Mohamad Z. Koubeissi
Nabil J. Azar *Editors*

Epilepsy Board Review

A Comprehensive Guide

Springer

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This book is dedicated to my mother, Haja Jammoul, whose love has been my nest, my wings, and my sky.

Mohamad Z. Koubeissi

I dedicate this book to my wife Joelle, my sons Michel and John, for their endless love, support, and encouragement.

Nabil J. Azar

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Part I
The Normal EEG

Physiologic Basis of EEG and Epilepsy

1

Susanta Bandyopadhyay, Mohamad Z. Koubeissi and Nabil J. Azar

Organization of the Cerebral Cortex

The cerebral cortex is organized into six horizontal layers with layer I being the most superficial underneath the pial surface and layer VI being the deepest overlying subcortical white matter:

Layer I	Molecular layer containing dendrites and axons from other layers
Layer II	External granular layer containing cortico-cortical connections
Layer III	External pyramidal layer containing cortico-cortical connections
Layer IV	Internal granular layer receiving input from thalamus
Layer V	Internal pyramidal layer sending output to subcortical structures
Layer VI	Multiform layer sending output to thalamus

Extensive horizontal cortico-cortical connections in layers I, II, and III make up the vast majority of the cortical synapses. Thalamocortical projections have an important role in modulating inhibition via thalamic fibers from the reticular nucleus of the thalamus.

The electrical activity recorded on electroencephalogram (EEG) arises from the extracellular field potential generated by changes in membrane potential of neurons for the most part with some contribution from glial cells.

Neuronal Resting Membrane Potential, Postsynaptic Potentials, and Action Potential

A typical neuron has a cell body (soma) and processes (axons and dendrites), which may be considered as extensions of the soma. Cell membranes of neurons have several different ion channels including sodium and potassium leak channels as well as voltage-gated sodium and potassium channels that permit the passage of ions depending on their electrochemical gradients. Equilibrium potential for an ion is the membrane potential at which there is no net movement of that ion across the cell membrane. Equilibrium potential can be calculated using the Nernst equation. The resting membrane potential of a neuron is typically −70 mV, the inside of the neuron being negative in relation to the outside. The resting membrane potential is determined by the movement of potassium, sodium, and chloride ions along their electrochemical gradient across

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the cell membrane. Table 1.1 shows the intracellular and extracellular concentrations of these ions and their equilibrium potentials in a typical mammalian neuron. The membrane potential at which there is no net flow of ions across the cell membrane is the resting membrane potential which can be calculated using the Goldman–Hodgkin–Katz equation. The major contributor of resting membrane potential is the potassium leak channels with a net outward flow of potassium ions (K^+) under resting conditions. An action potential is generated when the negativity in the interior of the neuron, i.e., the resting membrane potential, decreases to a critical point (typically around −40 mV). The voltage-gated sodium channels play a major role in the generation and propagation of action potential by allowing sodium to enter into the soma. Once generated, the action potential—a short duration (usually less than 2 ms) high-amplitude wave of depolarization—travels through the neuronal processes and reaches synapse, a specialized contact between neurons usually between axons and dendrites.

Synaptic transmission is the major mode of transmission of information from one neuron to another. Each synapse has a presynaptic terminal containing neurotransmitters in vesicles and a postsynaptic terminal containing receptors for the neurotransmitters. Neurotransmitters are released from the presynaptic terminal when an action potential causes sufficient change in the voltage (depolarization) at the presynaptic terminal to activate voltage-gated calcium channels allowing calcium to enter into the presynaptic terminal. This triggers a cascade of events leading to the fusion of presynaptic vesicles with the membrane of the presynaptic terminal, thereby releasing neurotransmitter molecules into the synaptic cleft. Binding of neurotransmitters to the receptors on the postsynaptic terminal activates ion channels associated with them, allowing the passage of ions leading to local changes in membrane potential (Fig. 1.1). Such local changes in membrane potential are known as postsynaptic potentials (PSPs) which are nonpropagated small-amplitude potentials lasting 10–100 ms. PSPs can be excitatory (excitatory postsynaptic potential (EPSP)) or inhibitory (inhibitory postsynaptic potential (IPSP)) depending on the type of ion channel activated and the electrochemical gradient for ions that can pass through the channel. EPSPs generally result from an inward flow of positive ions such as sodium or calcium and cause depolarization (excitation), thus decreasing the threshold for triggering an action potential in the postsynaptic terminal. On the other hand, IPSPs result from an inward flow of negative ions (e.g., chloride) or outward flow of positive ions (e.g., potassium) and cause hyperpolarization (inhibition), thus increasing the threshold for triggering an action potential in the postsynaptic terminal.

