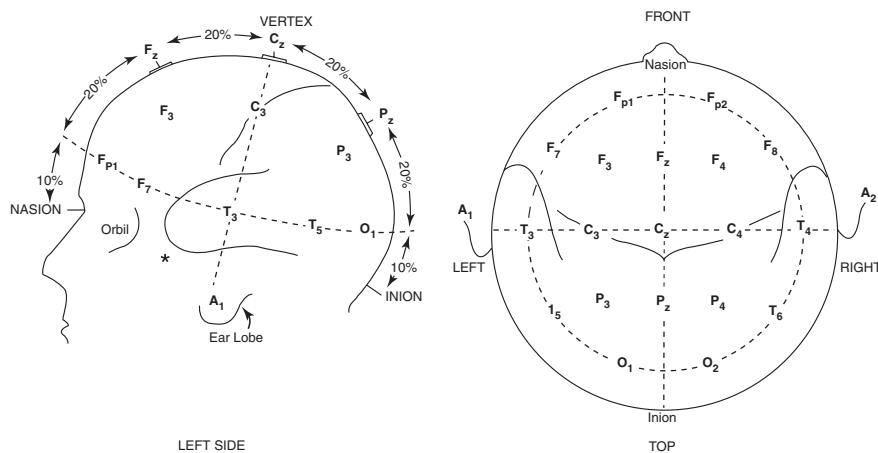


Fig. 5.1 The international 10–20 system is used for electrode placement

- The letter “z” designates midline. For example, Cz is midline central
- The numbers increase from anterior to posterior of the head
- These electrodes include:
 - Fronto-polar (Fp)
 - Frontal (F)
 - F3 and F4 are frontal
 - F7 and F8 are inferior frontal
 - F7 and F8 often record the anterior temporal regions
 - Central (C)
 - Temporal (T)
 - T3, T7, T4, and T8 are anterior temporal
 - T5, P7, T6, and P8 are posterior temporal
 - Parietal (P)
 - Occipital (O)
 - Auricular or earlobe (A)

5.3 Application of Electrodes Based on 10-20 System

- The distance between inion and nasion landmarks on the scalp is measured along the midline
 - The Fpz is marked at 10% of the measured nasion-inion distance above the nasion
 - Fz, Cz, Pz, and O are marked at 20% intervals along the midline
- The distance between the two periauricular points A1 and A2 is measured along a transverse line crossing Cz
 - T3, C3, C4, and T4 are marked at 20% intervals of the above measured line as shown in the above figure

- The circumference of the brain is measured crossing the occipital, temporal, and fronto-polar points (O, T3, T4, Fpz)
 - Fp1 and Fp2 are marked at 5% of the above distance to the left and right, respectively
 - F7, T3, T5, O1, O2, T6, T4, and F8 are marked at 10% of the circumference measured above
- The distance between Fp1-C3-O1 and Fp2-C4-O2 is measured. Halfway between Fp1 and C3 is where F3 is marked. Halfway between C3 and O1 is where P3 is marked. The same method is followed on the right to obtain the placement marks for F4 and P4
- T1 and T2 are true anterior temporal electrodes and are sometimes used for better localization [2]
 - T1 is placed between F7 and T3
 - T2 is placed between F8 and T4

5.4 Modified 10–20 System

- T3 = T7, T5 = P7, T4 = T8, T6 = P8
- Additional electrodes are placed for better localization and increasing spatial resolution and according to the American Clinical Neurophysiology Society guidelines (Fig. 5.2)

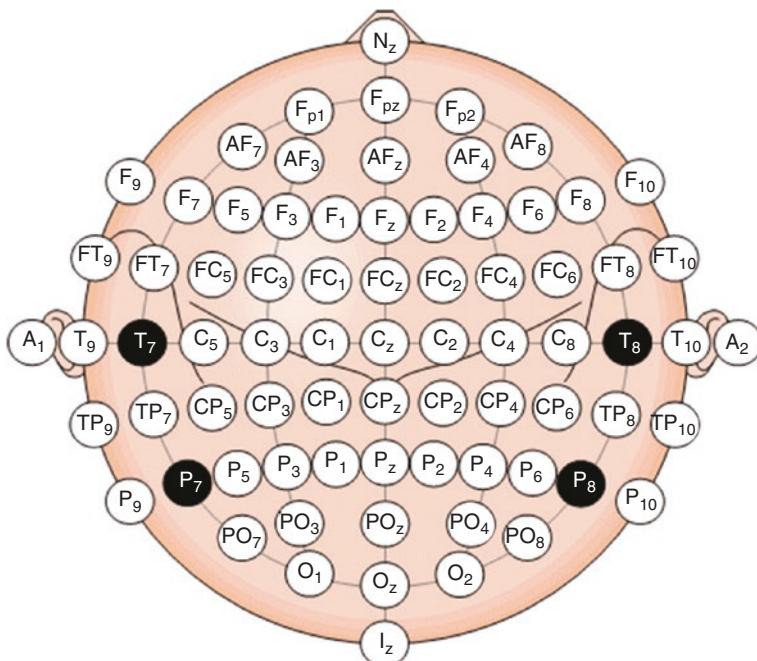


Fig. 5.2 Modified expanded 10–20 system according to the American Clinical Neurophysiology Society (ACNS) guidelines

5.5 Additional Electrodes

- Eye movements:
 - Recorded in two channels
 - One electrode is placed above and to the side of one eye and connected to input 1 of the first channel (E1 or PG1). A second electrode is placed below and to the side of the other eye and connected to input 1 of the second channel (E2 or PG2)
 - Input 2 of both eye movement channels are connected to the same reference electrode (e.g., E1-A2, E2-A2)
- EKG electrode for monitoring the heart
- EMG monitoring with electrode placed on the chin or other muscles to monitor muscle activity. This may be helpful in detecting REM sleep especially in neonatal EEG
- Photic marker for monitoring photic stimulation

5.6 Common EEG Montages (Table 5.1)

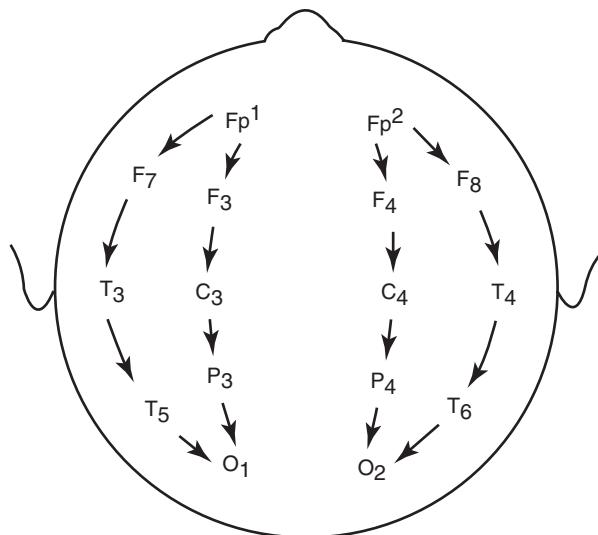
- *Longitudinal Bipolar Montage (Double Banana)*
 - Inputs 1 and 2 consist of adjacent electrodes of the 10–20 system

Table 5.1 Typical longitudinal bipolar (AP stands for anterior-posterior), referential ear, and transverse bipolar montages used in our institution

	AP bipolar	Ref ear	Transverse
1	Fp1 – F7	Fp1 – A1	F7 – F3
2	F7 – T3	F7 – A1	F3 – FZ
3	T3 – T5	T3 – A1	FZ – F4
4	T5 – O1	T5 – A1	F4 – F8
5	Fp2 – F8	FP2-A2	A1 – T3
6	F8 – T4	F8-A2	T3 – C3
7	T4 – T6	T4-A2	C3 – CZ
8	T6 – O2	T6-A2	CZ – C4 C4 – T4
9	Fp1 – F3	F3-A1	T4 – A2
10	F3 – C3	C3-A1	
11	C3 – P3	P3-A1	T5 – P3
12	P3 – O1	O1-A1	P3 – PZ PZ – P4
13	Fp2 – F4	F4 – A2	P4 – T6
14	F4 – C4	C4 – A2	
15	C4 – P4	P4 – A2	FP1-A1
16	P4 – O2	O2-A2	FP2-A2 O1-A1
17	FZ – CZ	FZ-A1	O2-A2
18	CZ – PZ	CZ-A1	
19	Photic marker		
20	LUE RLE	LUE RLE	LUE RLE
21	EKG	EKG	EKG

Note that since Fp1, Fp2 and O1, O2 are close to each other, we do not link them in our transverse montage

Fig. 5.3 Bipolar longitudinal montage



- Chain link connection where input 2 becomes input 1 in the next channel of recording (Figs. 5.3 and 5.4)
- Best for analyzing low- to medium-amplitude waveforms that are highly localized
- If the electrode in input 1 is more negative than the electrode in input 2, the waveform deflection is upward
- If the electrode in input 1 is more positive than electrode in input 2, the waveform deflection is downward
- In a bipolar montage, the localization of the cerebral potential is based on the direction of deflection of the waveform between two channels, and a *phase reversal* helps in localization of epileptiform abnormality

- *Transverse Bipolar Montage*
 - Similar to longitudinal bipolar but electrode derivations are arranged around transverse lines from left to right (Figs. 5.5 and 5.6)

- *Referential Montage*
 - The same electrode is used in input 2 of each amplifier (Figs. 5.7 and 5.8)
 - The reference should be chosen carefully, so it is inactive and not contaminated by the activity of input 1 electrode
 - Referential montage produces a higher-amplitude waveform due to longer interelectrode distance

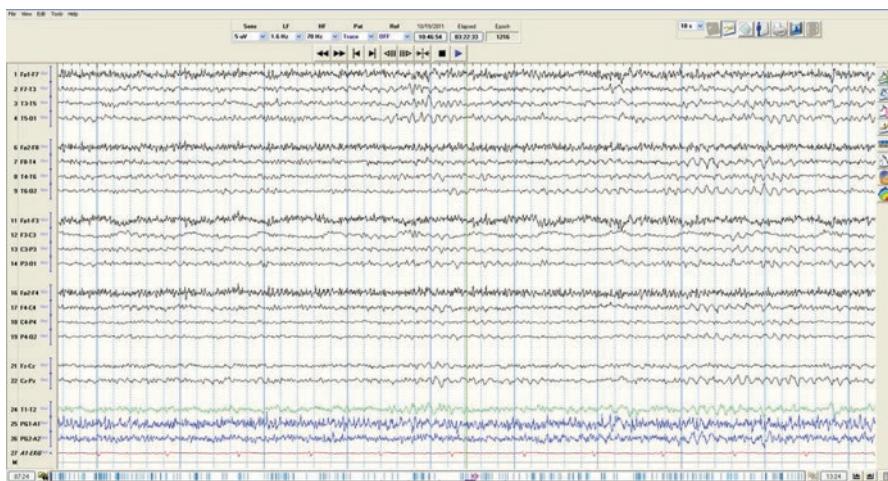
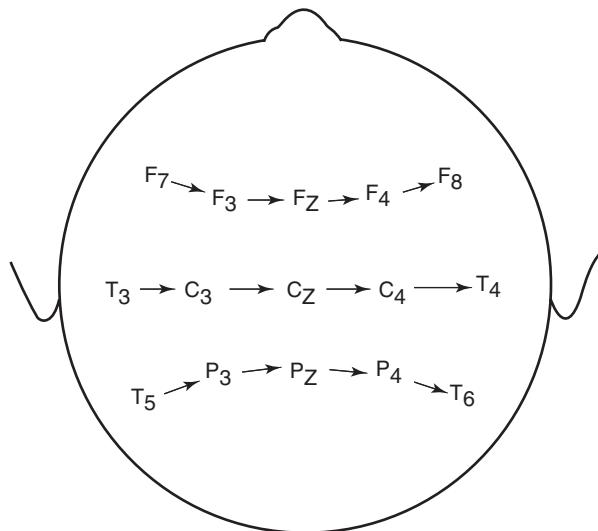


Fig. 5.4 Example of a longitudinal bipolar montage recording

Fig. 5.5 Transverse bipolar montage



- In referential montage, *the amplitude of the waveform* (not phase reversal) determines localization of epileptiform abnormality
- If all channels show similar activity in a referential montage, then the activity is coming from the reference electrode
- The reference electrode is commonly selected as the earlobe electrodes (A1 and A2) or the average of a combination of electrodes

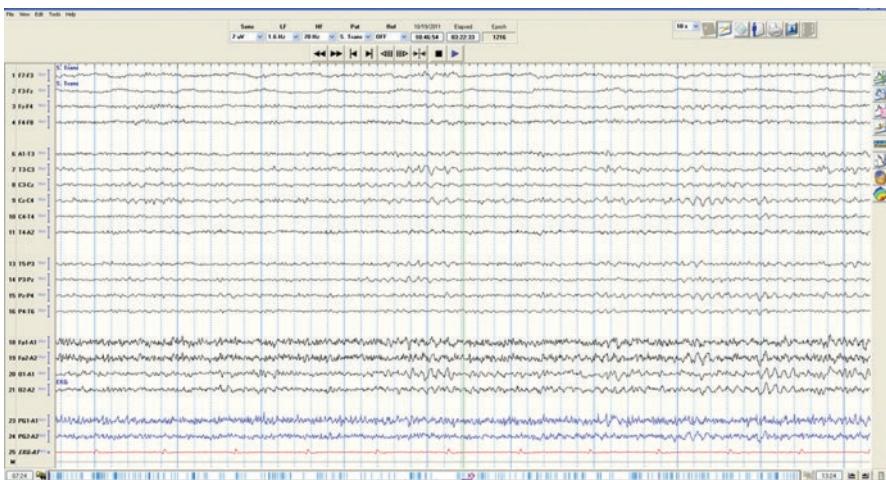
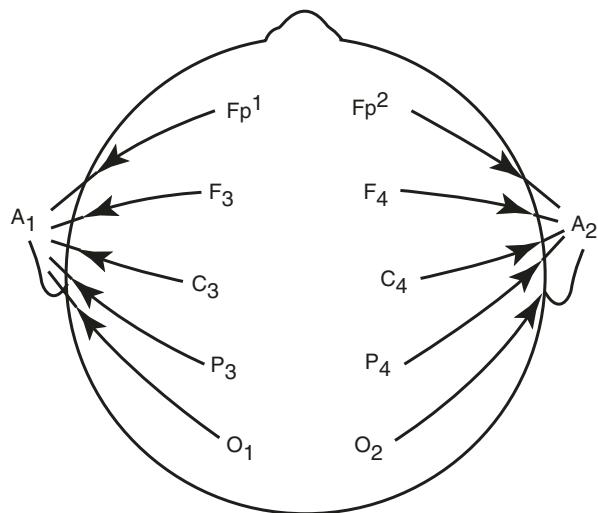


Fig. 5.6 Example of a bipolar transverse montage recording

Fig. 5.7 Referential ear montage



- **Laplacian Montage**

- For analysis of spatial sampling of EEG (Fig. 5.9)
- It uses weighted average of the nearest neighboring electrodes surrounding input 1 of an electrode
- Extremely helpful in detecting focal abnormality on EEG and electrographic seizure topography

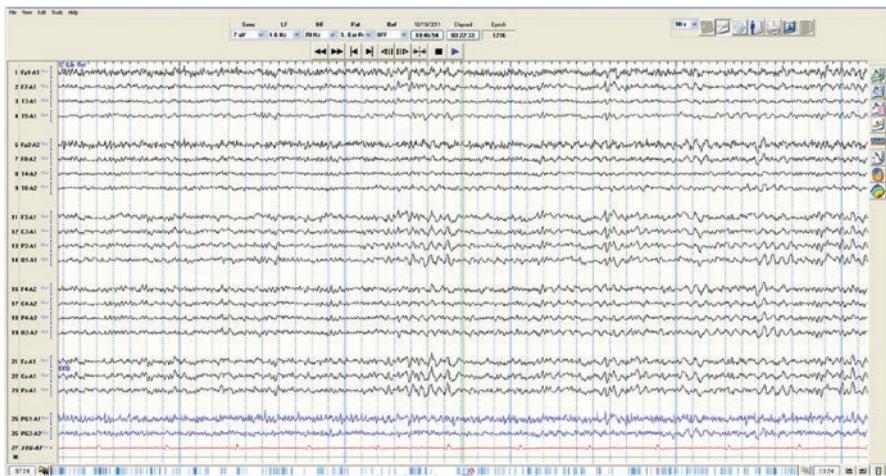


Fig. 5.8 Example of a referential montage recording



Fig. 5.9 Example of laplacian montage recording

5.7 EEG Filters/Paper Speed/Impedance/Sensitivity

- Set low-frequency filter at 1 Hz and high-frequency filter at 70 Hz for routine recording
- The EEG reader should be aware of any changes made to filter setting during the recording, which may be misleading
- Lowering the high-frequency filter to 35 or 15 Hz may filter too much myogenic artifact and make the myogenic activity look like epileptiform spikes

- Increasing the low-frequency filter higher than 1 Hz may make the EEG look flat and filter out the slow activity
- A speed of 30 mm/second is routinely used to read EEGs
- Impedance of electrodes should be below 5000 ohms
- The sensitivity for a routine recording is set at 7 microvolts/mm

Take-Home Points

- EEG records electrical activity of neurons consisting of postsynaptic potentials generated by cortical neurons
- Postsynaptic potentials are alternation of EPSPs and IPSPs in apical dendrites
- Rhythmic EEG activity arises from interaction between the cerebral cortex and thalamus
- The standard set of electrodes in adults consists of 21 recording and 1 ground electrode
- The international 10–20 system is used for electrode placement
- Odd number electrodes are on the left, and even numbers are on the right with “z” indicating midline
- In bipolar montage, *phase reversal* helps in localization of epileptiform abnormality
- In referential montage, *the amplitude of the waveform* (not phase reversal) determines localization of epileptiform abnormality
- Laplacian montage is helpful in detecting focal abnormality on EEG and electrographic seizure topography
- Routine settings of EEG include:
 - Low-frequency filter at 1 Hz and high-frequency filter at 70 Hz
 - Speed 30 mm/s
 - Sensitivity 7 μ V/mm
 - Impedance of electrodes <5000 Ω

References

1. Guideline thirteen: guidelines for standard electrode position nomenclature. American Electroencephalographic Society. J Clin Neurophysiol. 1994;11(1):111–3.
2. Silverman D. The anterior temporal electrode and the ten-twenty system. Electroencephalogr Clin Neurophysiol. 1960;12:735–7.



Normal EEG Awake and Sleep

6

6.1 Basic Waveforms of EEG

- Four basic waveforms:
 - Alpha 8–13 Hz
 - Beta >13 Hz
 - Theta 4–7 Hz
 - Delta <4 Hz
- Alpha 8–12.9 Hz
 - Posterior rhythm generated by occipital areas during awake state (Fig. 6.1)
 - Waxes and wanes and shows attenuation of amplitude to eye opening

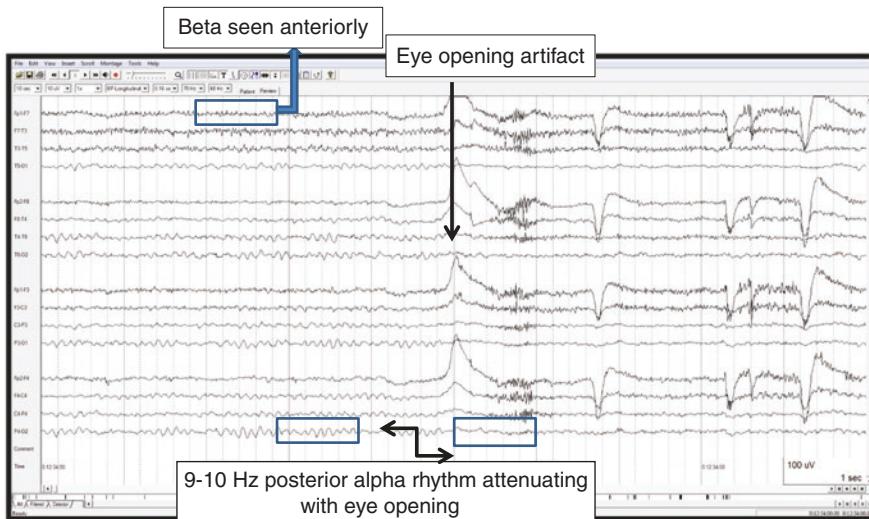


Fig. 6.1 Normal posterior alpha rhythm reactive and attenuating with eye opening

- Also attenuates with mental activity, auditory, and tactile stimuli
- Alpha enhances with eye closure and relaxation
- Alpha may decrease by 1–2 Hz during drowsiness
- Usual amplitude 20–60 microvolts
- Symmetric and synchronous
 - Greater than 1 Hz asymmetry between left and right is abnormal
 - Greater than 50% amplitude difference between left and right is abnormal
 - The right posterior hemisphere may have up to 20% higher-amplitude alpha compared with the left (normal)
- Alpha squeak:
 - Higher-frequency and slightly lower-amplitude alpha seen a few seconds after eye closure (Fig. 6.2)
 - Will return to normal alpha shortly after
 - A normal phenomenon
- The lower limit of alpha at 8 Hz is reached by age 3
- 9–12 Hz alpha is achieved by adolescence
- *Beta > 13 Hz*
 - Seen in fronto-central areas during awake state
 - Amplitude <25 microvolts in 98% of normal circumstances
 - Enhanced during early drowsiness

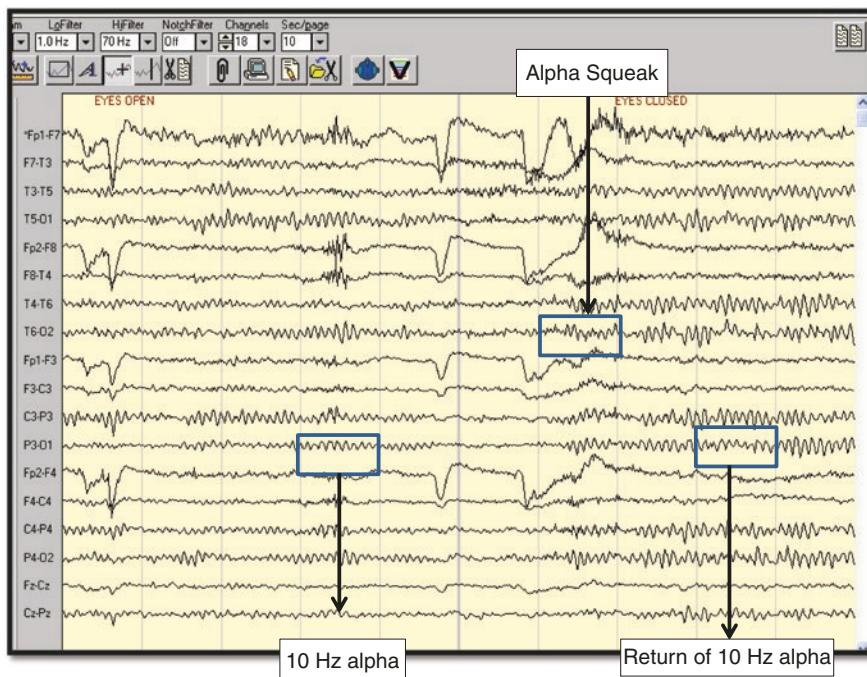


Fig. 6.2 Alpha squeak shortly after eye closure

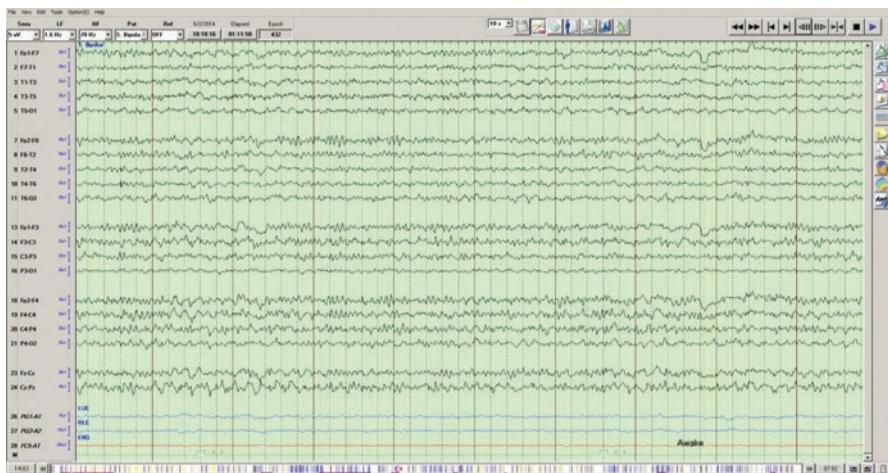


Fig. 6.3 Mild diffuse excess beta activity in a 29-year-old taking clonazepam

- Enhanced with some medications (Fig. 6.3):
 - Benzodiazepines
 - Phenobarbital
 - Chloral hydrate
 - Tricyclic antidepressants
 - Neuroleptics
 - Low-dose propofol
- Enhanced with mental activity, early sleep, and REM sleep
- *Theta* 4–7.9 Hz
 - Normal in young children and during drowsiness in adult EEG
 - Normal in young adults in fronto-central areas
 - See during early stages of sleep in adults (N1, as well as REM)
 - Generalized theta in an adult patient in the absence of drowsiness may indicate diffuse cerebral disturbance, encephalopathy, and/or medication effect
 - Focal and asymmetric theta activity may indicate focal disturbance of cerebral function
- *Delta* < 4 Hz (3.9 Hz or slower)
 - Present in sleep (especially stage N3)
 - Not present during awake state (in normal adults)

6.2 Other Normal Waveforms in the Awake State

- *Mu Rhythm*
 - Also known as comb rhythm, wicket rhythm, rythme rolandique en arceau, alphoid activity, precentral alpha, rolandic alpha

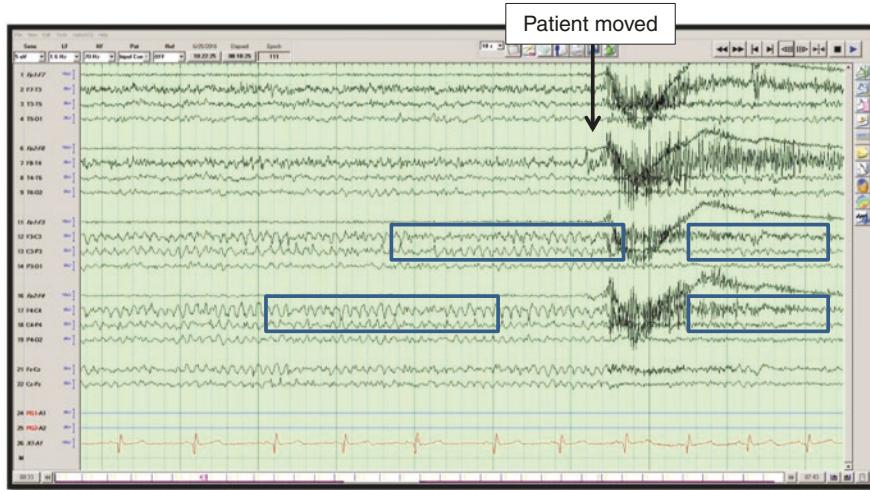


Fig. 6.4 Mu (μ) rhythm in C3 and C4 region attenuating with movement

- 7–12 Hz comb-like or arch-shaped pattern
- Present at rest over the somatosensory area of the brain (C3 and C4) (Fig. 6.4)
- Observed in about 20–30% of young adults
- Enhances with immobility during wakefulness
- Attenuates with problem-solving, movement of the contralateral limb, and fatigue
- *Lambda*
 - Biphasic or triphasic sharp transients
 - Present bilaterally over the occipital regions during visual scanning such as a patterned design (Fig. 6.5)
 - Reduced with eye closure, dim lighting, or having person look at blank screen
 - Enhanced by increased complexity of the visual stimulus, rapid gaze shift, and saccadic eye movements
 - Surface positive, sharply contoured, 4–5 Hz, 160–250 msec duration
 - The wave is similar to Greek letter for lambda (λ)
 - Subjects with lambda waves tend to have prominent POSTS (positive occipital sharp transients of sleep) and photic driving responses
 - Present in about 65% of the population
- *Alpha Variants*
 - *Slow Alpha Variant*
 - Subharmonic relation to alpha rhythm with similar reactivity and distribution
 - Notched waveforms with a frequency of half the resting alpha (4–5 Hz)
 - Alternates with normal alpha activity

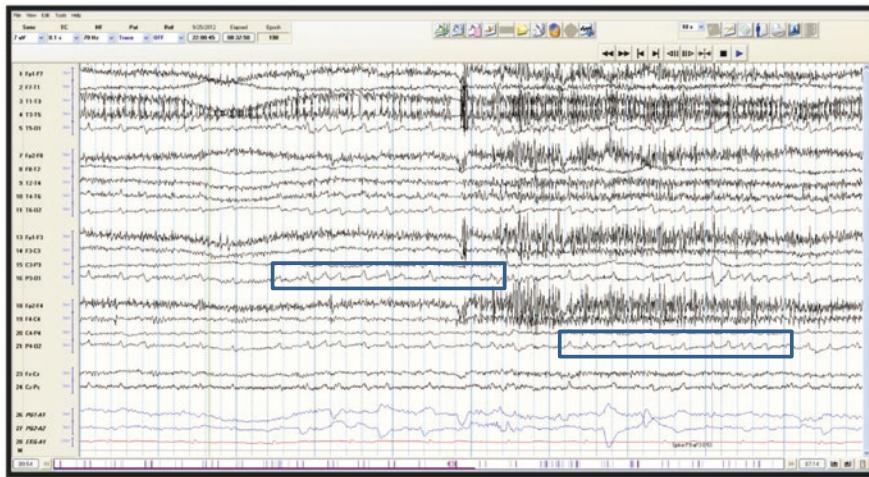


Fig. 6.5 Lambda waves (λ) in a 56 year old lady looking at her laptop computer

- *Fast Alpha Variant*
 - Suprharmonic relation to alpha rhythm with similar reactivity and distribution
 - Usually around 14–16 Hz and with a voltage of 20–40 microvolts
 - *Paradoxical Alpha*
 - Return of alpha with eye opening or alerting stimulus in a drowsy person
 - This is the reverse of usual attenuation of alpha to alerting stimulus
 - Some alpha may return when the eyes are open for more than a few seconds
 - If alpha fails to attenuate to eye opening on one side (Bancoud's phenomenon), there is an abnormality on the side that fails to attenuate
 - *Temporal Alpha*
 - Older patients may have alpha activity over the temporal head regions
 - Temporal alpha may occur in trains and synchronously
 - May persist during drowsiness when occipital alpha disappears
 - May be of higher amplitude on the left
 - *Frontal Alpha*
 - Usually related to drugs such as propofol-induced anesthesia
 - On occasions during arousal from sleep, alpha may appear in anterior head regions

6.3 Hyperventilation (HV)

- One of the activation procedures used during EEG recording
 - Performed for 3–5 min

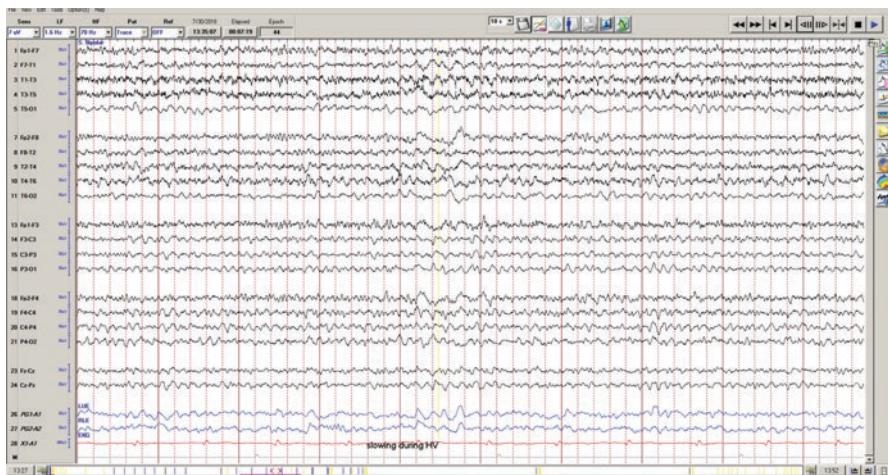


Fig. 6.6 Generalized slow activity during hyperventilation in a 48 year old female

- <10% of focal epilepsies and up to 80% of generalized epilepsies are activated with hyperventilation especially in absence seizures
- Often produces no change or generalized slow activity in the theta/delta range (Fig. 6.6)
- The slow activity may have gradual or abrupt onset and is more prominent in children
- More prominent hyperventilation response seen in:
 - Younger subjects
 - Subjects with more vigorous attempt
 - Subjects with low blood sugar
- Abnormal activations with HV include:
 - Epileptiform discharges
 - Focal or lateralized slowing
 - EEG asymmetry
- HV is contraindicated to use in:
 - Recent stroke
 - Intracerebral hemorrhage
 - Significant cardiac condition
 - Significant cerebrovascular disease
 - Significant respiratory disorders
 - Aneurysm
 - Sickle cell disease
 - Moyamoya (buildup of slow waves after HV ends may be diagnostic)

6.4 Photic Stimulation (PS)

- One of the routine activation procedures during EEG recording
- A range of 1–30 Hz frequencies of flashing light is used with the lamp distance 12–18 inches from the nose (30 cm)/stimulus 10 s on and 10 s off
- May produce occipital potentials locked in frequency with the flash light called *photic driving response* (Normal) (Fig. 6.7)
- Photic driving response may be subharmonic (1/2 the frequency of flash stimulus) or suprharmonic (double the frequency of flash stimulus)
- *Photomyogenic response* is the myogenic artifact due to contractions of frontalis muscle during the PS. The response is normal and of non-cerebral origin
- If intermittent head jerks are seen during PS, it is called *photomyoclonic response*. This response is normal
- *Photoparoxysmal response (PPR)* is when a burst of generalized spike and wave or polyspike and wave is activated during photic stimulation
- Photoparoxysmal response is abnormal and indicates a tendency for generalized epilepsy or an inherited trait for epilepsy
- The PPR is best provoked at 10–20 Hz flash frequencies
- Rarely focal epileptiform discharges may also be evoked by photic stimulation
- If the PPR outlasts the duration of stimulus, it is more likely to be associated with clinical epilepsy

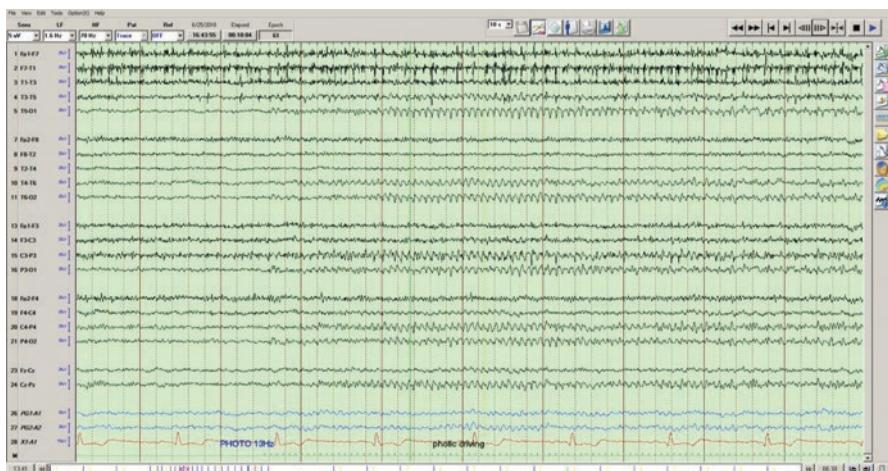


Fig. 6.7 Photic driving response in a 73-year-old man

6.5 Normal Sleep EEG

6.5.1 Non-REM Sleep: Stages N1, N2, N3

- N1: 5–10%
- N2: 30–50%
- N3: 20–40%

6.5.2 REM Sleep: 20–25%

- 4–5 cycles per night
- Starts around 90 min after sleep onset
- Increases in intensity and frequency toward the end of sleep cycle

6.5.3 Drowsiness and Stage N1 Non-REM Sleep

- Disappearance of eye blink and onset of slow eye movements (SEMs) (Fig. 6.8)
- Dropout of alpha, slowing of background, appearance of theta (Fig. 6.8)
- Temporary diffuse beta activity, maximal fronto-central
- A few vertex waves in central areas (Fig. 6.8)
- Positive occipital sharp transients of sleep (POSTS) (Fig. 6.9):
 - During drowsiness and light sleep

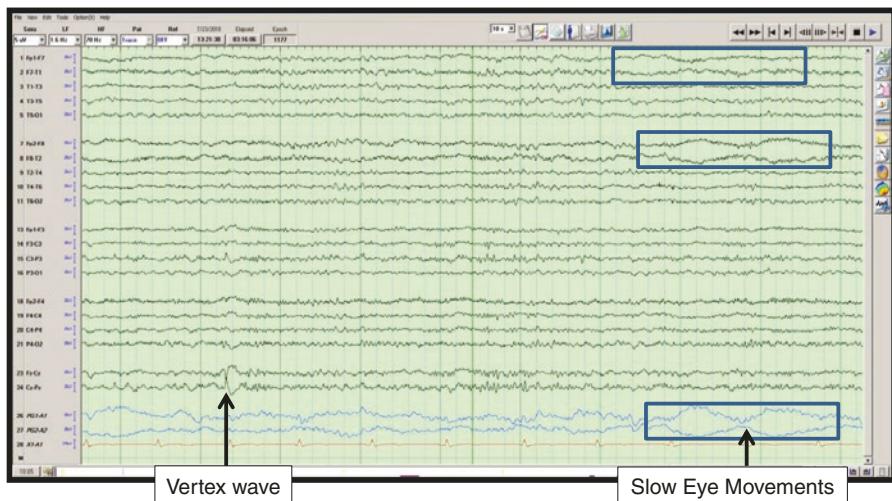


Fig. 6.8 Drowsiness and N1 stage of sleep. Note diffuse beta, some intrusion of theta frequency, slow eye movements seen in frontal and eyelid electrodes, and lone vertex wave



Fig. 6.9 Positive occipital sharp transients of sleep (POSTS). This patient also showed prominent lambda waves during awake and photic driving response

- Mostly in train of 4–5 Hz
- Surface-positive sharp transients in occipital head regions
- Mostly bilaterally synchronous but at times asymmetric
- More commonly seen in young adults

6.5.4 Stage N2 Non-REM Sleep

- Sleep spindles, vertex waves (V-waves), and K-complexes present [1]
 - Spindles
 - Have a frequency of 11–14 Hz and are sinusoidal in appearance
 - Occur in intervals of 5–15 s each lasting 0.5–1.5 s
 - Become symmetric and synchronous by 2 years of age
 - V-waves
 - Spiky and sharp, high-voltage waves in central area
 - May occur in clusters and short trains
 - Have more blunted appearance in elderly
 - K-complex (Fig. 6.10)
 - A combination of broad vertex wave (>500 msec in duration, biphasic or polyphasic), more frontally dominant and followed by spindle activity
 - May occur in response to afferent stimulation such as sudden noise
 - Benzodiazepines make N2 more prolonged
- Eye movements stop and EMG becomes quieter compared with N1

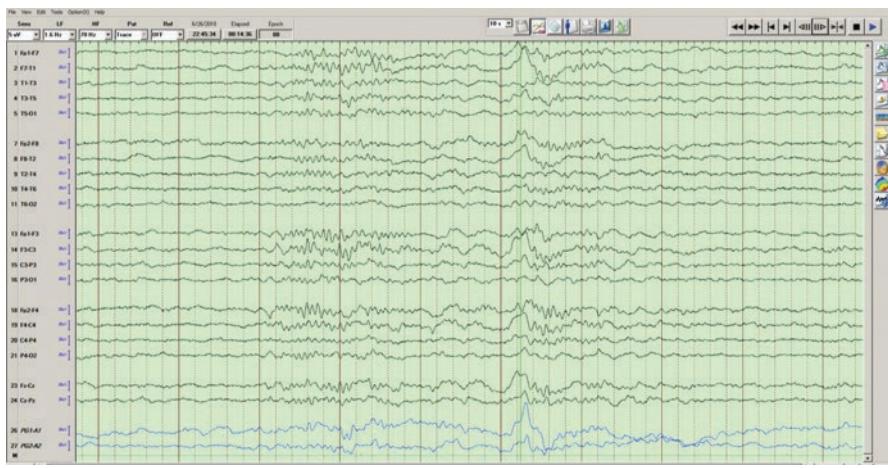


Fig. 6.10 K-complex in stage N2 of non-REM sleep

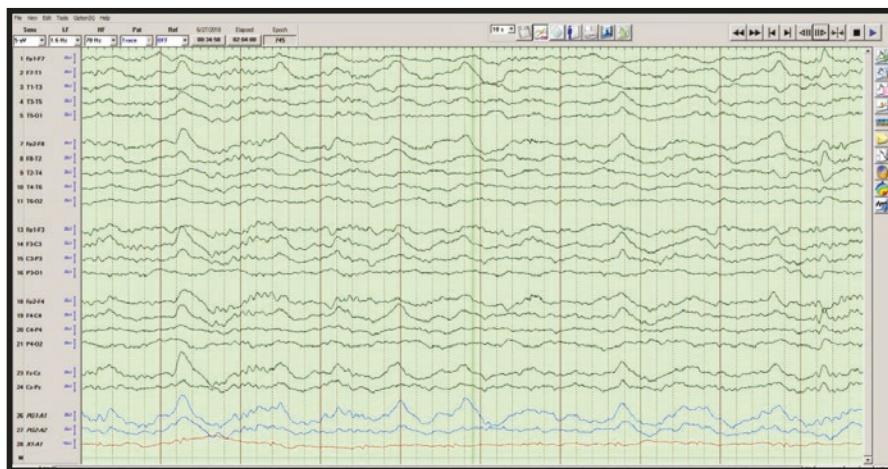


Fig. 6.11 Predominant delta in stage N3 non-REM sleep

6.5.5 Stage N3 Non-REM Sleep

- Slow wave of sleep or deep sleep (Fig. 6.11)
- Delta activity predominates (low frequency up to 2 Hz and high amplitude $>75 \mu\text{V}$)
- There is decreased muscle activity but muscles retain their ability to function
- Occurs within 15–45 min of sleep onset and occurs more in the first half of the night
- If awakened from this stage, people feel groggy and confused