A single EPSP or IPSP is not sufficient enough to move the membrane potential of the postsynaptic terminal to or away from the threshold for triggering of action potential. Summation of several PSPs is necessary for that purpose. Such summation can be spatial

Table 1.1 Intracellular and extracellular concentrations of ions that play a major role in determining the resting membrane potential in a mammalian neuron

Ion	Intracellular (mM)	Extracellular (mM)	Equilibrium potential (mV)
Potassium (K*)	140–150	5	–90
Sodium (Na*)	5–15	145	+60
Chloride (Cl)	4–30	110–125	–70

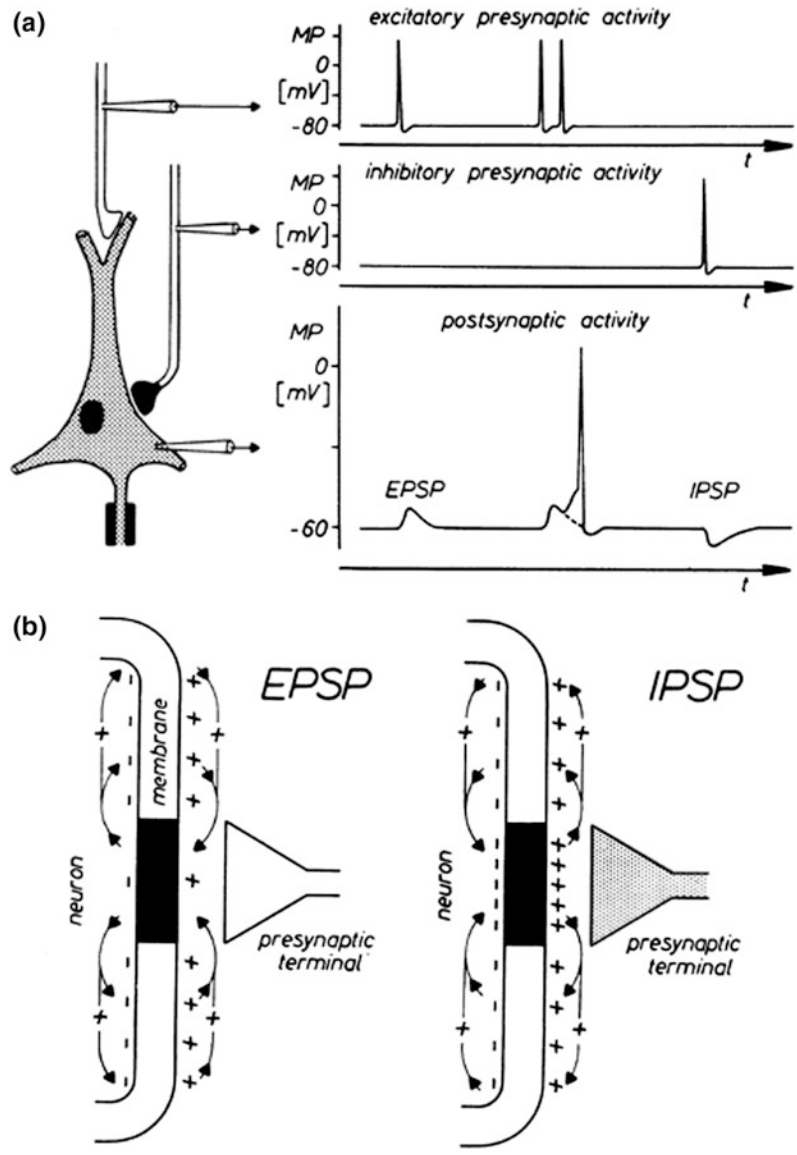


Fig. 1.1 Membrane potential (MP) changes and current flows during synaptic activation. **a** The MP of the postsynaptic neuron and the MP of the presynaptic fibers are recorded by means of intracellular microelectrodes. Action potentials in the excitatory and inhibitory presynaptic fibers lead to excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP), respectively, in the postsynaptic neuron. Two EPSPs sum up to a superthreshold potential, triggering an action potential in the postsynaptic neuron. **b** During EPSP and IPSP, ionic current flows occur through as well as along the neuronal membrane, as shown by *arrows*. The density of + and – signs indicates the polarization of the subsynaptic (*dark area*) as well as that of the postsynaptic membrane during synaptic activation. Adapted from [1]

(summation of several PSPs in the vicinity) or temporal (summation of several PSPs occurring in quick succession). Neurons generally have extensive dendritic arborization, and hundreds to thousands of axons can form synapses on a neuron's dendrites. Each neuron receives synaptic inputs from multiple sources at the same time—spatial and temporal summation of these inputs determines whether or not the neuron fires an action potential.

EEG Generator

A large number of EPSPs and IPSPs generated in a complex network of neurons alter the overall excitability of the neurons in the network. Such PSPs generate an extracellular field potential (Fig. 1.2) that changes over time which is believed to be the basis of potentials recorded on EEG. The extracellular field potential is a

secondary phenomenon resulting from the development of potential gradients between areas of localized membrane potential change and the remaining areas of the neuronal membrane. A 'sink' is generated at the site of an EPSP because of an inflow of positive ions into the localized area of the neuron, and there is a corresponding 'source' at a distance where positive ions come out of the neuron; current flows from the 'source' to the 'sink' in the extracellular space giving rise to the extracellular field potential. Thus, a recording electrode close to the synapse receiving an excitatory input (EPSP) would record a negative potential because of an inward flow of positive ions causing negativity in the extracellular space nearby, whereas a deep recording electrode at a distance would record positivity because of an outflow of positive ions associated with the current flowing through the extracellular space. The reverse is true for an inhibitory input (IPSP): A recording electrode close to the synapse receiving an inhibitory input (IPSP) would record a positive potential because of an inward flow of negative ions (or an outward flow of positive ions), whereas a recording electrode at a distance would record negativity because of an outflow of negative ions (or an inflow of positive ions) associated with the current flowing through the extracellular space.