- Parasomnias such as night terrors, sleepwalking, sleep talking, and bedwetting occur in N3 stage
- Benzodiazepines, tricyclic antidepressants (TCAs), and barbiturates reduce the N3 stage [2, 3]

6.5.6 REM Sleep (Stage R)

- Low-voltage, mixed-frequency activity on EEG, similar to awake state
- Loss of voluntary muscle tone, except for extraocular muscles and diaphragm
- Rapid eye movements (conjugate, irregular, sharply peaked eye movements) (Fig. 6.12)
- Sawtooth waves (Fig. 6.13)
 - 2–6 Hz vertex-negative sharp waves
 - Seen in frontal and central leads in brief bursts
 - Concomitant or following rapid eye movements
- Cardiac rhythm and respiratory irregularity
- REM sleep occurs every 90–120 min
- Associated with vivid dreams and more frequent and longer duration apneas, hypopneas, and severe hypoxemia
- Plays a role in memory consolidation, cognition, and physiological homeostasis
- Amphetamines, barbiturates, TCAs, monoamine oxidase inhibitors (MAOIs), anticholinergics, and alcohol may suppress REM sleep [2, 3]
- Sleep apnea, REM behavior sleep disorder, and nightmares may occur in REM sleep [2]

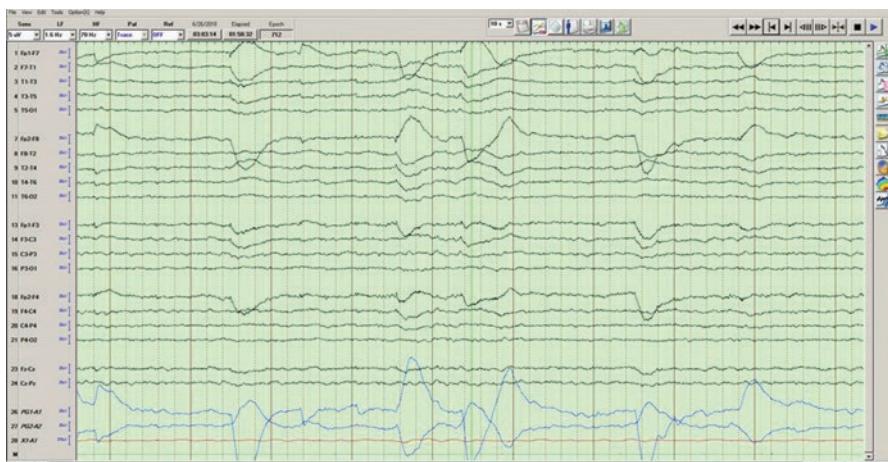


Fig. 6.12 REM sleep 10 s epoch



Fig. 6.13 REM sleep 30 s epoch. Note rapid eye movements in lateral frontal electrodes and saw tooth waves shown in the box

- In infants, REM sleep constitutes 50% of sleep (called active sleep), and non-REM sleep (called quiet sleep) comprises the remaining 50%
- By age 2, the sleep cycle duration is comparable with adults with 75% non-REM and 25% REM sleep
- Narcolepsy is a REM sleep disorder
- *Phasic REM sleep phase*
 - Bursts of rapid eye movements some associated with bursts of EMG twitches
 - Sudden increase in sympathetic activity
- *Tonic REM sleep phase*
 - More consistent muscle atonia

Take-Home Points

- Basic waveforms are important to be recognized for an EEG recording interpretation
- *Alpha* ($8\text{--}13\text{ Hz}$) is seen in posterior region in awake and alert state and attenuates to eye opening
- *Beta* ($>13\text{ Hz}$) is seen in anterior head regions during awake state
- *Theta* ($4\text{--}7\text{ Hz}$) is seen in drowsy and light sleep state and is otherwise abnormal in an awake adult
- *Delta* ($<4\text{ Hz}$) is seen in N2 and N3 of sleep and is abnormal in normal awake adult
- *Mu (μ) rhythm* is $7\text{--}12\text{ Hz}$ comb-like rhythm over C3 and C4 generated by the somatosensory cortex. Mu is a normal finding and attenuates with moving the opposite limb

- *Lambda* (λ) is a normal activity consisting of 4–5 Hz positive occipital sharp transients during visual scanning
- People with lambda will generally show prominent *POSTS* during light sleep and photic driving response
- *POSTS* are positive occipital sharp transients of sleep, normal surface positive sharp transients (4–5 Hz) in occipital area during light sleep
- Generalized slow activity is a normal response to hyperventilation and more prominent in younger patients
- *Photic driving* response is a normal phenomenon of no clinical significance
- *Photomyogenic* response is a non-cerebral and normal phenomenon, but *photoparoxysmal* response is abnormal and likely suggestive of a tendency for epilepsy
- Sleep cycles last 90–120 min and consist of non-REM sleep (75%) and REM sleep (25%)
- *Non-REM sleep* consists of N1(5–10%), N2 (30–50%), and N3 (20–40%) stages of sleep
- Sleep spindles, vertex waves, and K-complexes are prominent features of N2
- In N3 stage, delta activity is predominant, and parasomnias (night terrors, sleep walking, and sleep talking) may occur
- *REM sleep* consists of low-amplitude, mixed-frequency activity similar to awake state
- Rapid eye movements, EMG silence, and *sawtooth waves* are seen in REM sleep
- Sleep apnea, REM behavior sleep disorder, and nightmares may occur in REM sleep

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2. Shrivastava D, et al. How to interpret the results of a sleep study. *J Community Hosp Intern Med Perspect.* 2014;4(5):24983.
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Benign or Normal EEG Variants

7

7.1 Benign EEG Variants

- Spiky or rhythmic patterns with no clinical significance
- Mostly appear during drowsy state or lighter sleep
- Disappear in deeper stages of sleep

7.2 Benign Spiky Variants

7.2.1 14 and 6 Positive Spikes

- Primarily seen in 12–20 years of age and decrease in prevalence with age
- Occur during drowsiness and light sleep
- Arch-shaped or comb-like appearance with alternating positive spiky component
- Best seen in referential montage with greater inter electrode distance (e.g., contralateral ear)
- Maximum amplitude in posterior temporal areas (T5 and T6)
- Alternating bursts of 14 Hz or 6–7 Hz surface positive spikes ranging from 0.5 to 1 s in duration [1] (Fig. 7.1)
- Seen independently over the two hemisphere and may be asymmetric, varying in occurrence from side to side
- 14 Hz bursts are more frequently seen compared with 6 Hz bursts

7.2.2 Small Sharp Spikes (SSS)

- AKA: benign small sharp spike (*BSSS*)
- AKA: benign epileptiform transients of sleep (*BETS*)
- Best seen in temporal leads, bilateral, and mostly asynchronous (Fig. 7.2)
- Low voltage (50 µV) and short duration (<50 msec)



Fig. 7.1 Fourteen and six (14 and 6) positive spikes, in this case seen maximally in the left posterior temporal and parietal areas ($T5 > P3$)

- Monophasic or diphasic, steep ascending and descending limbs
- Alternating between left and right temporal lobe
- Occur during drowsiness and sleep/disappear during deeper sleep
- Incidence is about 25%
- Do not occur in trains and are not associated with focal slowing

7.2.3 6 Hz Spike and Wave

- AKA: *phantom spike and wave*
- Brief low-amplitude spike (at times difficult to detect) with a high-amplitude prominent slow wave
- May occur as a small train of spike and wave discharges at 5–7 Hz lasting under 2 s (Fig. 7.3)
- Usually diffuse and bilaterally synchronous
- Occurs in adolescents and adults with an incidence of 0.4–2.5%
- Hughes described two variants [2]:
 - WHAM: wake, high amplitude, anterior, male
 - May overlap with potentially epileptogenic discharges
 - More in patients with seizures
 - FOLD: female, occipital, low amplitude, drowsy
 - More benign variant of 6 Hz spike and wave

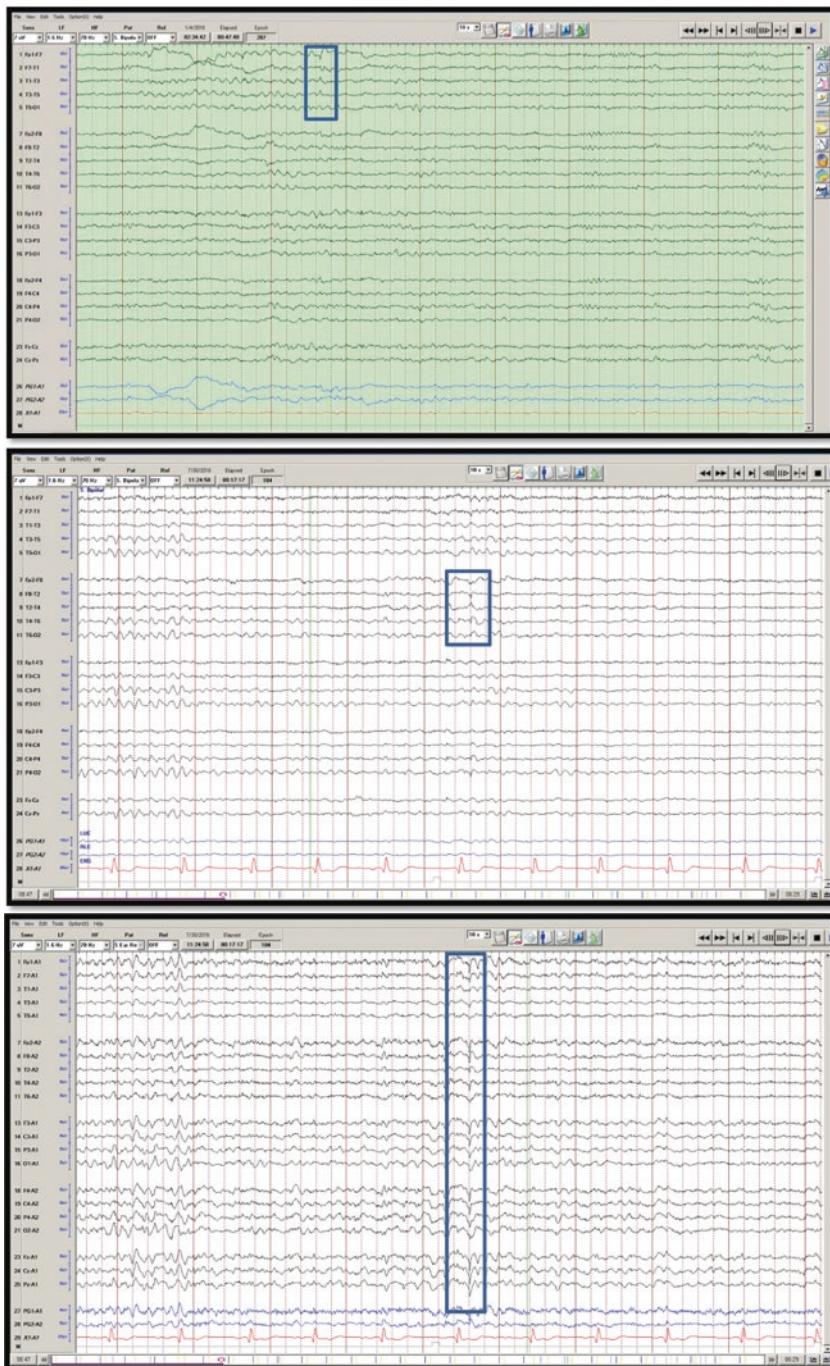


Fig. 7.2 Benign epileptiform transients of sleep (BETS) in the left anterior and mid-temporal area (top) and right anterior and mid-temporal (middle) in bipolar montage. The bottom image shows the same right temporal BETS in ear reference montage which looks more widespread

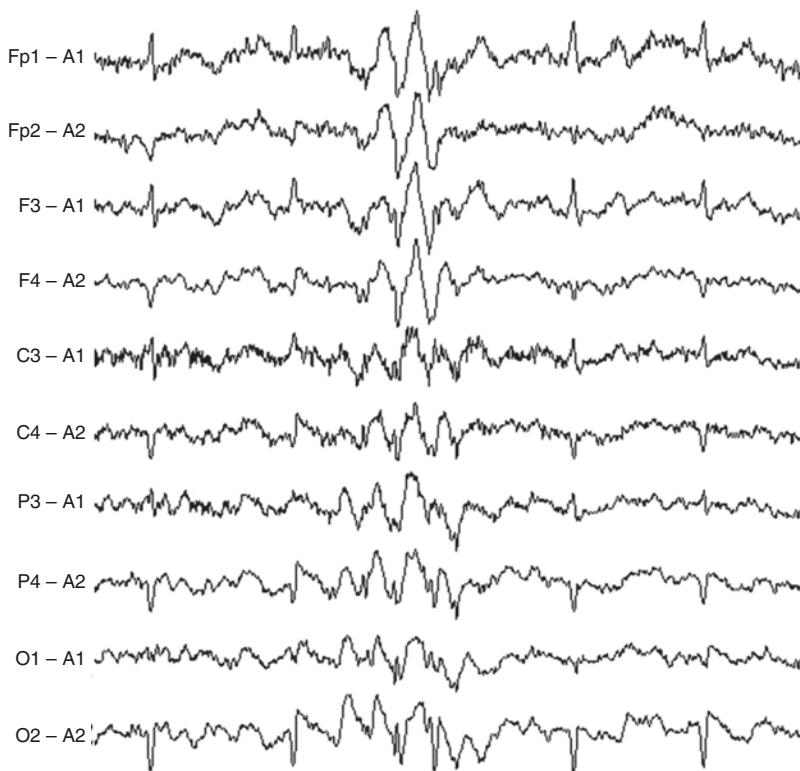


Fig. 7.3 6 Hz (phantom) spike and wave

7.2.4 Wicket Spikes (Wicket Waves)

- Normal variant present in the temporal region in older adults (usually >50 years)
- Mostly seen during drowsiness and light sleep but may occur during awake state
- Alternates between left and right temporal lobe but may be more frequent on one side (Fig. 7.4)
- Single spike or trains of mu (μ) like waves and arch shaped
- To differentiate from true epileptiform temporal spikes:
 - Wicket spikes do not have after coming slow wave
 - They do not disrupt background EEG
 - The appearance of single spikes are similar to when they occur in trains
 - No focal temporal slowing or TIRDA (no temporal intermittent rhythmic delta activity)
- Frequency 6–11 Hz, amplitude 60–200 microvolts

7.2.5 Breach Rhythm

- Enhanced higher-amplitude activity recorded over the area of a skull defect
- First described by Cobb in 1979 [3]



Fig. 7.4 Wicket spikes. Note alternating left and right wicket waves maximal in the anterior and mid-temporal area

Fig. 7.5 A picture of wicket showing set of three stumps with two bails across the top



Wicket Definition (Oxford dictionary): (Fig. 7.5)

A small door or gate, especially one beside or in a larger one

In Cricket: Each of the sets of three stumps with two bails across the top at either end of the pitch, defended by a batsman.

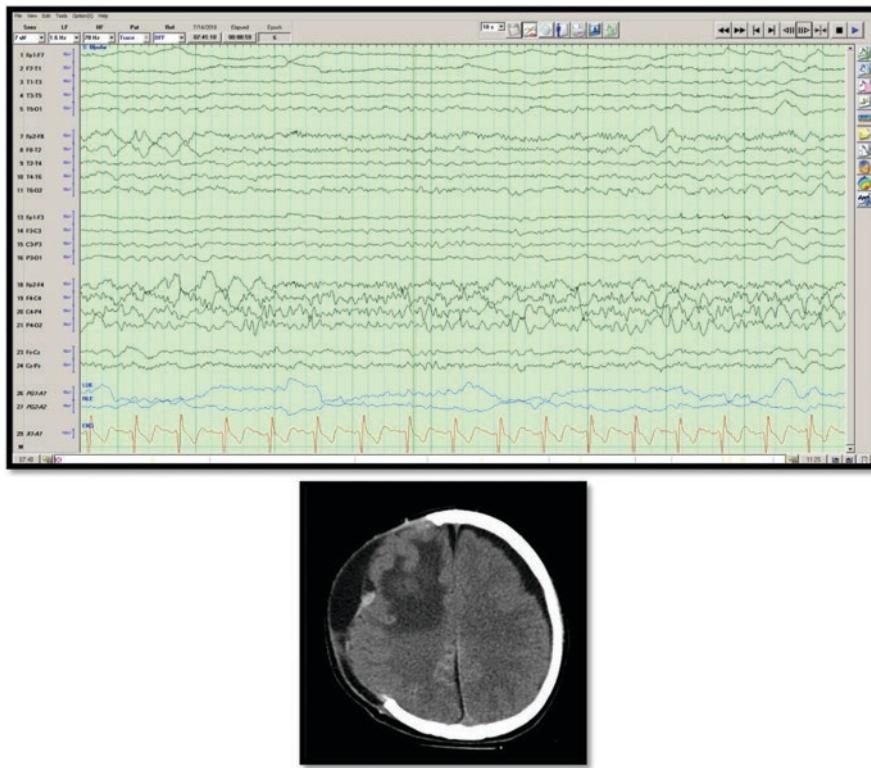


Fig. 7.6 Breach rhythm in the right hemisphere (top EEG tracing), maximal right fronto-centro-parietal region in a 21-year-old man with right frontal hematoma status post evacuation and hemi-craniectomy to relieve cerebral edema. Note higher amplitude and sharply contoured beta activity. There is intermixed delta/theta slowing secondary to traumatic injury. Below the EEG tracing is his CT head image showing the skull defect and right cerebral edema and encephalomalacia

- When the skull has been breached (broken, ruptured, torn), the amplitude is increased, and the activity may have a sharper appearance (Fig. 7.6)
- The spiky appearance makes it difficult to distinguish true epileptiform discharges

7.3 Rhythmic Benign EEG Variants

7.3.1 Rhythmic Temporal Theta of Drowsiness (RTTD)

- AKA: rhythmic mid-temporal theta of drowsiness (*RMTD*)
- AKA: *psychomotor variant pattern* first coined by Gibbs in 1963 [4]

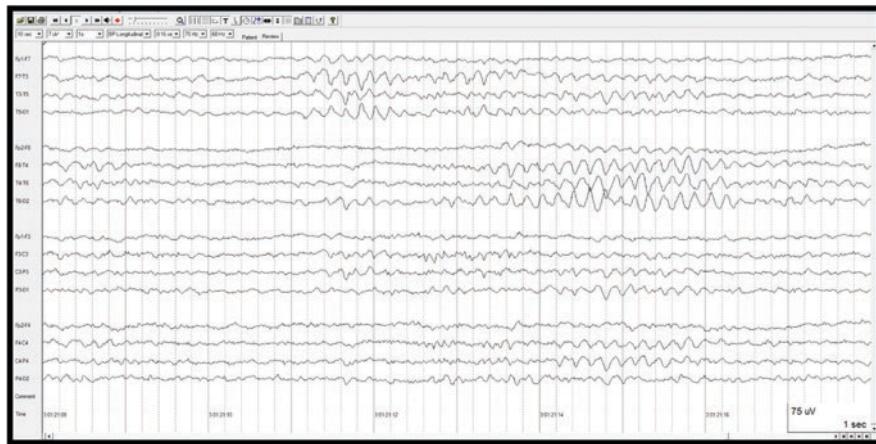


Fig. 7.7 Rhythmic temporal theta of drowsiness (RTTD) alternating between left and right temporal regions

- Flat-topped or notched appearance rhythmic theta or alpha activity
- Bursts alternate between left and right temporal region but may have a field to adjacent parasagittal area
- Most commonly 4–7 Hz in mid-temporal areas (T3, T4)
- Monorhythmic with no evolution in frequency or morphology
- Alternating left and right temporal predominance
- Mostly seen during drowsiness or relaxed wakefulness
- Primarily seen in adolescents and adults with incidence of 0.5% (Fig. 7.7)

7.3.2 Subclinical Rhythmic Electrographic Discharge of Adults (SREDA)

- Was described by Westmoreland and Klass in 1981 [5]
- Resembles a subclinical seizure discharge but has no known clinical significance
- Rhythmic, sinusoidal 5–7 Hz theta sustained on average for 40–80 s (varies from 20 s to a few minutes)
- Maximal posterior temporal and parietal but could be widespread
- Abrupt onset, monophasic
- Seen mostly in adults >50 years and during awake state but may continue to drowsiness and sleep
- There is no evolving pattern and patient shows no clinical signs of seizure (Fig. 7.8)

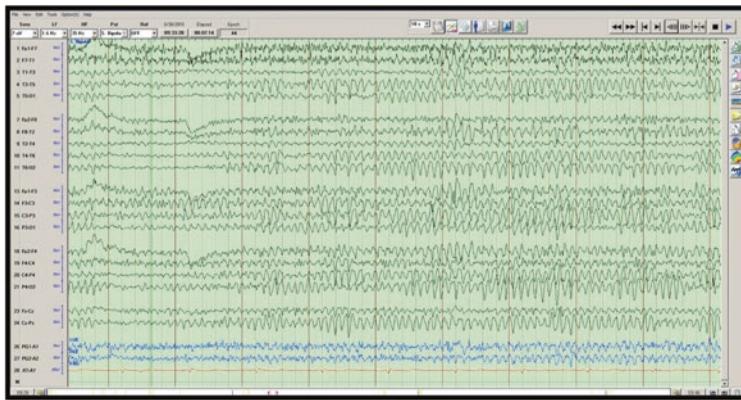


Fig. 7.8 Subclinical rhythmic electrographic discharges of adults (SREDA). Patient is a 69-year-old female presenting with persistent headaches. She was alert, awake, and oriented and followed commands throughout the rhythmic diffuse EEG discharges

Take-Home Points

- Benign (normal) EEG variants are *spiky or rhythmic* activity in EEG that do not have clinical significance
- Benign variants mostly occur during drowsy and light-sleep stage
- *Spiky* benign variants are:
 - 14 and 6 positive spikes, generalized max posterior temporal, 12–20 years of age, drowsy state
 - BETS or BSSS, temporal, <50 msec, <50 µV), drowsy and light sleep
 - 6 Hz (phantom) spike and wave, generalized, adolescent and adults, rare, small spike component, and large waves
 - Wicket spikes, temporal, >50 years of age, drowsy and light sleep > awake
 - Breach rhythm over a skull defect
- *Rhythmic* benign variants
 - RTTD, temporal, children and adults, drowsy and light sleep
 - SREDA, adults usually >50 years, diffuse or posterior temporal, awake

References

1. Gibbs EL, Gibbs FA. Electroencephalographic evidence of thalamic and hypothalamic epilepsy. *Neurology*. 1951;1(2):136–44.
2. Hughes JR, Schlagenhauff RE, Magoss M. Electro-clinical correlations in the six per second spike and wave complex. *Electroencephalogr Clin Neurophysiol*. 1965;18:71–7.
3. Cobb WA, Guilloff RJ, Cast J. Breach rhythm: the EEG related to skull defects. *Electroencephalogr Clin Neurophysiol*. 1979;47(3):251–71.
4. Gibbs FA, Rich CL, Gibbs EL. Psychomotor variant type of seizure discharge. *Neurology*. 1963;13:991–8.
5. Westmoreland BF, Klass DW. A distinctive rhythmic EEG discharge of adults. *Electroencephalogr Clin Neurophysiol*. 1981;51(2):186–91.