Therefore, polarity of extracellular field potentials recorded by surface electrodes on EEG depends on the direction of current flow as well as on the position of the electrode relative to the location of the generator. This translates to the fact that superficial EPSPs and deep IPSPs will show the same polarity (negative) on a surface recording electrode. Likewise, superficial IPSPs and deep EPSPs will show the same polarity (positive) on a surface recording electrode (Fig. 1.3). Thus, orientation of neurons and their processes, as well as location of synaptic contacts with respect to the cortical surface, are important determinants of extracellular field potentials recorded by EEG electrodes.

Pyramidal neurons in the cerebral cortex are arranged in vertical columns with their cell bodies typically in the layer III or V and their processes (dendrites and axons) spanning the entire column and receiving thousands of synaptic contacts. This allows for summated

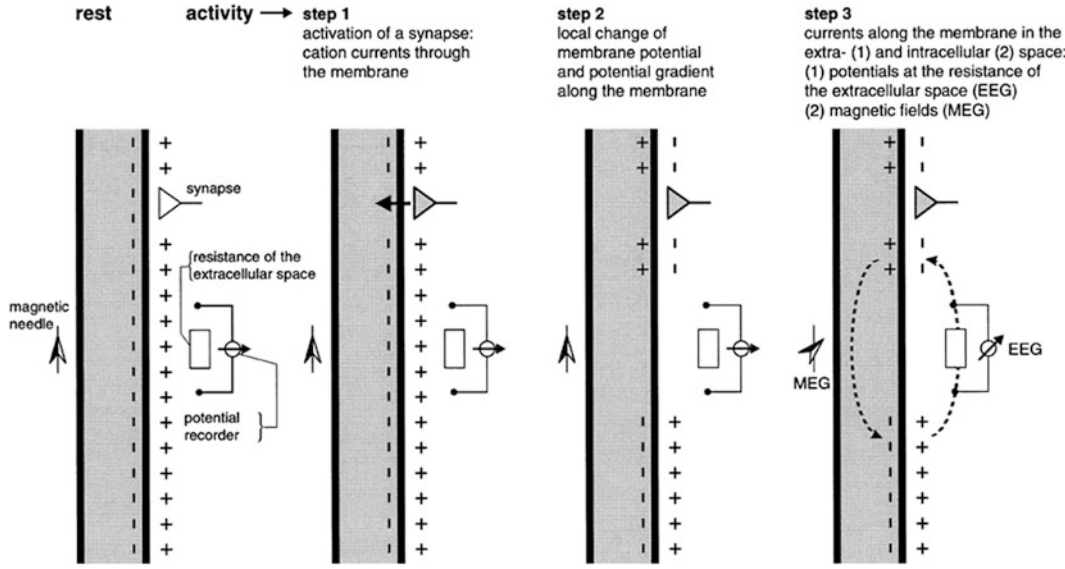
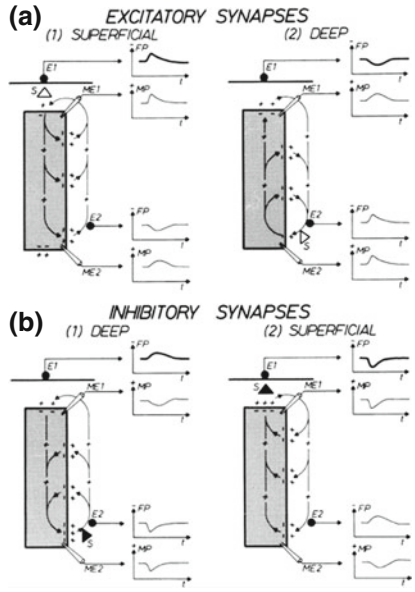


Fig. 1.2 Basic mechanisms underlying the generation of potentials (electroencephalogram (EEG)) and of magnetic fields (magnetoencephalogram (MEG)) in the extracellular space of central nervous system. The description is based on the assumption that an extended neuronal process, e.g., a dendrite, is locally depolarized by the activation of an excitatory synapse. Adapted from [1]



(c)

	EPSP	IPSP
Superficial	-ve	+ve
Deep	+ve	-ve

Fig. 1.3 Membrane potential (MP) changes and field potentials (FPs) elicited by the activation of excitatory and inhibitory synapses in the central nervous system. The elementary processes are explained by means of a neuronal element (*hatched area*), the one end of which contracts the surface of a structure in the central nervous system. The MP of the neuron element is recorded at both ends by the microelectrodes ME_1 and ME_2. The extracellular field is picked up at the surface of the neuronal structure by the electrode E_1, as well as in the vicinity of ME_2 by the electrode E_2. Active excitatory and inhibitory synapses are marked by *open triangles* and *black triangles* (S), respectively. **a**(*1*) The inward current at S generates an EPSP that appears in the region of ME_1, as well as in that of ME_2. Because S is located superficially, the FP generated, due to the direction of the extracellular current flow (*arrows*), is of negative polarity at the surface (E_1) and of positive polarity in the deeper recording (E_2). **a**(*2*) The activation of a deep excitatory synapse elicits a current flow with inverse direction as compared with **a**(*1*). Therefore, the extracellular FP consists in a positive deflection at the surface and in a negative one at the depth. **b**(*1*) The outward current at S generates an IPSP in the region of ME_2, as well as in that of ME_1. Due to the direction of the extracellular current flow, the FP generated consists in a positive fluctuation in the depth (E_2) and in a negative one in the surface recording (E_1). **b**(*2*) The current flow during the activation of a superficial inhibitory synapse is inverse as compared with **b**(*1*). Therefore, the FP recorded from the surface consists of a positive fluctuation. Differences in the time course of the various potentials are caused by the electrical properties of the tissue. **c** Schematic summary of the polarity of the potential recorded on the scalp with an EEG recording electrode based on the occurrence of (superficial vs. deep) EPSP or IPSP. Adapted from [1]