EEG Artifacts

8

8.1 EEG Artifacts

- Signals recorded on the EEG which are not generated by the brain
- Obscure or alter EEG patterns
- Confuse or prevent accurate EEG interpretation
- Non-cerebral artifacts:
 - Show illogical topographic field of distribution
 - Defy principles of localization
- There are two sources of artifacts:
 - *Nonphysiologic* artifact (not from the patient)
 - *Physiologic* artifact (from the patient)

8.2 Nonphysiologic Artifact Sources

- Electrodes
- Headbox
- Amplifier
- Cable
- Environment

8.2.1 Electrodes and EEG Equipment Artifacts

- Any unusual event confined to a single or common electrode is electrode artifact unless proven otherwise
 - Electrode pop or loose electrode (Figs. 8.1, 8.2, and 8.3)
 - Unequal impedance, *dissimilar metals*
 - High voltage, very brief, regional or moderately widespread artifact



Fig. 8.1 EEG tracing showing electrode pop artifact in C4 electrode



Fig. 8.2 EEG tracing showing T1 electrode artifact

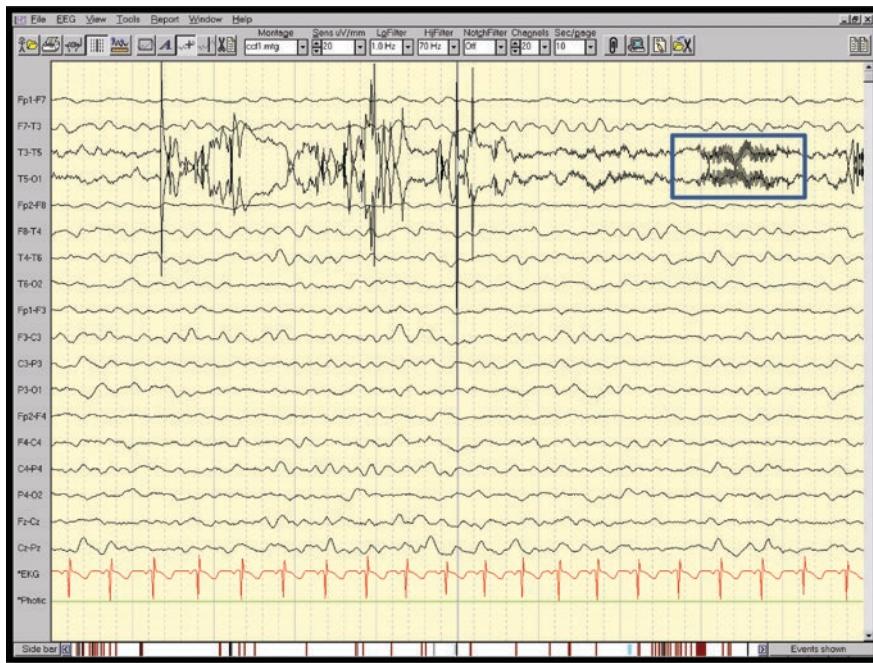


Fig. 8.3 Loose T5 electrode. Note also the 60 Hz fuzzy artifact shown in the blue box which is the result of high impedance in T5 electrode

- May occur when metals such as *dental fillings* rub against each other during mouth movements (Figs. 8.4 and 8.5)
- More abrupt, higher in voltage, and briefer than muscle artifact
 - 60 Hz artifact
 - Generally results from poor electrode application
 - Due to high impedance electrodes/fuzzy looking (Figs. 8.3 and 8.6)
 - If in all channels may represent a problem with electrical safety
 - Need to ensure electrode impedance is lower than $5000\ \Omega$
 - Use 60 Hz notch filter to remove the artifact
 - If in one or two channels, need to reapply the affected electrode or try new jack
 - If in all channels, reapply ground or reference electrode and turn off lights or other equipment in the room
 - Patient touching electrode or wire
 - Broken wire/salt bridge/other electrolyte problems



Fig. 8.4 Another example of more continuous *dissimilar metal artifact* in the right temporal area

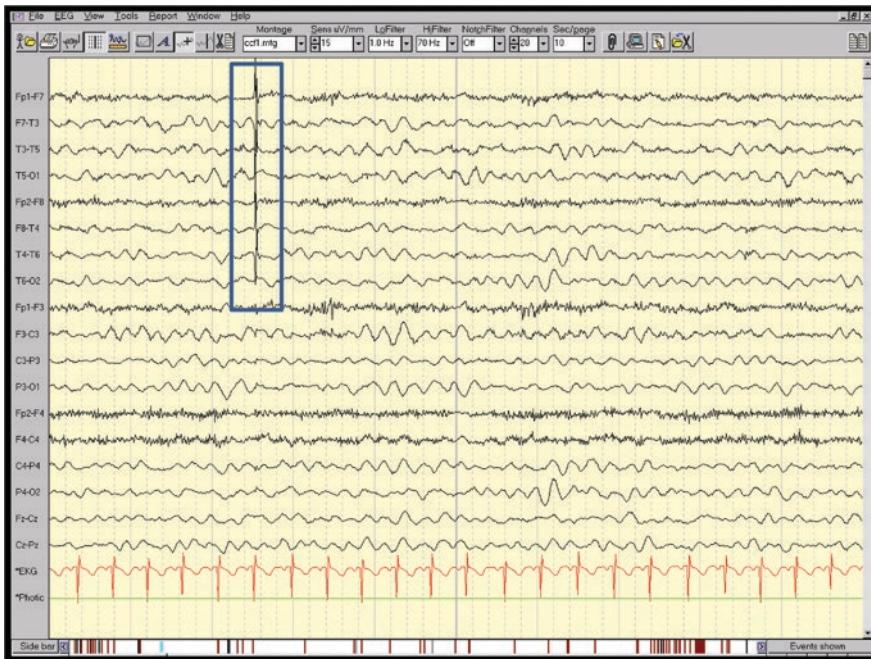


Fig. 8.5 EEG tracing showing *dissimilar metal artifact* related to dental filling

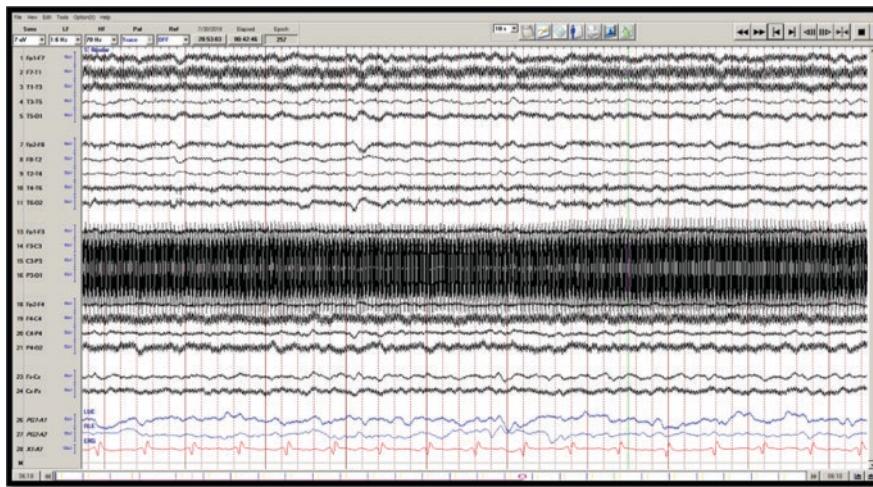


Fig. 8.6 EEG tracing showing more diffuse 60 Hz artifact. This may present an electrical safety issue and the cause needs to be investigated

8.2.2 Environment-Related Artifacts

- Equipment in the patient's room or attached to the patient:
 - Laptop and electronic devices (Fig. 8.7)
 - IV drip
 - Respirator
 - Phone ringing (Fig. 8.8)
 - Bed/patient movements (Figs. 8.9 and 8.10)

8.3 Physiologic Artifact Sources

- Artifacts related to the patient
 - EKG/ pulse/pacemaker artifact (Figs. 8.11 and 8.12)
 - Respiration artifact
 - Eye movements artifact
 - Vertical eye movements (Figs. 8.13, 8.14, and 8.15)
 - Horizontal eye movements (Fig. 8.16)
 - Electrical field of the eye: cornea, positive; retina, negative
 - Monitor eye movements with eyelid electrodes
 - Glossokinetic artifact
 - Caused by talking and tongue movements (Figs. 8.17 and 8.18)
 - The tongue has electrical field

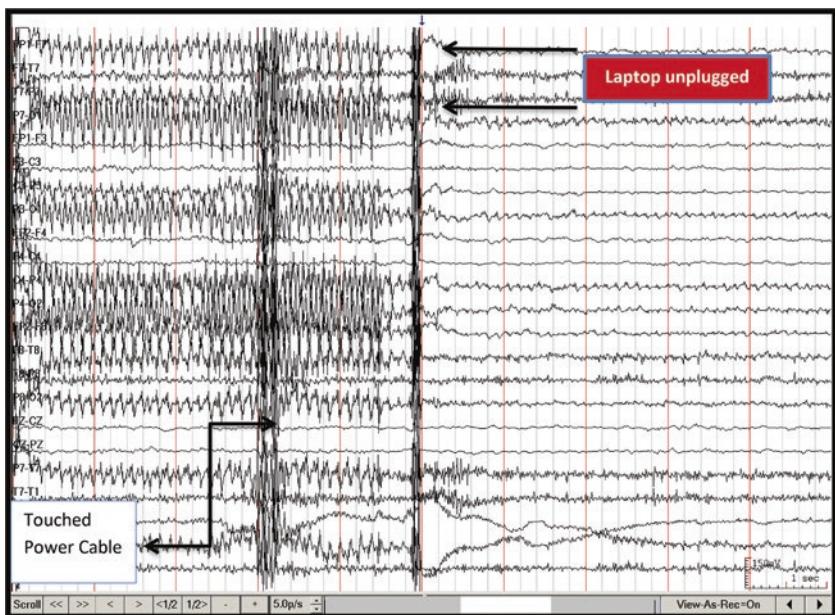


Fig. 8.7 Artifact created by laptop being plugged in for charging. It resolves with unplugging the laptop

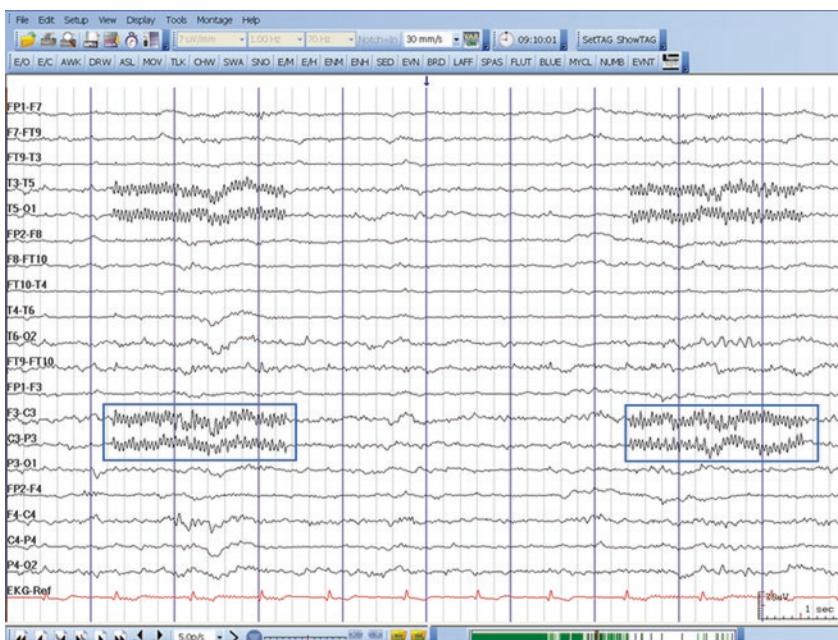


Fig. 8.8 EEG tracing showing a phone ringing in the room at 3–4 s intervals

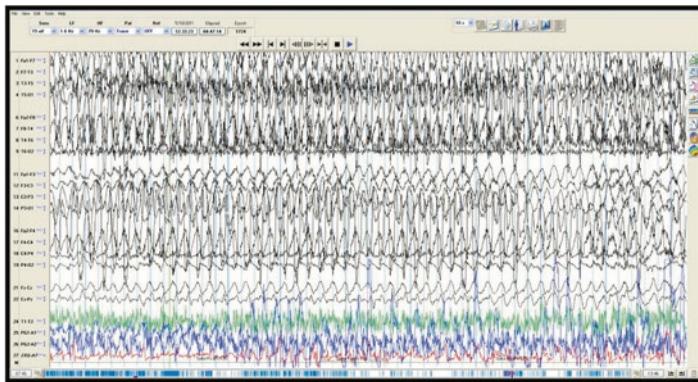


Fig. 8.9 Bed rocking as a result of a non-epileptic side-to-side body jerking event

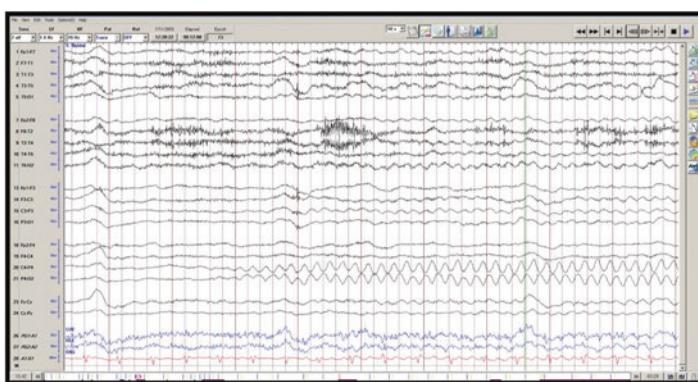


Fig. 8.10 EEG tracing showing rhythmic artifact in P4 as a result of patient undergoing chest physiotherapy

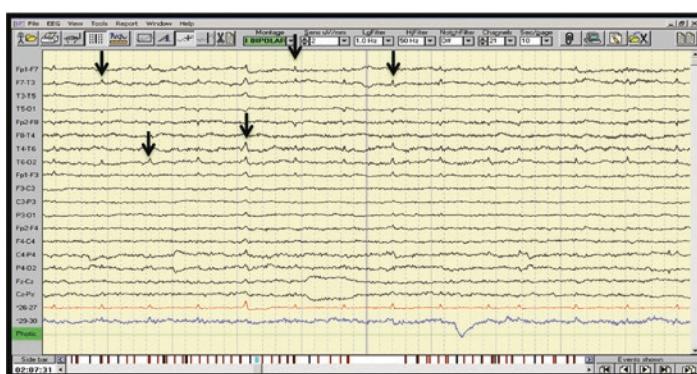


Fig. 8.11 EEG tracing showing widespread EKG artifact (black arrows) lining up with the peaks of EKG channel (red) in a young, obese man. His short neck facilitated transmission of EKG activity to other electrodes



Fig. 8.12 EEG tracing showing pulse artifact in C3 and C4 electrodes



Fig. 8.13 EEG tracing showing rapid eye fluttering with rhythmic artifact seen maximal in fronto-polar leads

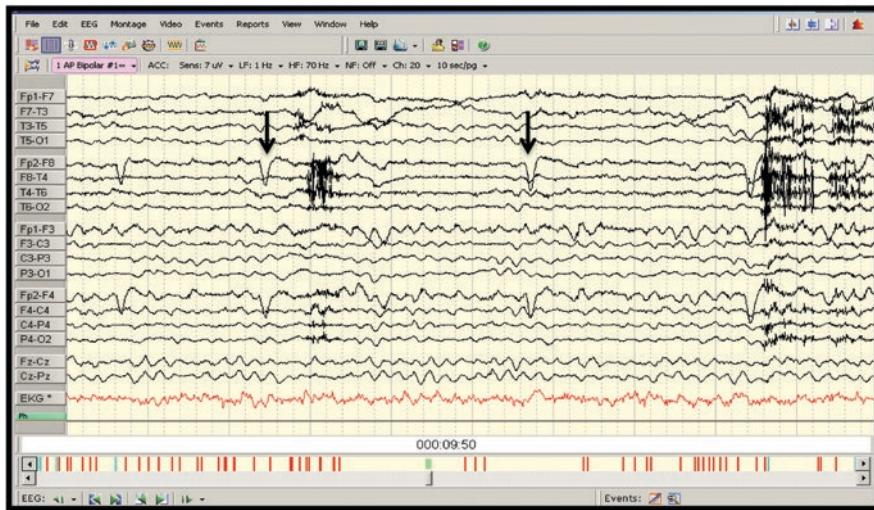


Fig. 8.14 EEG tracing showing unilateral eye blink on the right (black arrows). Patient has left eye prosthesis



Fig. 8.15 EEG tracing showing vertical eye movements (black arrows) with patient blinking intermittently seen maximal in fronto-polar leads and confirmed in the eyelid electrodes (blue lines)

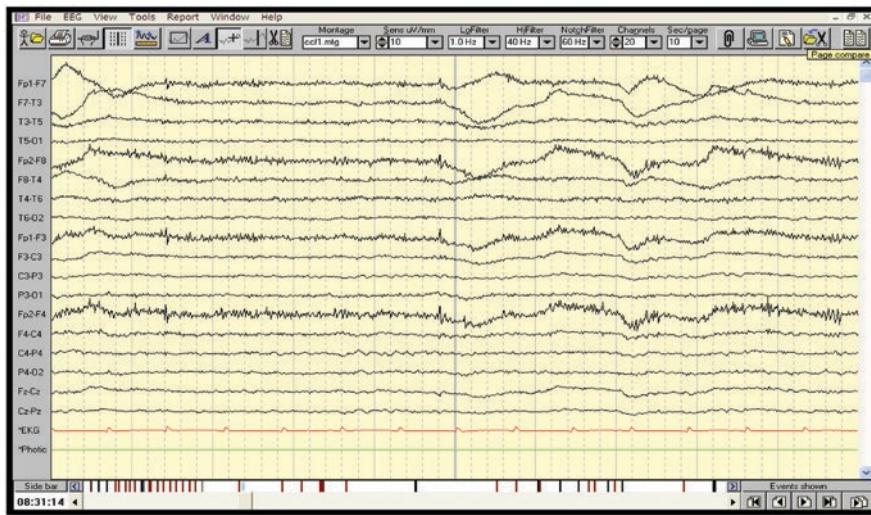


Fig. 8.16 EEG tracing showing lateral eye movement artifact maximal in F7 and F8 electrodes