potentials with a vertical dipole or a dipole oriented at an angle to the recording electrodes (discussed further below) which can be recorded on EEG. On the other hand, summated potentials resulting in horizontal dipoles (oriented parallel to the recording electrodes) cannot be generally recorded on EEG. Subcortical structures have an indirect influence on scalp EEG. Of note, to produce a scalp EEG signal, 6 cm^2 or more of synchronously active area of cortex is required. Scalp electrodes record volume-conducted potentials. Signal decreases proportionally to the square of the distance between the source and the electrode. Most of the cortical activity recorded from subdural or depth electrodes is not evident in the scalp EEG due to the attenuation by the intervening scalp and skull.

The EEG pattern is thought to depend on numerous areas of the cerebral cortex with opposite electrical poles (dipoles) that constantly fluctuate. Thus, the EEG signal at a scalp electrode can be viewed as a result of currents generated by a negative and a positive dipole layer in the electrode 'view.' The potential recorded at the electrode is proportional to the solid angle subtended by the dipole layer as shown in Fig. 1.4.

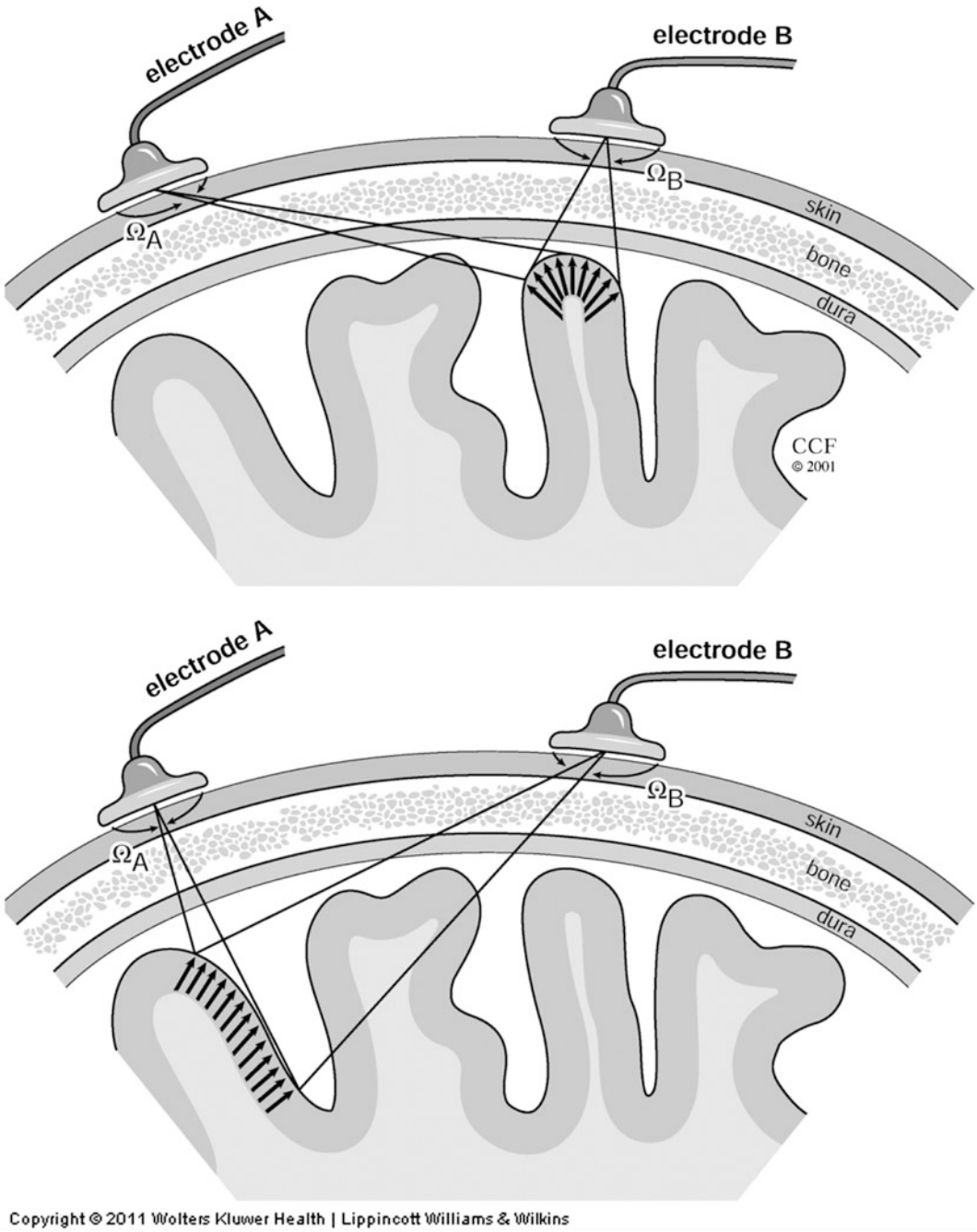


Fig. 1.4 Use of the solid angle rule to ascertain the signal measured on the scalp surface relative to the orientation of the dipole. *Top* Surface electrode B sees a large electrical potential because of the orientation and proximity of the dipole layer, as borne out by the solid angle ΩB. *Bottom* In this case, the potential seen by the electrode A is actually lower than that measured by the more distant electrode B because of the arrangement of the dipoles in the discharging region. The smaller solid angle, ΩA, is proportional to the voltage measured on the scalp. Adapted from [2]

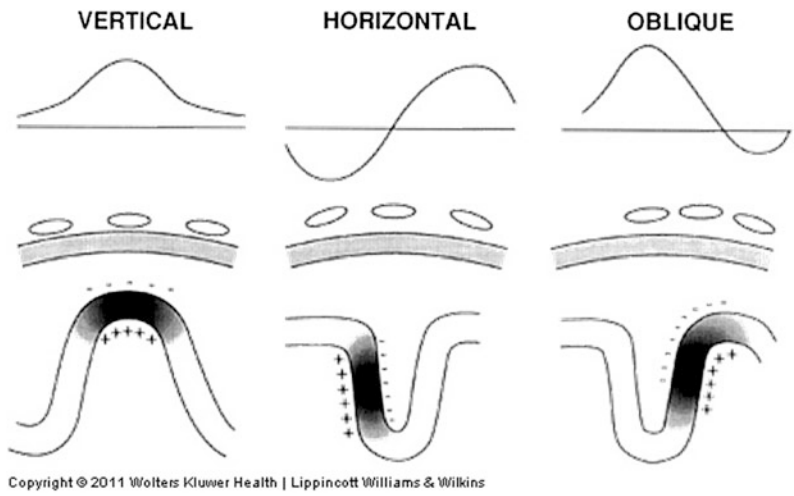


Fig. 1.5 There are unusual sources wherein both the negative and the positive poles are recorded on the surface. The *bottom row of figures* shows a patch of cortex containing gyri and sulci. The *darker areas* represent the cortical mantle that is activated by an epileptic discharge, with negative and positive poles highlighted. In the *middle row* of illustrations, the positions of the electrodes on the scalp, relative to the discharging cortex, are shown. The *top row* illustrates the voltage that would be recorded on the EEG as a function of the distance along the scalp right below it. Adapted from [2]