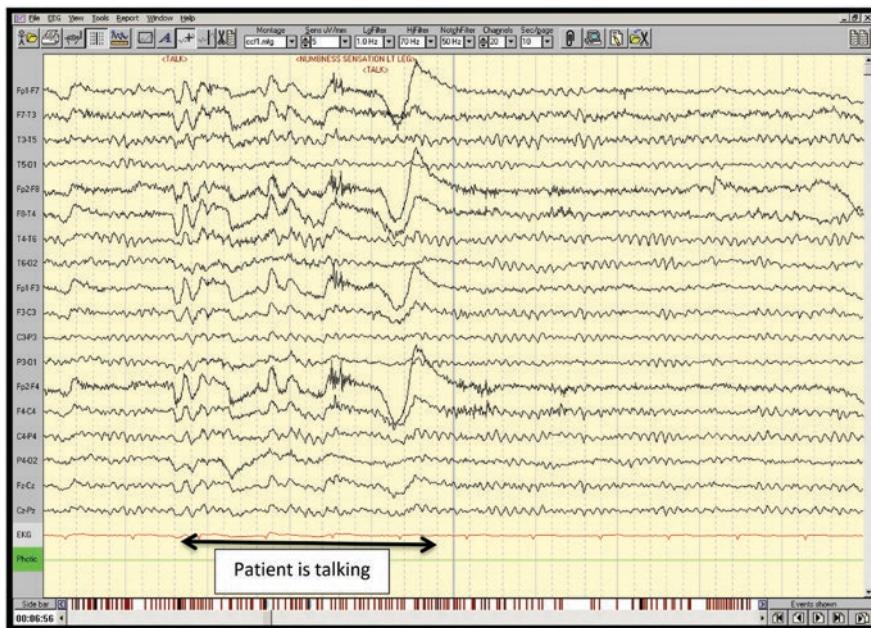


Fig. 8.17 EEG tracing showing glossokinetic artifact as the patient starts to talk



Fig. 8.18 EEG tracing showing chewing and tongue movements causing a combination of rhythmic myogenic and glossokinetic artifact

- Tip of the tongue, negative; back of the tongue, positive
- Artifact looks like repetitive slow waves in frontal leads (mimics frontal intermittent rhythmic delta activity or FIRDA)
- Having patient say words with “L” or “T” sounds (Tom thumb, Lilt, etc.) will reproduce this artifact
- Myogenic artifact
 - 20–35 Hz EMG, single motor neuron potential (Fig. 8.19)
 - Chewing/swallowing artifact (Figs. 8.18 and 8.20)
 - Lateral rectus muscle twitch artifact (Fig. 8.21)
- Sobbing/hiccupping artifact/sniffling (Fig. 8.22)
- Shudder/shiver/tremor artifact (Fig. 8.23)
- Sweat artifact – slow sway of signal (Fig. 8.24)
 - Galvanic skin response
 - High amplitude, very-low-frequency potentials (0.5–1 Hz)
 - Standard low-frequency filter may reduce this artifact

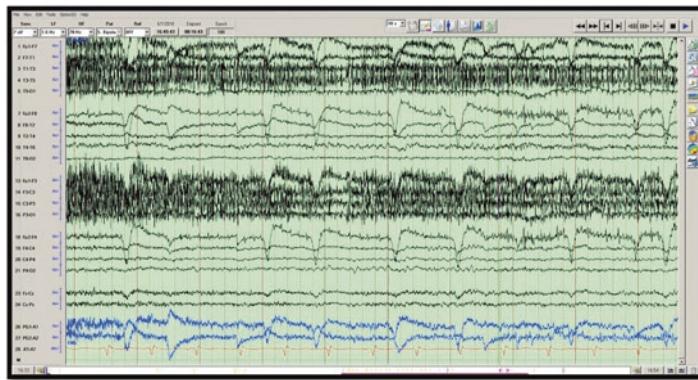


Fig. 8.19 EEG tracing showing left hemispheric myogenic artifact due to patient touching the left side of head

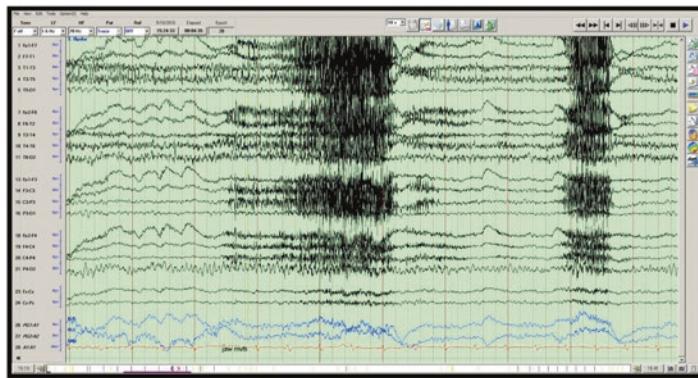


Fig. 8.20 EEG tracing showing jaw movement followed by swallowing artifact



Fig. 8.21 EEG tracing showing repetitive lateral rectus myogenic spikes (black arrows) in fronto-polar electrodes



Fig. 8.22 EEG tracing showing repetitive sniffling artifact (black arrows)

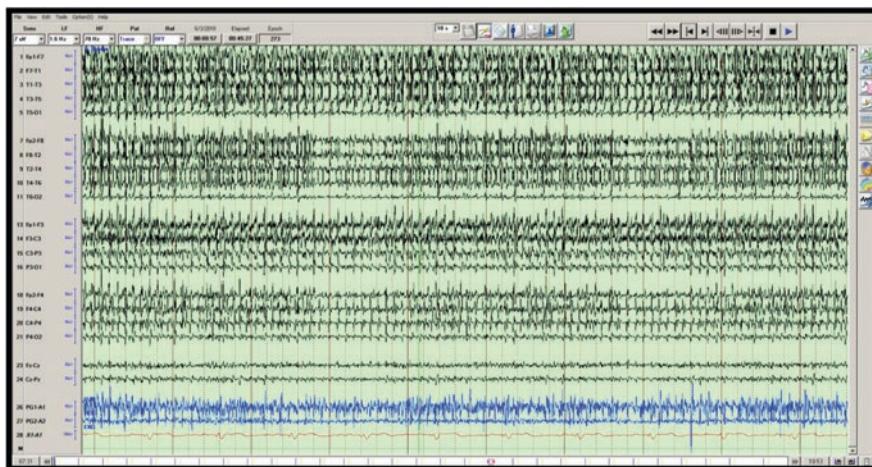


Fig. 8.23 EEG tracing showing generalized shivering artifact in an ICU-hospitalized patient

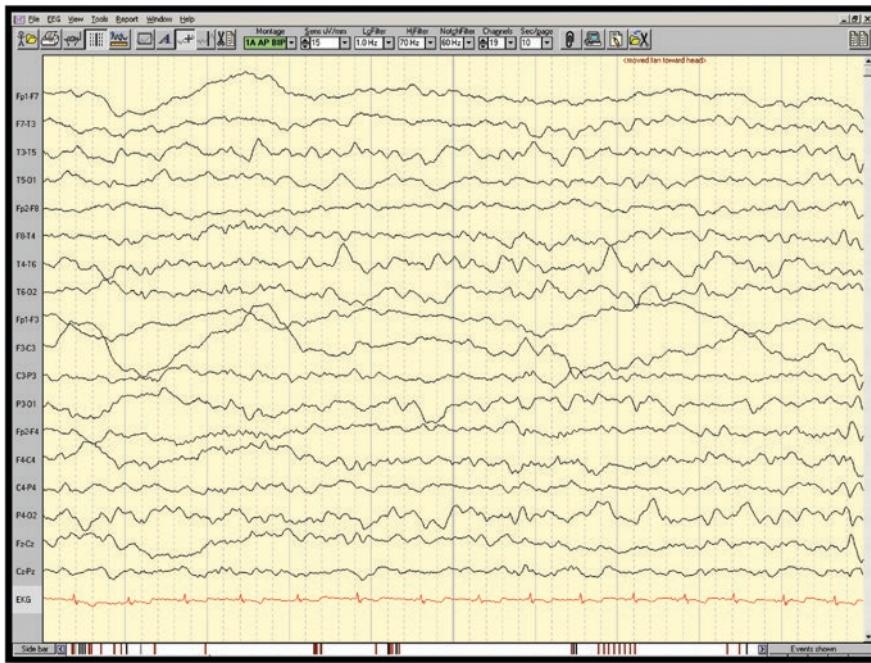


Fig. 8.24 EEG tracing in a sweating patient with F3 and F7 showing sway artifact

Take-Home Points

- Artifacts are either physiologic (related to patient) or non physiologic (related to environment around the patient)
- Physiologic artifacts include:
 - EKG, pulse, pacemaker, eye movements, myogenic, shivering, sniffling, hiccupping, and glossokinetic and sway artifact due to sweatiness
- Non physiologic artifacts include:
 - Loose electrodes, high impedance electrodes, 60 Hz artifact, bed movements, electronics plugged in the room, and equipment attached to the patient or around the patient
- Recognizing artifacts is important for the technician to try to resolve and for the EEG reader to make accurate interpretation



Interictal and Ictal EEG Patterns

9

9.1 Epileptiform Discharges

- *Spikes:*
 - <70 msec in duration
 - Steep ascending and descending limb
 - Spike and wave complex is a spike followed by slow wave
- *Sharp waves:*
 - Broader potentials with pointed peak
 - >70 and <200 msec in duration
- *Paroxysmal fast activity:*
 - A train of repetitive spike discharges or rhythmic fast activity at 8–20 Hz
- No difference between spikes and sharp waves in terms of clinical significance
- They stand out from background activity
- Usually followed by after coming slow wave
- Abruptly appear and disappear

9.2 Generalized Epileptiform Patterns

- Consists of generalized and bisynchronous, usually symmetric spike and wave pattern
- In most circumstances generalized discharges are frontally dominant
- *Types of generalized epileptiform discharges:*

9.2.1 3 Hz Spike and Wave

- Associated with absence seizures in 95% of cases (Fig. 9.1)
- Most often seen between age 3 and 15
- Often occur in rhythmic trains



Fig. 9.1 EEG tracing showing a train of 3 Hz spike and wave in a 7-year-old boy with absence seizures. He had sudden arrest of activity and mild shoulder clonic jerks as well as eye flutter during this event. His background EEG was otherwise normal and he was normal in intellectual ability

- If longer than 3–4 s may be associated with clinical absence seizure
- During sleep they occur in a more fragmented fashion
- Activated by hyperventilation and hypoglycemia
- Otherwise, the patient has normal awake and sleep background patterns
- Patients are usually cognitively and neurologically normal

9.2.2 Atypical Spike and Wave (>3 Hz)

- Higher-frequency generalized discharges compared with 3 Hz spike and wave (Fig. 9.2)
- Does not show the stereotype appearance of 3 Hz spike and wave
- The frequency varies from 4 to 7 Hz and may be asymmetric between the two hemispheres
- May be mixed with polyspikes and multiphasic spikes (Fig. 9.3)
- Usually duration is brief ranging from 1 to 3 seconds

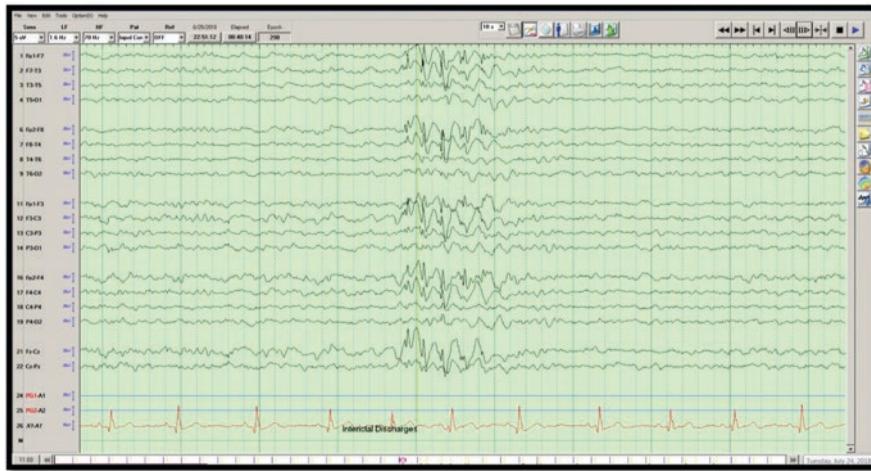


Fig. 9.2 EEG tracing showing 4 Hz generalized spike and wave in a 32-year-old man with juvenile myoclonic epilepsy (JME)

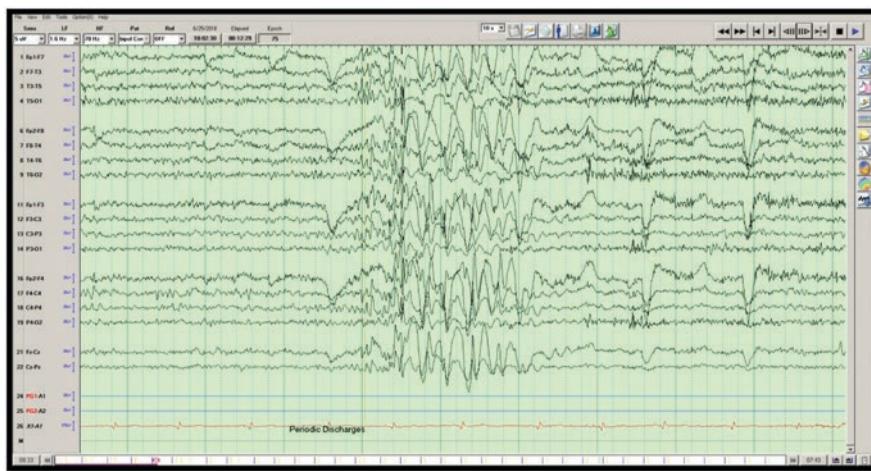


Fig. 9.3 EEG tracing showing polyspikes intermixed with 4 Hz generalized spike and wave in the same 32-year-old man with JME (Figs. 9.2 and 9.4)

- Can occur at any age group
- The interictal EEG may be normal or abnormal depending on the underlying condition of the patient
- Commonly associated with juvenile myoclonic epilepsy (JME) (Fig. 9.4)

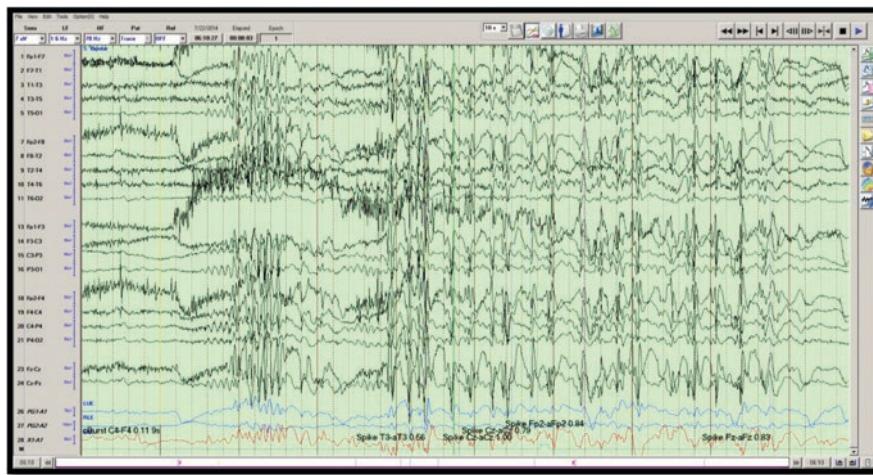


Fig. 9.4 EEG tracing showing bursts of generalized polyspike and wave intermixed with 4–5 Hz spike and wave in the same patient with JME (Figs. 9.2 and 9.3). The above discharges were associated with facial grimace and subtle body myoclonus

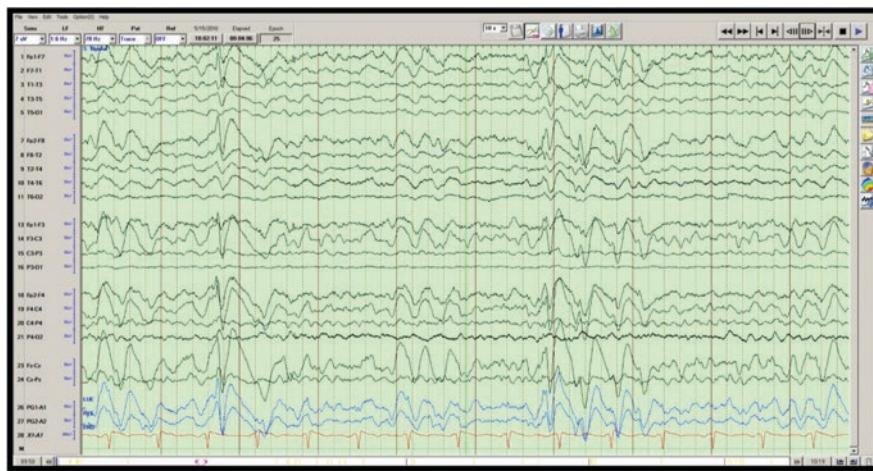


Fig. 9.5 EEG tracing showing slow spike and wave (2.5 Hz) in a 16-year-old adolescent with psychomotor slowing

9.2.3 Slow Spike and Wave (<3 Hz)

- AKA: sharp and slow wave complexes
- Occur at a frequency of 1–2.5 Hz, singly or in trains (Fig. 9.5)
- The discharges may be asymmetric and show alternating focal predominance between hemispheres
- May be enhanced during drowsiness

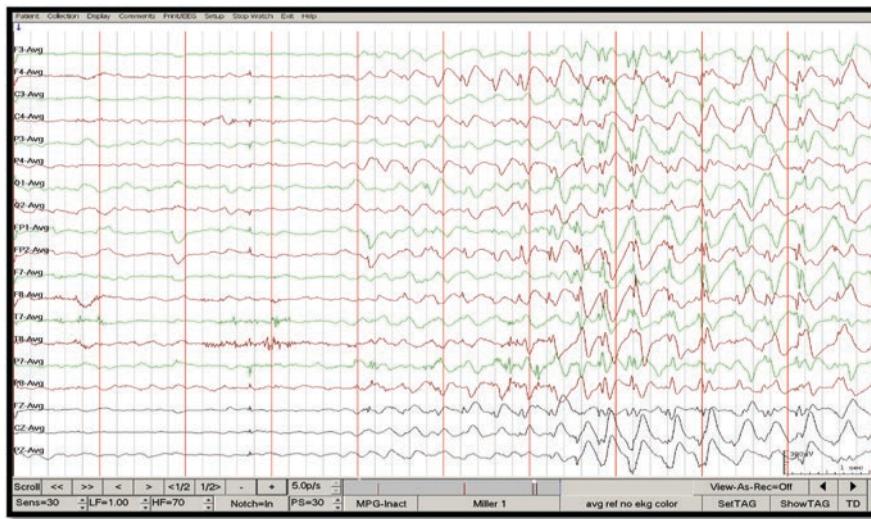


Fig. 9.6 EEG tracing in a 9-year-old boy with Lennox-Gastaut syndrome who showed signs of behavioral arrest and staring during the above EEG consistent with atypical absence seizure

- Typically not activated with hyperventilation, hypoglycemia, or photic stimulation
- The background EEG is often abnormal, showing:
 - Focal, multifocal, or generalized slowing
 - Multifocal spikes
 - Bursts of generalized paroxysmal fast activity
- Most commonly associated with:
 - Syndromes of childhood epilepsies such as Lennox-Gastaut syndrome (Fig. 9.6)
 - Psychomotor slowing and developmental disabilities
 - Underlying organic brain pathology
 - Medically refractory and severe epilepsy
- Associated seizures in patients with slow spike and wave pattern:
 - Tonic seizures/tonic-clonic seizures
 - Atypical absence seizures (Fig. 9.6)
 - Myoclonic seizures
 - Atonic seizures

9.2.4 Paroxysmal or Rhythmic Fast Activity

- Rhythmic usually low amplitude or repetitive spike activity at 8–20 Hz (Figs. 9.7 and 9.8)
- Associated with tonic seizures
- Also seen interictally in shorter trains in patients with generalized seizures

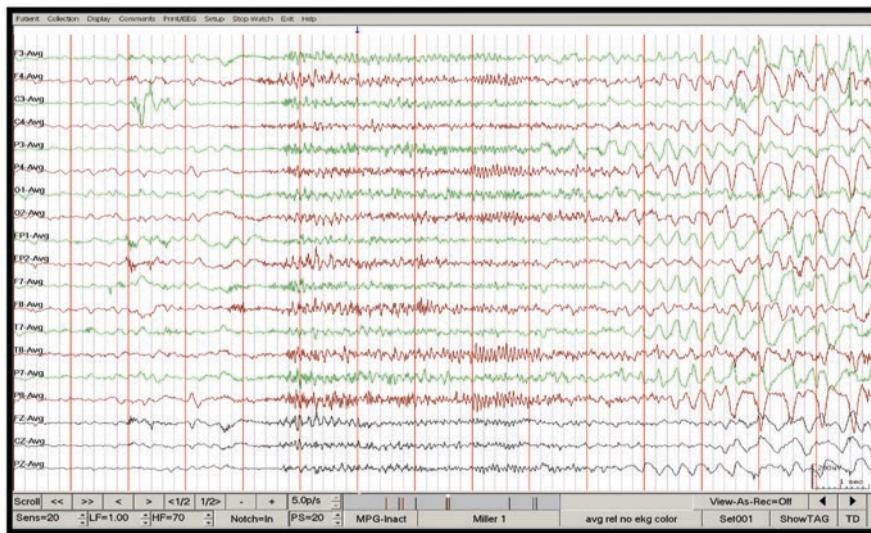


Fig. 9.7 EEG tracing showing tonic seizure in a 42-year-old man with Lennox-Gastaut syndrome since childhood. He showed sudden wide opening of his eyes accompanied with subtle body tensing and facial flushing/grimace during the above period of generalized rhythmic fast activity on EEG

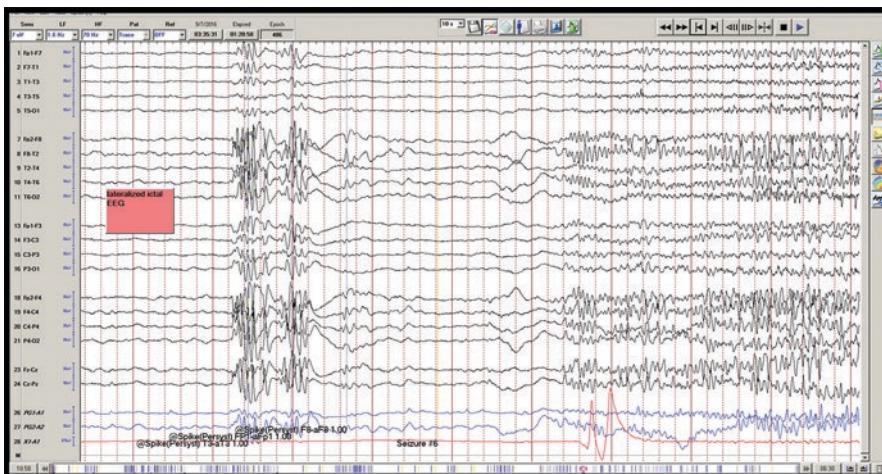


Fig. 9.8 EEG tracing in a 28-year-old man with sudden onset of lifting his head and unilateral tonic posturing of upper extremity (asymmetric tonic seizure). EEG showed a train of asymmetric paroxysmal rhythmic fast spikes, maximal on the right

9.2.5 Hypsarrhythmia

- A bisynchronous and multifocal pattern
- High-amplitude arrhythmic pattern with chaotic mixture of multifocal spikes and arrhythmic slow waves (the scrambled egg pattern)
- Seen most commonly between age 4 months and 2 years
- Often associated with severe cerebral insult in early infancy
- Rarely seen beyond 4–5 years of age
- Hypsarrhythmia pattern is associated with epileptic spasms and electrodecremental seizures
 - Electrodecremental pattern consists of a brief decrement of amplitude in the ongoing activity (Fig. 9.9)
 - Associated with epileptic spasms (formerly infantile spasms)
 - Also seen interictally in patients with hypsarrhythmia and no clinical seizures (Fig. 9.10)

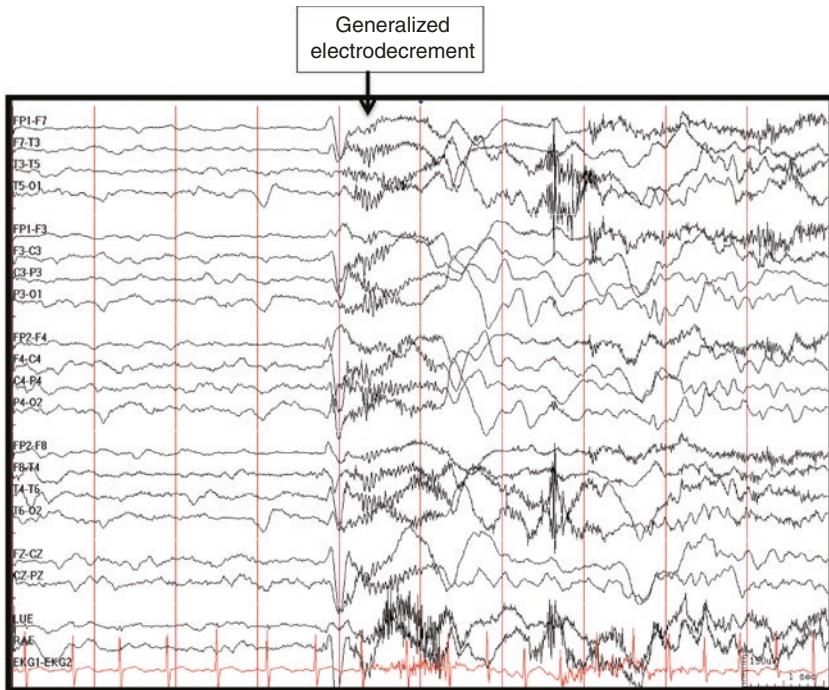


Fig. 9.9 EEG tracing showing epileptic spasm accompanied with generalized electrodecremental seizure in a 16-month-old boy with history of meningoencephalitis at 5 months of age

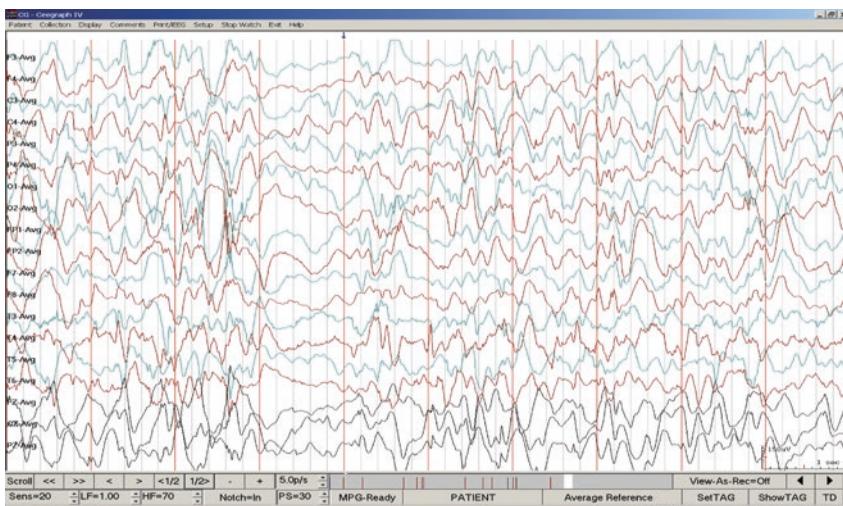


Fig. 9.10 Hypsarrhythmia pattern (interictal) in a 5-month-old baby girl with a history of intrauterine stroke and epileptic spasms. Note the chaotic, high amplitude, arrhythmic pattern with multifocal spikes and slow activity. The generalized electrodecrement seen on EEG was interictal and not accompanied with clinical epileptic spasm

9.3 Focal Epileptiform Patterns

- Certain areas of brain are more epileptogenic than others
 - Temporal lobe and rolandic motor strip are more epileptogenic
 - Parietal and occipital areas have the lowest degree of epileptogenicity
- Age also plays a role in spike distribution
 - Occipital spikes most often occur in young children under 3–5 years
 - Central-parietal spikes mainly occur at age 3–8
 - Central-temporal (rolandic-sylvian) spikes mainly occur at age 4–12
 - Anterior temporal spikes are most often seen in adults but may start at age 12–15

9.3.1 Occipital Spikes

- Most often seen in young children 3–5 years and resolve as the child gets older
- Unilateral or bilateral occipital spikes (Fig. 9.11)
- Only 30–40% of these children may have clinical epilepsy
- Forty percent of these children with occipital spikes complain of visual problems and may have strabismus or amblyopia
- May be associated with a history of premature birth and perinatal cerebral insult
- If happens in older children and adults, mostly represents occipital lesions
- *Benign occipital epilepsy*



Fig. 9.11 EEG tracing showing occipital spikes in a 10-year-old boy with benign occipital epilepsy

- Frequent occipital spikes enhanced with eye closure and attenuated with eye opening
- Seizures present with visual aura such as amaurosis, hemianopia, visual hallucinations, and illusions followed by sensory, motor, or autonomic phenomena and headache
- Normal children with no brain pathology
- Seizures usually resolve by adulthood

9.3.2 Central-Temporal (CT, Rolandic-Sylvian) Spikes

- Primarily seen between age 4 and 12 years
- Epileptiform discharges are primarily seen in central and mid-temporal electrodes (C3, C4, T3, T4) originating from rolandic region (Fig. 9.12)
- Spikes occur unilaterally or bilaterally or may show alternating left and right hemispheric predominance
- Characteristic spikes:
 - High amplitude, diphasic, and blunt, followed by after coming slow waves
 - May be quite frequent occurring in trains
 - The discharges are potentiated during sleep
- 60–70% of these children and adolescents with CT spikes will have seizures:
 - Benign rolandic seizures or benign epileptic seizures with central-temporal spikes
 - Twitching of the side of face
 - Tingling of the side of mouth, tongue, and cheek
 - Motor speech arrest



Fig. 9.12 EEG tracing showing characteristic centro-temporal spikes in an 11-year-old child with a history of a single focal seizure with progression to bilateral tonic-clonic activity

- Excessive salivation, difficulty swallowing
- Progressing to tonic-clonic activity
- Frequently nocturnal
- Easily controlled by AEDs
- May resolve in the second decade of life

9.3.3 Anterior Temporal Spikes

- Often seen in adulthood but may appear after age 12
- One of the most epileptogenic types of spikes
- High correlation with clinical seizure, seen in 90–95%
- Maximum amplitude in anterior temporal and inferior frontal areas (F7, F8, T1, T2) (Figs. 9.13 and 9.14)
- Markedly potentiated during sleep (increase from 30 to 35% during awake to 90% during sleep)
- May coexist with TIRDA (temporal intermittent rhythmic delta activity) (Fig. 9.15)

9.3.4 Frontal Spikes

- Highly epileptogenic spikes correlating with clinical seizures in 70–80% of patients [1]
- Frontal lobe seizures are the second most frequent seizures in adults after temporal lobe seizures

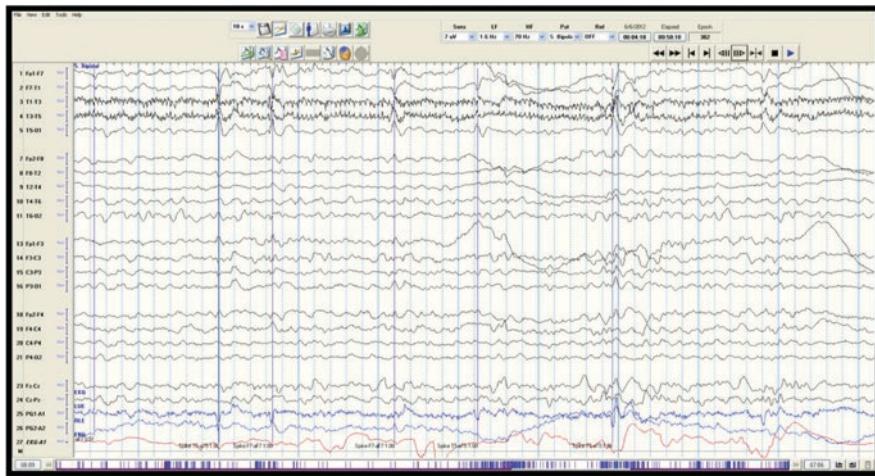


Fig. 9.13 EEG tracing showing periodic sharp waves in the left anterior and mid-temporal area (maximal F7-T1-T3). The sharp waves were occurring singly, but following several seizures during this patient's inpatient video-EEG monitoring, they became periodic

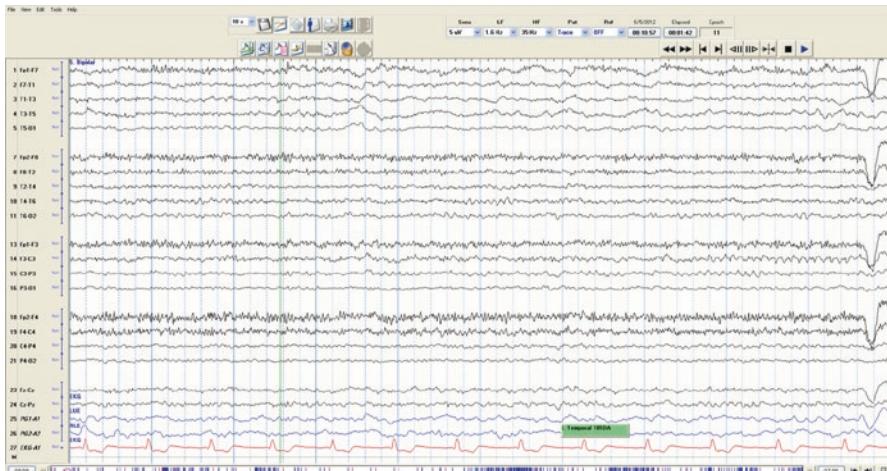


Fig. 9.14 EEG tracing showing independent left and right temporal sharp waves

- Often associated with underlying brain lesion
- Frontal spikes may occur at any age
- Frontal discharges may spread rapidly (Fig. 9.16)
- Mesial frontal, orbital frontal, and cingulum epileptogenic foci are hard to localize due to spikes not making it to the surface electrodes

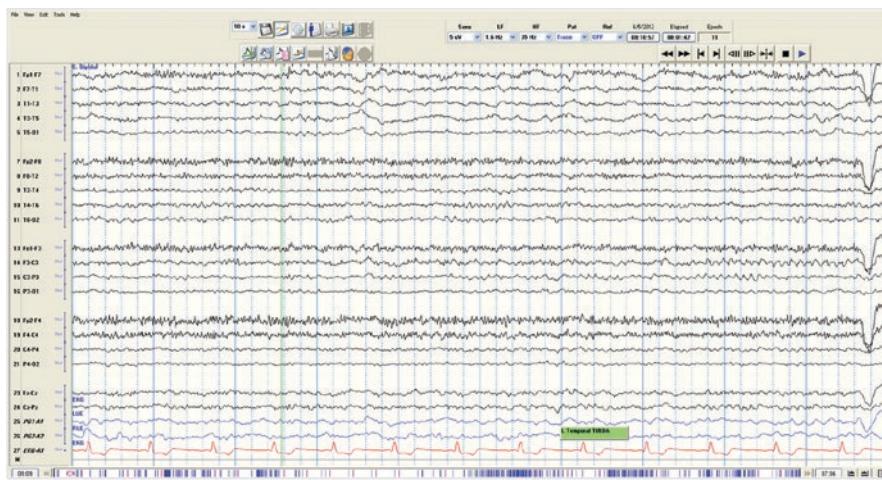


Fig. 9.15 EEG tracing showing left temporal intermittent rhythmic delta activity (TIRDA) in the same patient as in Fig. 9.13

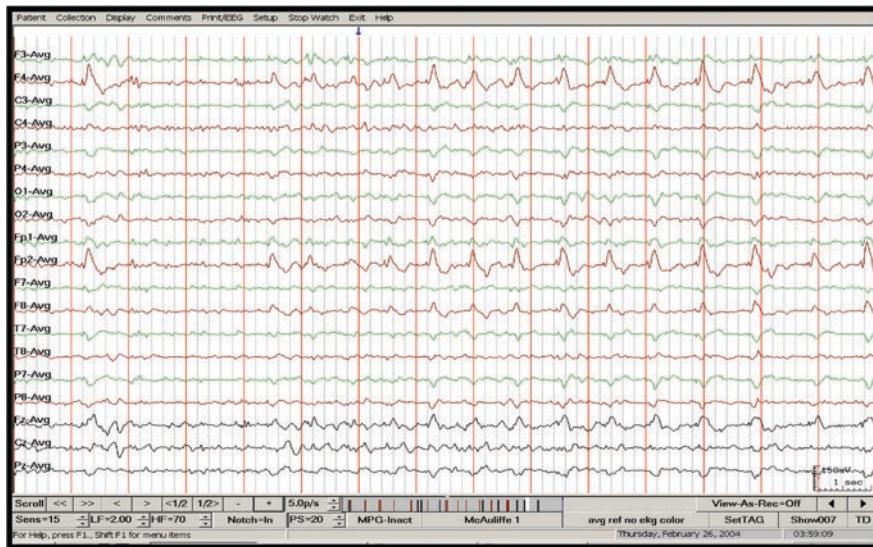


Fig. 9.16 EEG tracing showing interictal right frontal lobe sharp waves potentiated during sleep (referential common average montage, train of F4 sharp waves)

9.3.5 Midline Spikes

- Not as common as temporal or frontal epileptiform discharges
- May be missed by scalp surface electrodes if within mesial cortex
- Vertex spikes are highly associated with seizures in children
- May result in seizures involving lower extremity, atonic, and supplementary motor area (SMA) seizures [1] (Fig. 9.17)
- Potentiated during sleep and hard to distinguish from vertex waves



Fig. 9.17 This is the ictal EEG onset of an 18-year-old girl experiencing a vague body sensation followed by sudden right arm flexor followed by left arm extensor posturing, epileptic cry, and right head and eye version. She had left supplementary motor area seizures. Note the left hemispheric rhythmic evolving seizure. The blue box shows low-amplitude rhythmic fast activity in the left central (C3) area likely the area of seizure onset

- Seizures of supplementary motor area [2]:
 - Characterized by asymmetric tonic posturing of upper extremities (Fencer or Figure of 4 posturing)
 - Head and eye version due to involvement of frontal eye fields
 - Motor speech arrest
 - Generalized body or epigastric sensation

9.3.6 Periodic Lateralized Epileptiform Discharges (PLEDs) or Lateralized Periodic Discharge (LPDs)

- Focal sharp waves occurring unilaterally and in periodic fashion (Fig. 9.18)
- Sharp wave complexes with variable morphology (diphasic, or triphasic)
- PLEDs or LPDs are suggestive of an acute or subacute lesion, most likely vascular in nature
 - Stroke and other vascular insults
 - HSV and other encephalitis
 - Abscess
 - Tumor
 - Subdural hematoma

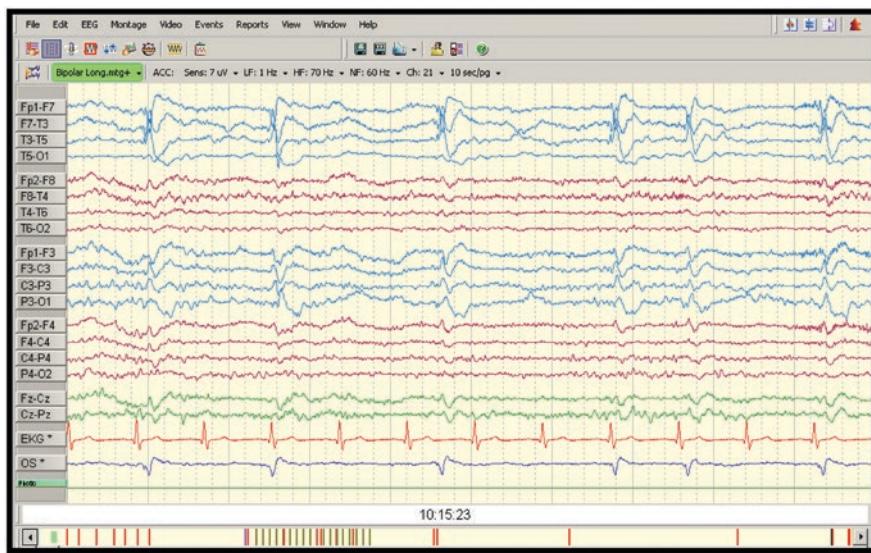


Fig. 9.18 EEG in a 79-year-old man with altered mental status and intermittent right facial twitches showing periodic lateralized epileptiform discharges (PLEDs or LPDs) in the left hemisphere, maximal left temporal area occurring at 1 per second intervals

- Usually resolve over 1–4 weeks
- May be associated with seizures, obtundation, and neurologic deficit
- If PLEDs are associated with intermittent rhythmic discharges, the term *PLEDs Plus* is used (Fig. 9.19)
- PLEDs Plus indicates impending focal seizures (Figs. 9.19 and 9.20)

9.4 From Spikes to Seizures

9.4.1 Electrographic Seizures

- Characterized by “rhythmicity” and “evolution” in frequency and amplitude
- Defined as sustained repetitive epileptiform activity, rhythmic theta and delta evolving in time and space (Figs. 9.21, 9.22, and 9.23)
- A seizure usually shows abrupt onset and offset
- The evolving seizure activity can contain spikes, sharp waves, spike and wave paroxysmal fast activity, or simply rhythmic slow activity (Figs. 9.24, 9.25, 9.26, and 9.27)
- If no clinical signs, the term subclinical electrographic seizure is used
- Ictal refers to clinical and electrographic occurrences during a seizure

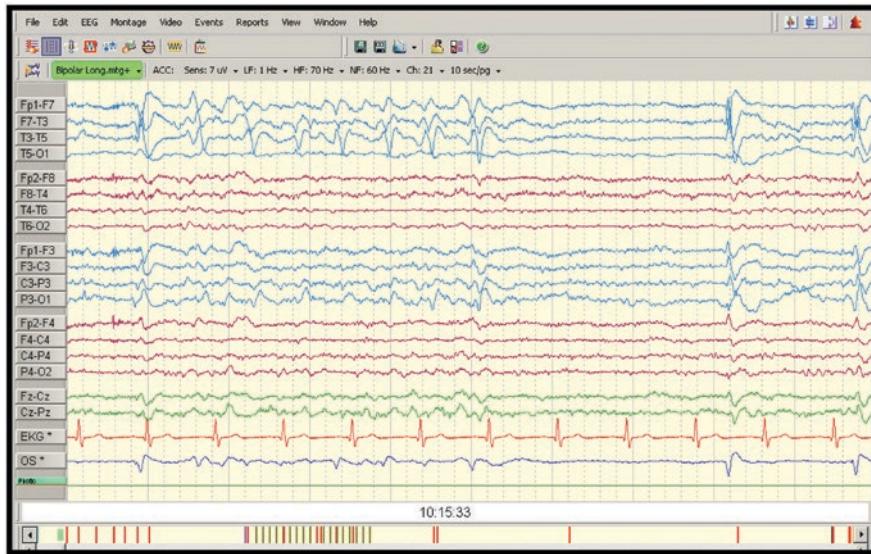


Fig. 9.19 Same 79-year-old gentleman as in Fig. 9.17 with intervals of rhythmic activity intermixed with PLEDs (PLEDs Plus). Seconds later, he experienced arrest of speech and right facial twitches with EEG showing evolving focal electrographic seizure (see Fig. 9.20)