If adjacent active regions of the cortex have voltage fields with different dipole orientations, they summate in relation to their representative field vectors. For example, if two cortical areas have an opposite dipole orientation such as the two sides of a sulcus, cancelation occurs, and no voltage field is evident at the scalp. When the dipole is vertical and the electrode is directly above it, the electrode records the field maximum (Fig. 1.5). As the orientation of the dipole becomes progressively less radial and more tangential to a recording electrode, the electrode records a voltage field of lesser amplitude. If the dipole is directly below the electrode but it is perfectly tangential, the electrode records no potential because of its location on the zero isopotential line of the source scalp field.

Wave Generation and Baseline Shifts

When an afferent fiber forming an excitatory synapse on an apical dendrite near the surface produces bursts of action potentials interrupted by periods of quiescence, EPSPs sum up during the bursts giving rise to fluctuating field potentials. When recording from surface is done with an amplifier with a finite time constant (as in conventional EEG), such fluctuations in field potential are recorded as waveforms (Fig. 1.6). Sustained firing of the afferent fiber leads to sustained depolarization of the apical dendrites causing a depolarization shift which is not reflected on the surface in conventional EEG recorded with an amplifier with a finite time constant. Sustained changes in field potential (baseline shifts) can be recorded using a direct current or DC amplifier that has an infinite time constant (Fig. 1.7). Such recordings are not done from the scalp because of technical difficulties and are usually performed in experiments in animal models. Of note, not only baseline shifts are generated by neurons; but glial cells also contribute to its generation. Increased firing of a deep-seated neuron causes rise in extracellular potassium concentration which in turn leads to depolarization of glial cell superficial to it. Such depolarization of the glial cell electrotonically spreads to the glial cell network coupled by gap junctions.