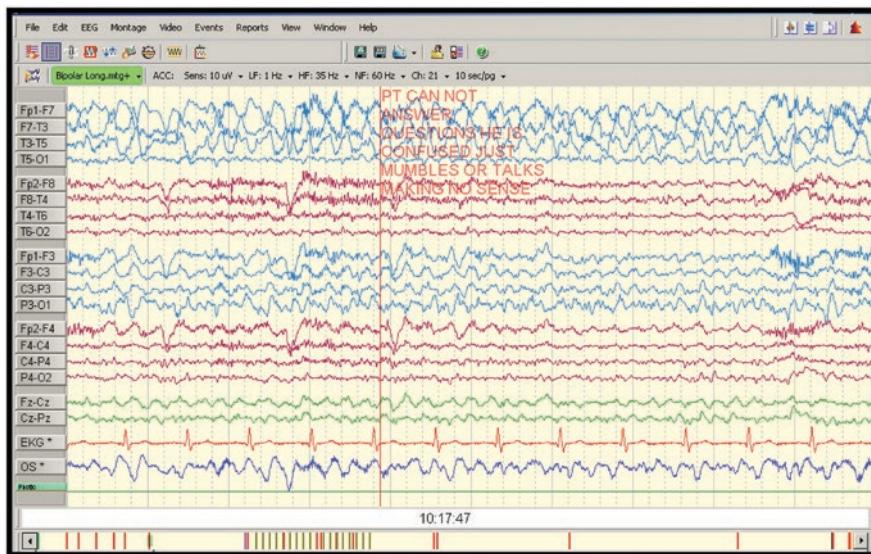


Fig. 9.20 Part of the ictal EEG tracing on the same 79-year-old gentleman with PLEDs Plus (Figs. 9.18 and 9.19) showing evolving electrographic seizure of left hemispheric origin associated with clinical seizure

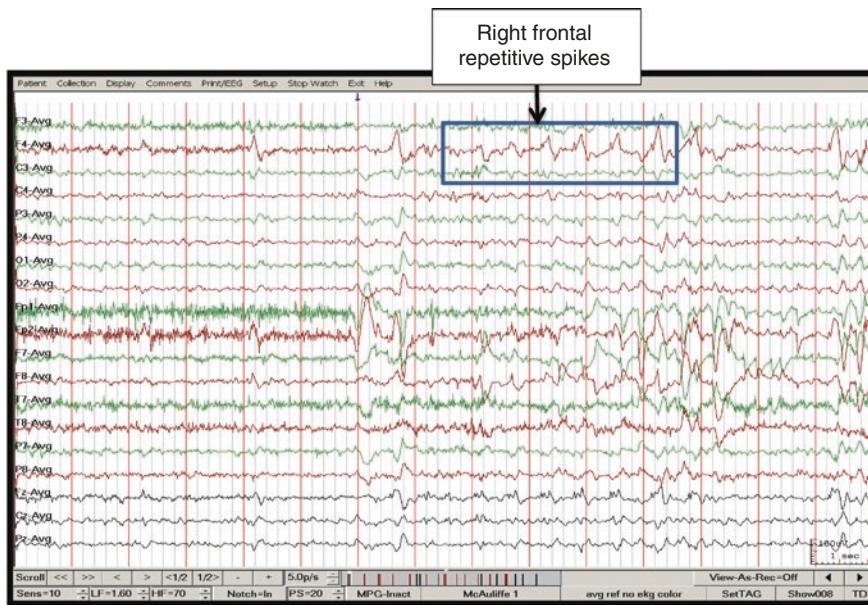


Fig. 9.21 The beginning of EEG tracing of a 15-year-old girl with frequent nocturnal frontal lobe seizures showing repetitive rhythmic spikes in the right frontal area. The patient proceeded to have an electroclinical seizure shown in Figs. 9.22 and 9.23

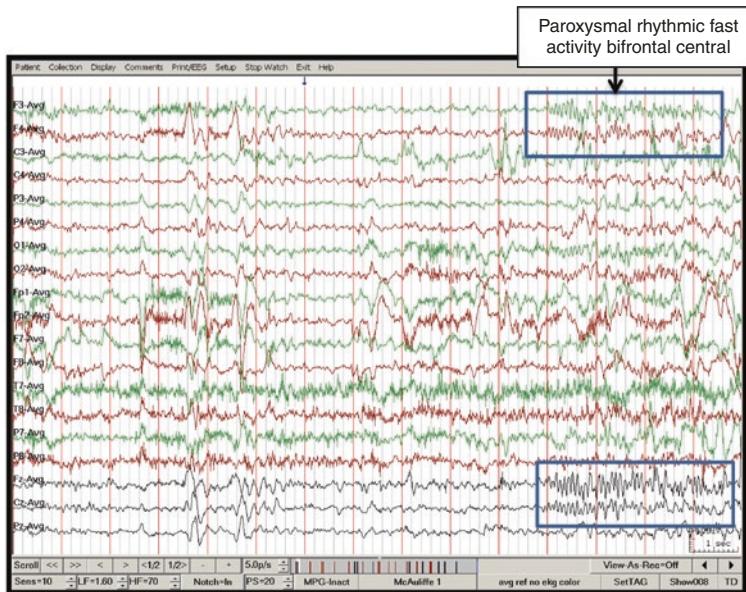


Fig. 9.22 This is the next page of EEG tracing in the same patient as in Fig. 9.21, showing brief period of rhythmic fast activity in fronto-central areas (F3, F4, Cz, Pz, average referential montage) intermixed with myogenic artifact. This correlated with patient's clinical seizure onset with flushing of her face and bicycling leg movements

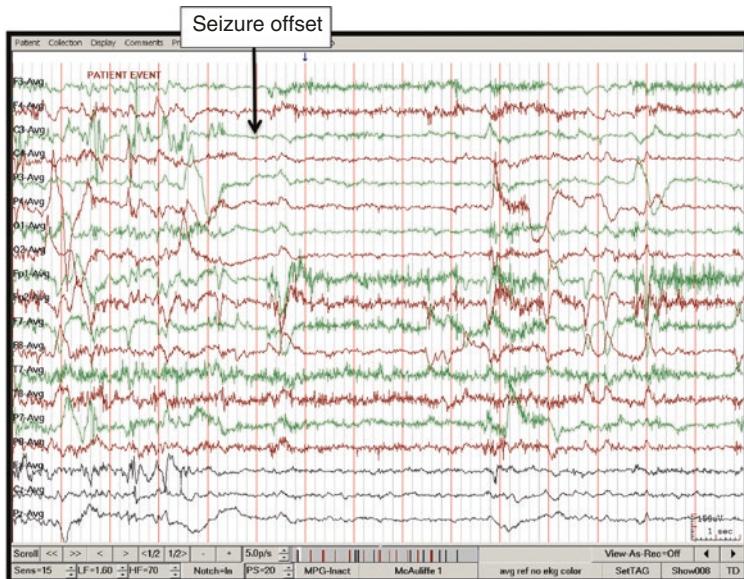


Fig. 9.23 This is the last of three pages of EEG tracings following Figs. 9.21 and 9.22, showing the end of a short frontal lobe seizure in a 15-year-old girl. Clinically, there was sudden flushing of her face, feeling of anxiety, bicycling movements of the legs, and hypermotor behavior. There was no alteration of her awareness

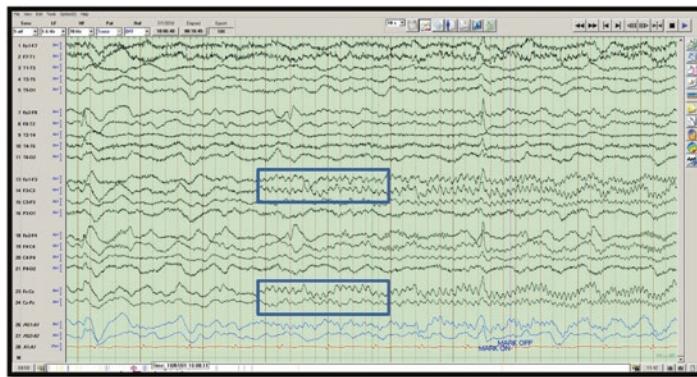


Fig. 9.24 Please see the caption at the bottom of Fig. 9.27

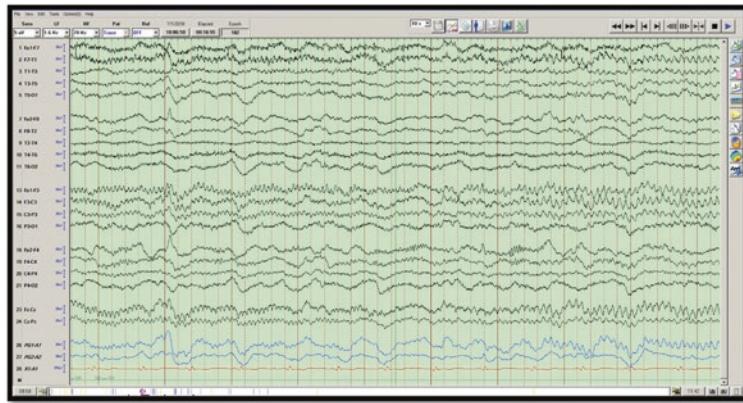


Fig. 9.25 Please see the caption at the bottom of Fig. 9.27

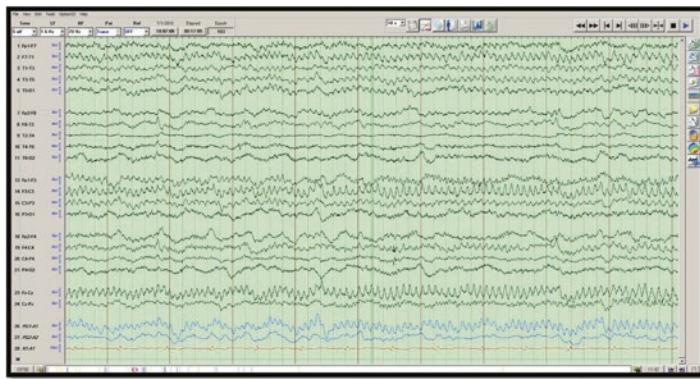


Fig. 9.26 Please see the caption at the bottom of Fig. 9.27

- Interictal refers to epileptiform discharges in between the seizures
- Postictal refers to the period of time after offset of clinical and electrographic seizure
- Confusion following a clinical seizure could be due to:
 - Postictal suppression and slowing of EEG activity
 - Ongoing subclinical seizures (Fig. 9.28)
- Todd's paralysis (lateralized body weakness) may occur postictally after a focal seizure likely secondary to lateralized suppression of activity on EEG

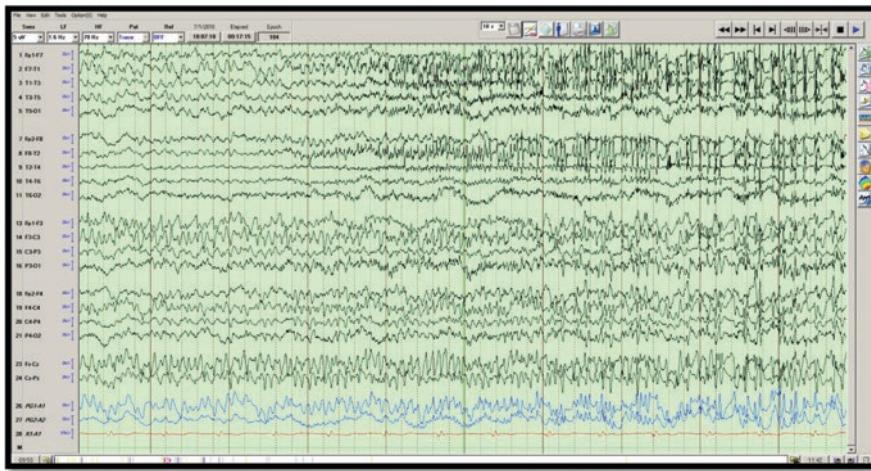


Fig. 9.27 The above four EEG tracings (Figs. 9.24, 9.25, 9.26, and 9.27) show evolution of L frontal seizure in an ICU patient with traumatic intracerebral hemorrhage. Note evolving rhythmic 9–10 Hz activity in the left and midline frontal area (F3–Fz–Cz) with subsequent spread in time to the left parasagittal, left temporal, then right frontal, and eventually bilateral hemispheres. The patient showed sudden right arm flexor posturing and clonic activity, right head and eye version and right sided followed by generalized tonic-clonic activity

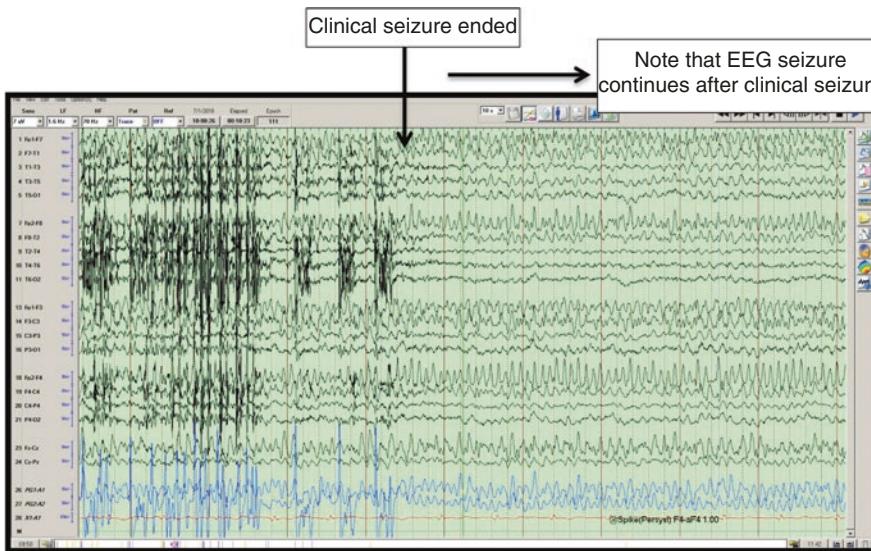


Fig. 9.28 EEG tracing showing that although the clinical seizure shown in Figs. 9.24, 9.25, 9.26, and 9.27 ended (vertical arrow), the electrographic seizure continued afterward. The continuous video-EEG monitoring was an important tool to detect the ongoing EEG seizure, despite clinical resolution. Patient was treated appropriately until the EEG seizure resolved

Take-Home Points

- Epileptiform discharges include spikes, sharp waves, and paroxysmal fast activity
- *Generalized epileptiform discharges:*
 - 3 Hz spike and wave (seen in absence seizures, otherwise normal background)
 - Atypical spike and wave (>3 Hz, seen in JME among other conditions).
 - Slow spike and wave (<3 Hz, seen in Lennox-Gastaut syndrome, abnormal EEG background)
 - Paroxysmal fast activity is associated with tonic seizures
 - Hypsarrhythmia, a high-amplitude, arrhythmic, chaotic pattern associated with epileptic spasms and electrodecremental seizures
- *Focal epileptiform discharges:*
 - Spikes in the anterior temporal, frontal, and midline central areas of brain are highly epileptogenic
 - Spikes in occipital and parietal areas have lower potential for epileptogenicity
 - PLEDs are periodic lateralized epileptiform discharges suggestive of an acute or subacute lesion, likely vascular in nature
 - PLEDs pattern is interictal but if associated with intermittent rhythmic activity (PLEDs Plus) suggests impending focal seizures
- *Seizures*
 - Characterized by:
 - Increasing rhythmicity of waveforms over time
 - Evolution in frequency and amplitude of the waveforms
 - If focal may spread to other areas of brain (evolution in space)

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Encephalopathies, Brain Death, and EEG

10

- EEG is an important tool in evaluation of patients with altered mental status:
 - It can rule out subclinical status epilepticus
 - It can show diagnostic EEG patterns for certain types of encephalopathies
 - It can determine metabolic encephalopathies vs. encephalopathies due to structural focal lesions
 - It can help with determining patient prognosis

10.1 Four EEG Patterns in Encephalopathies and Altered Mental Status

- Slow wave patterns
- Epileptiform patterns
- Periodic patterns
- Coma patterns

10.1.1 Slow Wave Patterns

- Non-specific diffuse theta slowing in somnolent or confused patients (Fig. 10.1)
 - This usually indicates a mild degree of encephalopathy
- Generalized polymorphic or rhythmic delta activity in obtunded or comatose patients
 - This suggests a moderate encephalopathy (Fig. 10.2)
 - If the polymorphic or rhythmic delta activity occurs unilaterally, it usually indicates a brain lesion contributing to the patient's encephalopathy (Fig. 10.3)
- Low amplitude delta activity in deep coma
 - This pattern is seen in severe encephalopathy such as late in anoxic brain injury or with deep anesthesia (Fig. 10.4)

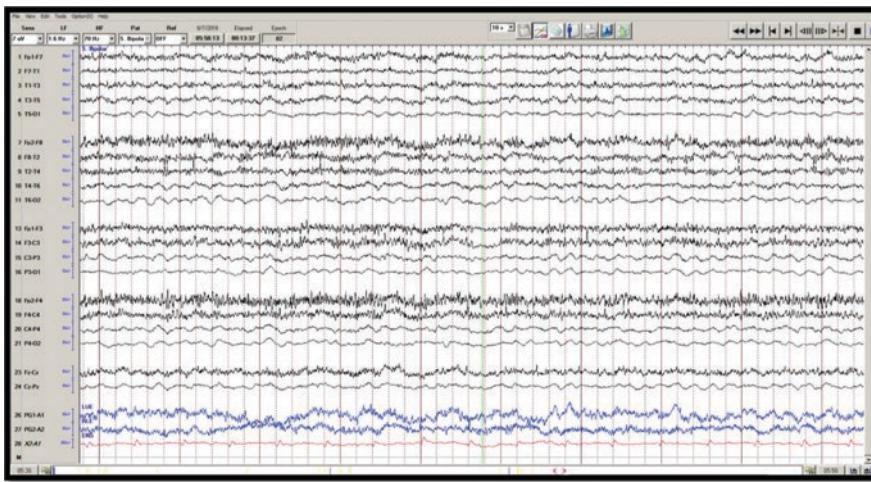


Fig. 10.1 EEG tracing showing non-specific diffuse 4–6 Hz theta frequency activity in an 85-year-old man with Parkinson's disease presenting with a fall and altered mental status

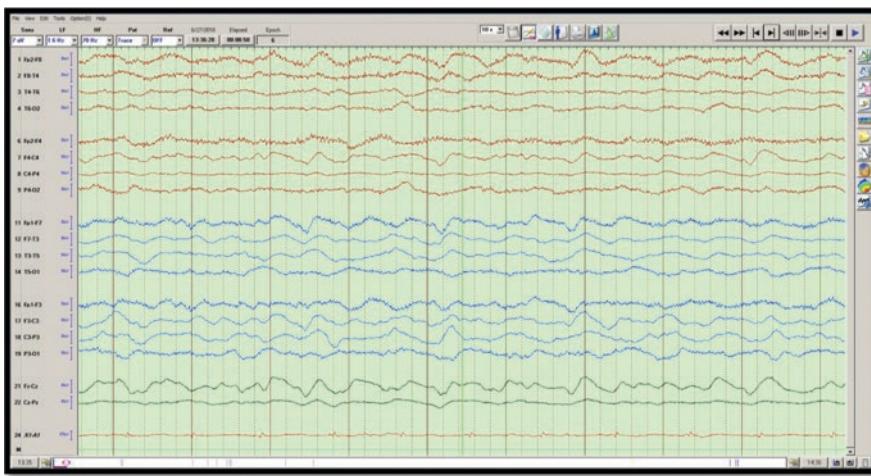


Fig. 10.2 EEG tracing showing generalized delta activity suggestive of a moderate diffuse encephalopathy in a comatose patient

- Frontal intermittent rhythmic delta activity (FIRDA)
 - First described as associated with deep midline and posterior fossa pathology [1, 2]
 - But also is reported in patients with brain tumors, ischemic brain injury, or metabolic and toxic encephalopathy, increased intracranial pressure [3, 4]

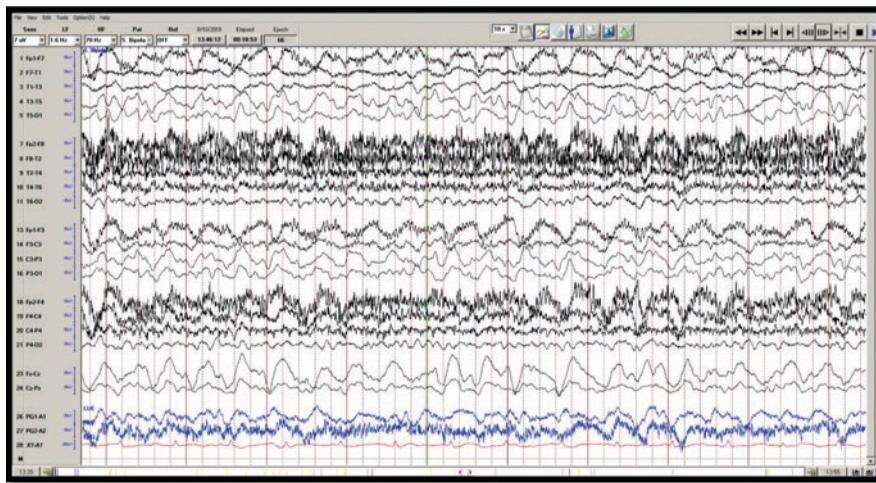


Fig. 10.3 EEG tracing in a patient with altered mental status and unilateral left hemispheric rhythmic notched delta activity in a 61-year-old woman with subarachnoid hemorrhage due to ruptured left A1–2 aneurysm



Fig. 10.4 EEG tracing showing severe suppression of EEG activity in a comatose patient with postanoxic brain injury 3 days after cardiac arrest. Patient's EEG initially showed burst-suppression pattern on the first day

- Rhythmic high-voltage delta activity at 2–3 Hz
- Occurs intermittently in bursts of 2–6 s
- Seen in awake and drowsy states and is frontally dominant
- No association with seizures

10.1.2 Epileptiform Patterns

- Status Epilepticus
 - Nonconvulsive status epilepticus
 - Associated with altered mental status, confusion, and various degrees of altered consciousness and abnormal behavior
 - Generalized nonconvulsive status is accompanied with generalized spike and wave discharges
 - Focal nonconvulsive status epilepticus is associated with continuous focal epileptiform discharges or frequent intermittent evolving focal seizures
 - Generalized convulsive status epilepticus

10.1.3 Periodic Patterns

- Periodic lateralized epileptiform discharges (PLEDs) or lateralized periodic discharges (LPDs)
 - Periodic focal or lateralized epileptiform discharges over one hemisphere (Figs. 10.5 and 10.6)
 - Consists of spikes or sharp wave complexes or trains of repetitive fast spikes
 - Sharp waves have variable morphology and may be diphasic or triphasic



Fig. 10.5 EEG tracing showing periodic lateralized epileptiform discharges (PLEDs or LPDs) in a 71-year-old lady with diabetes and hypertension presenting with altered mental status. The epileptiform discharges occur at a frequency of 1 Hz and are left hemispheric, maximal left occipital area. The patient also had intermittent lack of response and gaze deviation to the right accompanied with evolving left hemispheric seizures

Fig. 10.6 CT head of the same 71-year-old lady with left PLEDs as in Fig. 10.5 showing left parieto-occipital stroke



- Indicates *acute or subacute focal cerebral disturbance*
- Often associated with seizures and *highly epileptogenic* but an interictal pattern
- May be associated with focal neurologic deficit and altered mental status
- *Most common cause is vascular event* such as stroke but also in these conditions:
 - HSV encephalitis
 - Brain abscess
 - Brain tumor
 - Subdural hematoma
- Usually resolve in 1–4 weeks
- Generalized periodic epileptiform discharges (GPED)
 - Widespread generalized periodic sharp waves (Figs. 10.7 and 10.8)
 - Can be seen in Creutzfeldt-Jacob disease at frequency of about 1 Hz
 - In CJD chronologic EEG finding are:
 - Background slowing early on
 - Focal or diffuse slowing
 - Sporadic sharp waves or LPDs (Fig. 10.9)
 - Generalized bisynchronous sharp waves at 0.5–1 Hz with duration of 200–400 msec (Fig. 10.10)
 - Hypoxic brain insult/cardiorespiratory arrest
 - Metabolic encephalopathies



Fig. 10.7 EEG tracing showing generalized periodic epileptiform discharges (GPED) in a comatose ICU patient



Fig. 10.8 EEG tracing showing generalized periodic epileptiform discharges (GPED) which is slower in frequency compared with Fig. 10.7 in a comatose ICU patient

- Drug toxicities
- Inflammatory disorders
- Burst-Suppression Pattern
 - Bursts of spikes and sharp waves or mixed frequency activity followed by intervals of relative attenuation of activity (Fig. 10.11)
 - The bursts may be associated with body myoclonus (Fig. 10.12)



Fig. 10.9 EEG tracing in a 49-year-old man presenting with near continuous left-hand twitching consistent with epilepsia partialis continua. He developed rapid gait disturbance, cognitive impairment, and hyperreflexia. CSF was positive for RT-QuIC and a diagnosis of CJD was made. EEG in this stage showed subtle periodic right central sharp waves correlating with patient's near continuous left-hand posturing and twitches



Fig. 10.10 EEG tracing showing late-stage CJD finding of periodic generalized epileptiform discharges (GPED) at 0.5–1 Hz, in the same patient as in Fig. 10.9. Patient passed away 2 months after onset of symptoms

- The bursts become less frequent as the brain loses more function and suppression becomes more prolonged (Fig. 10.13)
- Seen after a severe brain insult such as cardiopulmonary arrest
- Indicates a poor prognosis for recovery

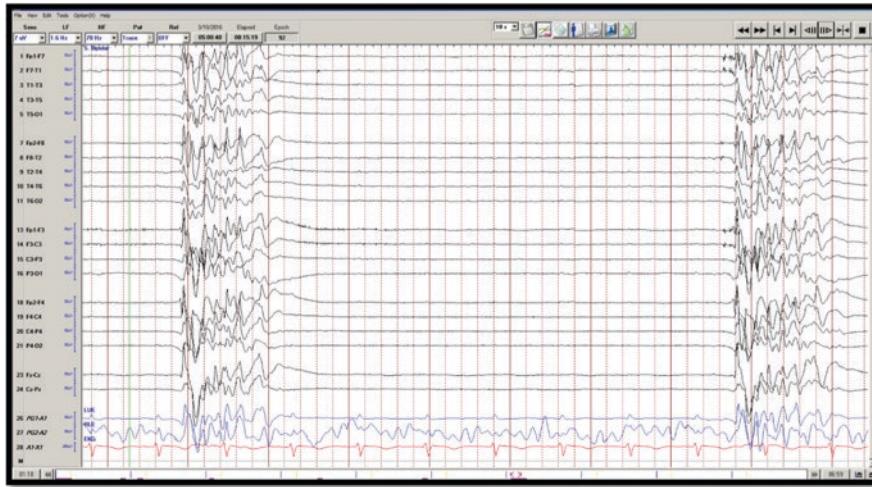


Fig. 10.11 EEG tracing showing burst-suppression pattern in a patient 5 h post-cardiac arrest. Bursts of spike/polyspikes are followed by periods of suppression of activity lasting 5 s in duration

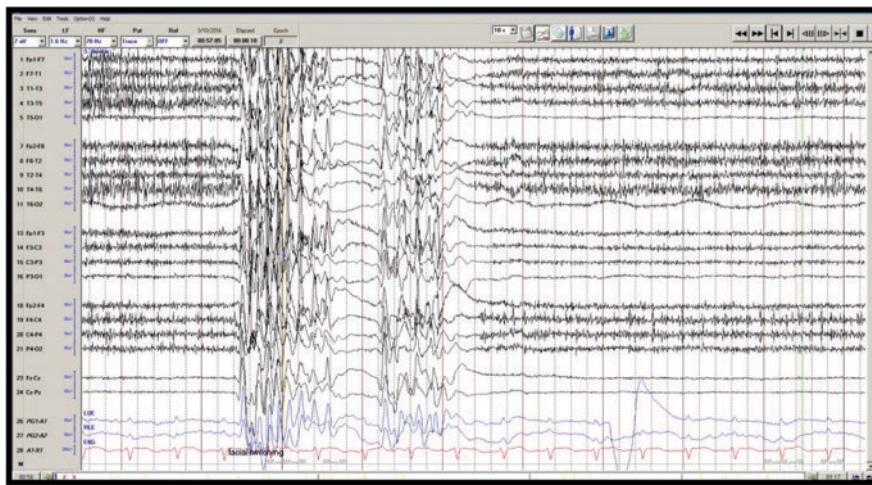


Fig. 10.12 EEG tracing on the same patient as Fig. 10.11 with anoxic brain injury. This burst of polyspike and wave discharges was accompanied with sudden body myoclonic jerk and facial twitch

- Also can occur temporarily with anesthesia, drug overdose, or hypothermia
- Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges (SIRPID)
 - Described by Hirsch in 2004 in critically ill patients [5]
 - Commonly provoked by alerting stimulation of patient (Figs. 10.14 and 10.15)
 - Likely due to dysregulation of thalamo-cortical pathways in an abnormal and hyperexcitable cortex
 - The relationship of SIRPIPs with seizures is not clear



Fig. 10.13 EEG tracing in the same patient as Figs. 10.11 and 10.12. Three days after anoxic brain injury, the EEG showed more continuous suppression pattern



Fig. 10.14 EEG tracing of a 31-year-old female with a history of Wolf-Hirschhorn syndrome and focal epilepsy presenting with encephalopathy and focal status epilepticus. After treatment of her focal status, there were persistent left hemispheric periodic rhythmic discharges (SIRPDs) provoked by patient's stimulation which subsided when she was left alone. Figure 10.15 shows the same patient during period of quiescence

- Only focal or ictal appearing SIRPDs are correlated with clinical status epilepticus
- Intracranial hemorrhage is independent predictor for focal SIRPDs
- Triphasic Waves
 - Broad-contoured waveforms with three phases (Fig. 10.16)



Fig. 10.15 EEG tracing in the same patient as in Fig. 10.14 with SIRPIDs. This EEG shows that during a period of non-stimulation and quiescence there is decreased rhythmicity of left hemispheric activity



Fig. 10.16 EEG tracing in a 62-year-old man with metabolic encephalopathy showing generalized 1–2 Hz triphasic waves with anterior to posterior lag

- Usually bilaterally synchronous, 1–2 Hz
- Time lag between the anterior and posterior head regions
- More often seen in hepatic encephalopathy, metabolic encephalopathy, medication toxicity, hypoxic brain injury, and degenerative processes

10.1.4 Coma Patterns

- Theta coma pattern
 - Rare EEG finding, described by Synek and Synek [6]
 - May occur in postanoxic and posttraumatic patients
 - Bilaterally synchronous and symmetric rhythmic theta activity (Fig. 10.17)
 - Maximal frontal central and constant throughout the recording
 - Intermittent periods of suppression of activity
 - Non reactive to stimuli
 - Poor prognosis of recovery if the pattern shows no variability [7]
 - Alpha, theta, and spindle coma patterns may coexist [8]
- Alpha coma pattern
 - Generalized, monorhythmic, invariant alpha
 - Nonreactive to stimuli
 - 2–3 days after cardiopulmonary arrest and anoxic brain insult
 - Poor prognosis of recovery/risk of death or persistent vegetative state
- Spindle coma pattern
 - Associated with head injury, drug toxicity, intracranial hemorrhage, and anoxic brain injury (Fig. 10.18)
 - Resembles sleep pattern
 - Better prognosis compared with alpha coma pattern [9]
- Beta coma pattern
 - Generalized beta frequency activity superimposed on delta
 - Most common following drug ingestion such as barbiturates or benzodiazepines



Fig. 10.17 EEG tracing in a 45-year-old comatose man with severe traumatic brain injury showing theta coma. His EEG shows monotonous theta activity with intermittent periods of suppression and lack of variability and reaction to stimuli

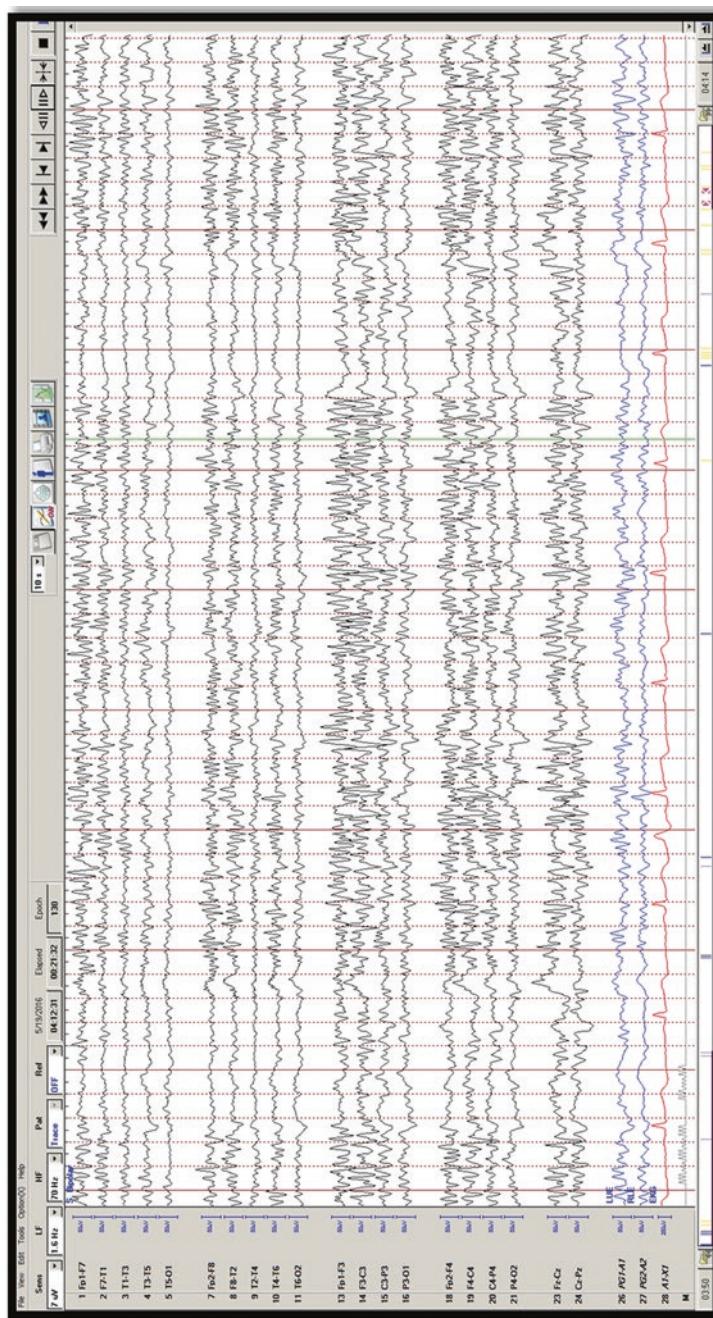


Fig. 10.18 EEG tracing in a 54-year-old man showing spindle coma as a result of benzodiazepine overdose

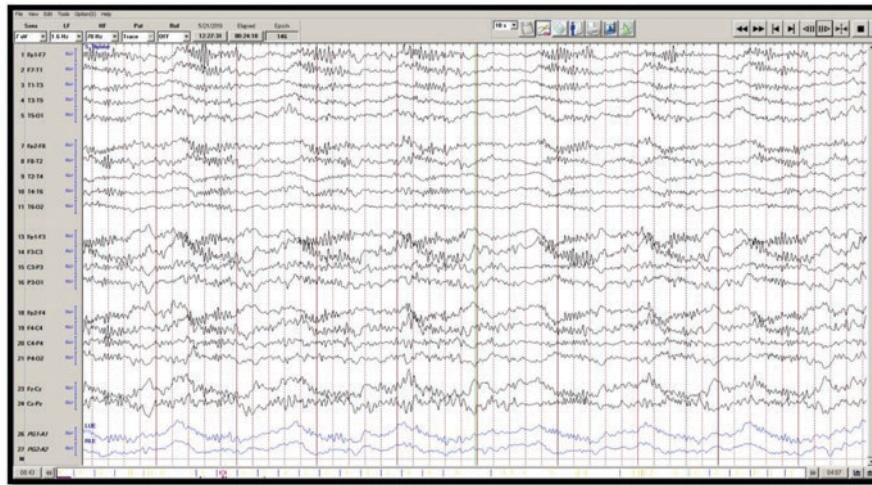


Fig. 10.19 EEG tracing in a 41-year-old man presenting with NMDA receptor positive encephalitis showing extreme delta brush pattern (EDB)

- Seen with anesthetic pattern and may resolve when the medication effect resolves
- Extreme delta brush in NMDAR encephalopathy (EDB) [10]
 - A newly described EEG finding seen in patients with anti-NMDAR encephalitis
 - Rhythmic delta activity 1–3 Hz
 - Superimposed bursts of rhythmic 20–30 Hz beta frequency activity “riding” on each delta wave (Figs. 10.19 and 10.20)
 - The presence of this pattern is associated with a more prolonged illness
 - Anti-NMDA receptor encephalitis is a syndrome characterized by:
 - Encephalopathy
 - Neuropsychiatric symptoms
 - Seizures
 - Autonomic instability
 - Hypoventilation

10.2 Prognosis of Coma Based on EEG

- *Poor prognosis*
 - No variability in state
 - No reactivity to stimuli
 - Spontaneous burst suppression pattern
 - Periodic discharges or burst suppression associated with myoclonus
 - Monorhythmic pattern

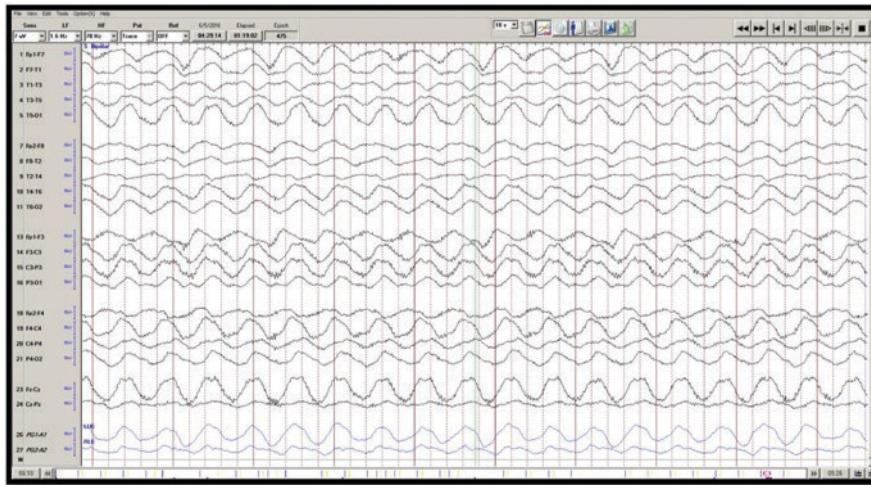


Fig. 10.20 EEG tracing in the same patient as in Fig. 10.19 with NMDAR encephalitis, showing deeper stage of coma and remnants of extreme delta brush pattern superimposed on rhythmic delta activity

- *Potential for improvement*
 - Spontaneous variability and change in state
 - Reactivity to stimuli
 - Return of some normal baseline pattern

10.3 Brain Death and Electrocerebral Silence

- Defined as no cerebral activity over two microvolts
- Brain death is accepted as legal definition of death
- Irreversible cessation of clinical brain functions [11]
- A clinical diagnosis based on absence of brain stem reflexes, coma, and apnea
- EEG is just an ancillary test and not a requirement for brain death diagnosis
- Minimum criteria for EEG testing in determining electrocerebral silence (ECS) based on 1994 ACNS criteria include:
 - Minimum of eight scalp electrodes
 - Interelectrode impedances less than $10,000 \Omega$ but more than 100Ω
 - Tap each electrode to verify the integrity of the recording system
 - Interelectrode distance at least 10 cm
 - Record at sensitivity of $2 \mu\text{V}$ for at least 30 min
 - Appropriate filter setting
 - High-frequency filter above 30 Hz and low-frequency filter below 1 Hz
 - Monitor EKG and respiration
 - No EEG reactivity to stimulation of patient

- Must be done by qualified technologist
- Repeat EEG if necessary and in case of doubt
- Rule out drug overdose, sedation and anesthetic agents, and hypothermia
- Rule out neuromuscular blocking agents

Take-Home Points

- There are four EEG patterns in encephalopathies and coma:
 - Slow wave patterns
 - Epileptiform patterns
 - Periodic patterns
 - Coma patterns
- EEG in comatose patients is helpful to rule out subclinical seizures
- EEG in comatose patients can help with specific diagnosis and prognostication
- FIRDA is a non-specific pattern seen in brain tumors, ischemic brain injury, metabolic and toxic encephalopathy, and increased intracranial pressure
- PLEDs indicate acute or subacute lesion, most likely vascular in nature and high potential for epileptogenicity
- PLEDs are seen in stroke, HSV encephalitis, subdural hematoma, brain tumor, and abscess
- End-stage CJD can present with GPED at 1 Hz
- Early CJD may show background or focal slowing and PLEDs
- Postanoxic burst suppression pattern with or without myoclonus carries a poor prognosis for recovery
- The relationship of SIRPIPs with seizures is not clear
- Generalized triphasic waves are seen in:
 - Hepatic encephalopathy
 - Metabolic encephalopathy
 - Medication toxicity
 - Hypoxic brain injury
 - Degenerative processes
- Alpha coma pattern is associated with poor prognosis and risk of death or persistent vegetative state
- Spindle coma pattern has better prognosis compared with alpha coma pattern
- Extreme delta brush is a newly described EEG pattern in NMDAR encephalopathy
- An invariant, monorhythmic EEG with lack of reaction to stimuli has a poor prognosis
- Electrocerebral silence (ECS) is defined as no EEG activity over 2 microvolts
- Brain death is a clinical diagnosis and EEG is not mandatory

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