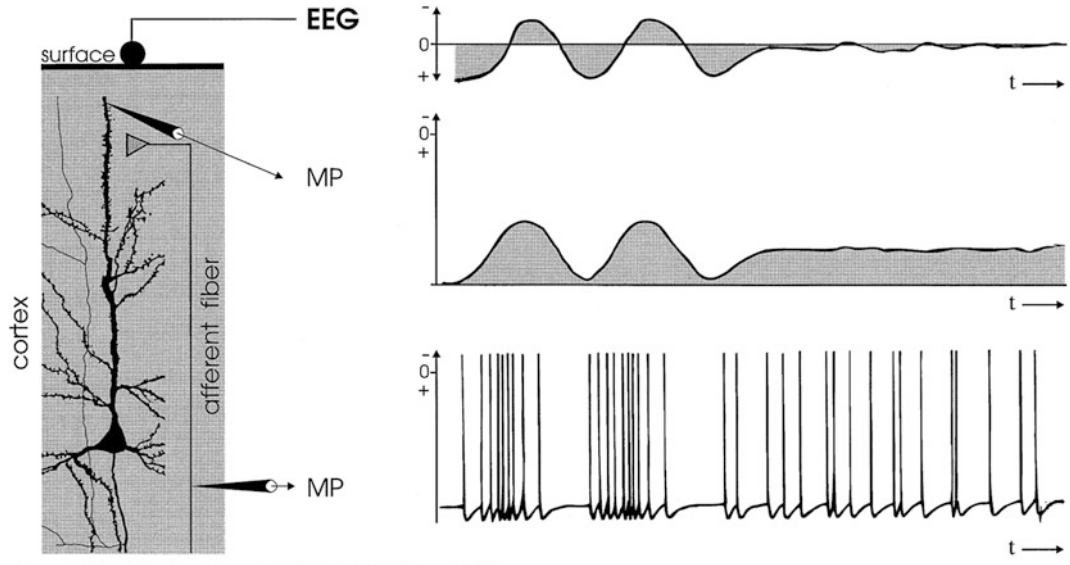


Fig. 1.6 Wave generation in the electroencephalogram (EEG) at the surface of the cerebral cortex. A perpendicular pyramidal neuron is shown. An afferent fiber formed an excitatory synaptic contact at the superficial part of the apical dendrite. Simultaneous recordings of the membrane potentials (MPs) of the afferent fiber and the dendritic element, as well as of the EEG, are displayed. Groups of action potentials in the afferent fiber generate wavelike excitatory postsynaptic potentials (EPSPs) in the dendritic region and corresponding waves in the EEG recording. Tonic activity in the afferent fiber results in long-lasting EPSP with only small fluctuations. The long-lasting depolarization is not reflected on the conventional EEG recording. Adapted from [2]

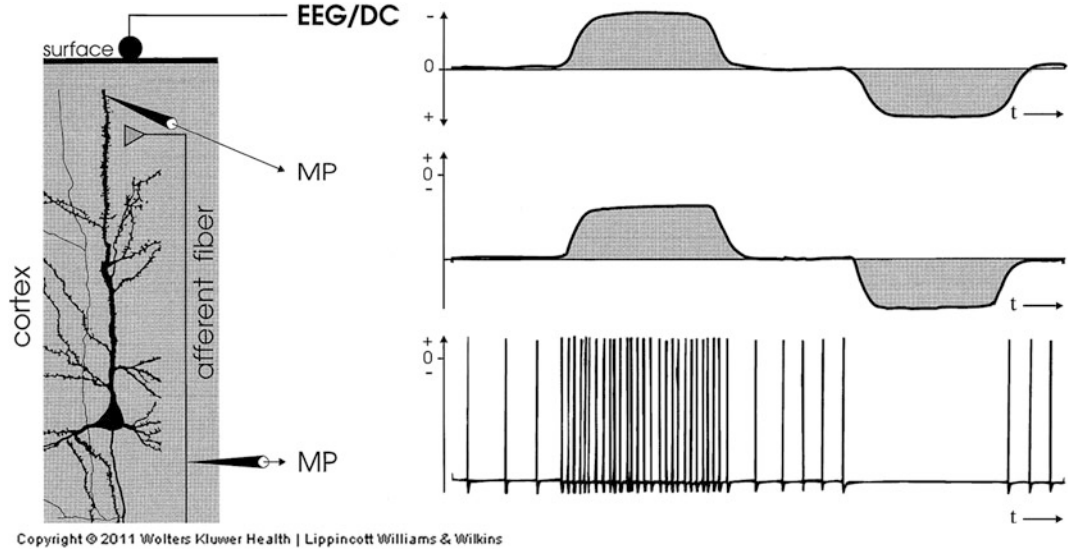


Fig. 1.7 Sustained shifts in the electroencephalogram (EEG) at the surface of the cerebral cortex resulting from sustained neuronal activities. If recordings are performed with a direct current (DC) amplifier (EEG/DC), sustained potentials can also be recorded at the surface. In the perpendicular pyramidal neuron depicted, an afferent fiber formed an excitatory synaptic contact at the superficial part of the apical dendrite. The membrane potentials (MPs) of the afferent fiber and the dendritic element were recorded simultaneously, as was the EEG/DC. Increased and decreased sustained activity in the afferent fiber generated sustained depolarizations and hyperpolarizations of the dendritic region and corresponding negative and positive shifts of the EEG/DC recording. Adapted from [2]

Focal Activity

Field potentials generated during epileptic activity are of higher amplitude than those generated by nonepileptic activity because epileptic field potentials are the result of highly synchronized neuronal activity. During focal epileptic activity, negative potentials of high amplitude, which repeat themselves in stereotyped form and periodicity, can be recorded from the area. Such oscillations of field potential occur in parallel with the fluctuation of membrane potential which is the characteristic of the epileptiform activity of individual neurons (Fig. 1.8). This is known as paroxysmal depolarization shift (PDS) which starts with a steep depolarization that triggers a series of action potentials followed by a plateau of continued depolarization; this is followed, after 80–100 ms, by a steep repolarization with or without an after-going hyperpolarization.

It is important to note that field potentials recorded from the surface may differ from those recorded from different layers of the cortex. This has been shown in animal experiments using local application of penicillin as trigger for focal epileptiform activity. Intracortical potential distribution that determines the occurrence of associated descending activity to the spinal cord may be different for the same epileptiform activity recorded from the surface; negative field potential in the layer V only was associated with the corresponding spinal field potentials.

Generalized Tonic–Clonic Activity

When tonic–clonic activity is triggered in experimental animals by repeated injections of pentylenetetrazol and membrane potential of a pyramidal tract in the layer V of the cortex is recorded during a convulsive seizure, typical PDSs can be seen which correlate with the potential fluctuations noted in the DC recording —with superficial negative potential fluctuations (corresponding to synchronized depolarization of pyramidal neurons) in the beginning and with superficial positive potential fluctuations (corresponding to postictal hyperpolarization of pyramidal neurons) at the end of the convulsive seizure (Fig. 1.9).

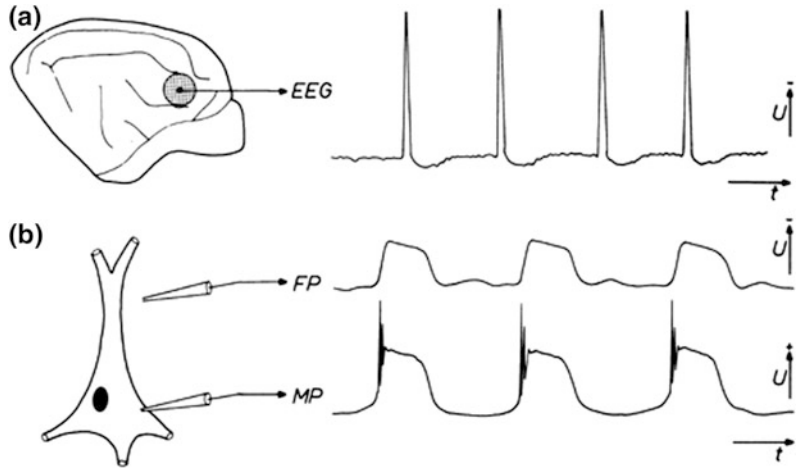


Fig. 1.8 EEG (**a**) and membrane potential (MP) changes of a pyramidal tract neuron and extracellular field potential (FP) recorded in the vicinity of the impaled neuron (**b**) during focal interictal activity elicited by the application of penicillin to the cortical surface (*hatched area* in **a**). Drawings of original tracings from experiments in the rat. The sweep speed in **b** is five times that in **a**. The recording sites are shown in the schematic drawings. Adapted from [1]

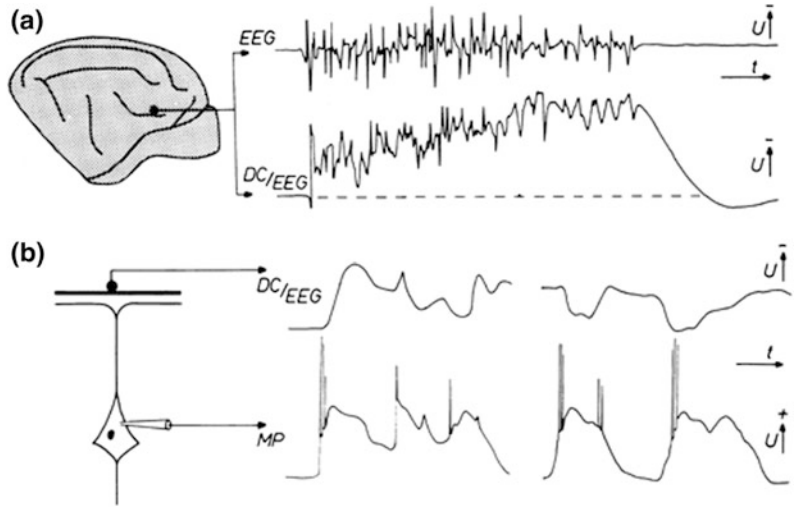


Fig. 1.9 Simultaneous recordings of EEG and DC/EEG (**a**) and of DC/EEG and membrane potential (MP) of a pyramidal tract neuron (**b**) during generalized tonic–clonic seizures elicited by pentylenetetrazol. (Drawings after original tracings from experiments in the cat's motor cortex. The sweep speed in **b** is 10 times that in **a**.) Adapted from [1]

Spreading Depression

Spreading depression (SD) is a strong and rapid depolarization of neurons that slowly propagates (3–5 mm/min) in nervous tissue. It has a prominent high-amplitude negative component followed by a smaller amplitude but longer duration positive wave; an initial small positive component may sometimes be seen. SD can have maximal amplitude of 5–30 mV and can last for 30–90 s. Initial brief period of excitation followed by prolonged depression which is then replaced by sustained increase in the neuronal activity is the key feature of SD. The initial and late increase in excitability seen in SD correlates with the burst of action potentials and intense synaptic noise associated with synchronized neuronal activity. SD has been implicated in the pathophysiology of several disorders including migraine, epilepsy, transient global amnesia, cerebrovascular disease, head injury, and spinal cord disorders.

Substrates of Brain Rhythms

The cerebral cortex, thalamus, and several generalized modulatory systems arising from the brain stem core, posterior hypothalamus, and basal forebrain are thought to be responsible for the generation, synchronization, and desynchronization of brain rhythms (regularly recurring waveforms of similar shape and duration) that can be recorded on EEG.

Slow delta rhythms: Delta activity represents 0–4 Hz frequency range. Thalamus and cortex are the two sources of delta activity. Thalamocortical neurons display rhythmic bursts of high-frequency spikes with an interburst frequency of 1–2 Hz which results from interplay between a transient calcium current (I_t) and hyperpolarization-activated cation current (I_h). Delta activity has been noted in cats with thalamic lesion suggesting a cortical source for delta oscillations as well.

The slow oscillation and the K-complex: The K-complex is a result of a sequence of depolarizing–hyperpolarizing episodes within a slow cortical oscillatory cycle. Such slow cortical oscillations are seen during sleep. Slow oscillation becomes more regular and faster with deepening of sleep. Firing rate of the midbrain reticular formation and mesopontine cholinergic neurons decrease at sleep onset removing steady excitatory drive to thalamocortical neurons. This leads to progressive hyperpolarization of these neurons which corresponds to deepening of sleep.

Theta rhythms: Theta rhythms are in the 4–7 Hz frequency range which is conspicuous in limbic regions in various animal species and in humans. It is thought to represent a dynamic state arising from neuronal networks in the hippocampus associated with spatial navigation and memory processes.

Alpha rhythms: Alpha rhythm represents the frequency range of 8–13 Hz. Aside from occipital cortex, alpha rhythm can be recorded from the somatosensory cortex (also called mu rhythm) and temporal cortex (also called tau rhythm). Alpha rhythms are mainly generated from the cortex with only moderate dependence on the thalamus.

Spindle (sigma) rhythms: Spindles (7–14 Hz) originate from the thalamus and are considered to be the first signs of EEG synchronization during early stages of sleep. The reticular nucleus of the thalamus is regarded as the pacemaker of the spindles.

Faster rhythms: Beta and gamma rhythms are faster rhythms associated with wakeful state or REM sleep. They arise when spindle and slower EEG rhythms are suppressed (probably mediated by acetylcholine, serotonin, and norepinephrine) upon stimulation of brain stem structures. Episodes of cortical oscillations faster (100–600 Hz) than beta–gamma frequency called ripples (100 to 200 Hz), or fast ripples (>200 Hz) have been described under both normal conditions and epileptic seizures. Ripples probably reflect synchronized IPSPs, whereas fast ripples appear to represent bursts of population spikes. While high-frequency oscillations like ripples and fast ripples may be normal, recent studies indicate that they may be the marker of epileptogenic region.

Further Reading

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EEG Instrumentation, Montage, Polarity, and Localization

2

Krikor Tufenkjian

The Source of EEG

The source of the EEG potentials recorded from the scalp is the excitatory and inhibitory postsynaptic potentials of pyramidal neurons. Each pyramidal neuron has an apical dendrite and multiple basal dendrites (Fig. 2.1). Excitation of the postsynaptic membrane at the apical dendrite leads to depolarization with an intracellular shift of positive ions (Na^+). Subsequently the extracellular space nearby becomes relatively negatively charged. This is coupled by an inhibitory potential at the basal dendrites with a relatively positive charge nearby. At cortical layers III, V, and VI, neurons are aligned in a perpendicular fashion with the cortex. This allows for summation of the small potentials generated by each neuron when they fire in a synchronous fashion (Fig. 2.2).

Cortical neuronal alignment effectively creates an electrical dipole. Whether a positive or negative potential is recorded on the scalp electrode depends on the location of the recording electrode with respect to these dipoles (Fig. 2.3). Epileptiform discharges (spikes or sharp waves) are commonly surface negative. Simultaneous intracranial and scalp recordings confirmed that at least 6 cm^2 of synchronous cortical activation is indeed necessary to detect an individual epileptic spike on scalp electrodes [1].

Recording the EEG

Commonly used electrodes for scalp EEG have a contact surface made of non-depolarizing chloride-treated silver. International standards specify that electrode resistance should be between 100 and 5000 Ω. Properly applied electrodes show a resistance of a few hundred ohms.

A minimum of 21 electrodes are recommended for scalp EEG. The international 10–20 system is commonly used for the placement of these electrodes (Fig. 2.4). With this system, inter-electrode distances average from 4 to 6 cm, as the "10" and "20" mean that the distances between adjacent electrodes are either 10% or 20% of the total nasion-inion or right ear–left ear distance of the skull. In addition, only the superior lateral temporal region is covered. The 10–10 system is more extensive and includes subtemporal electrodes.

The EEG potentials are displayed in channels; each channel represents the difference in potential between two electrodes. By convention, if the difference between two electrodes is negative, then it is represented by an upward deflection, while a downward deflection represents a positive difference.

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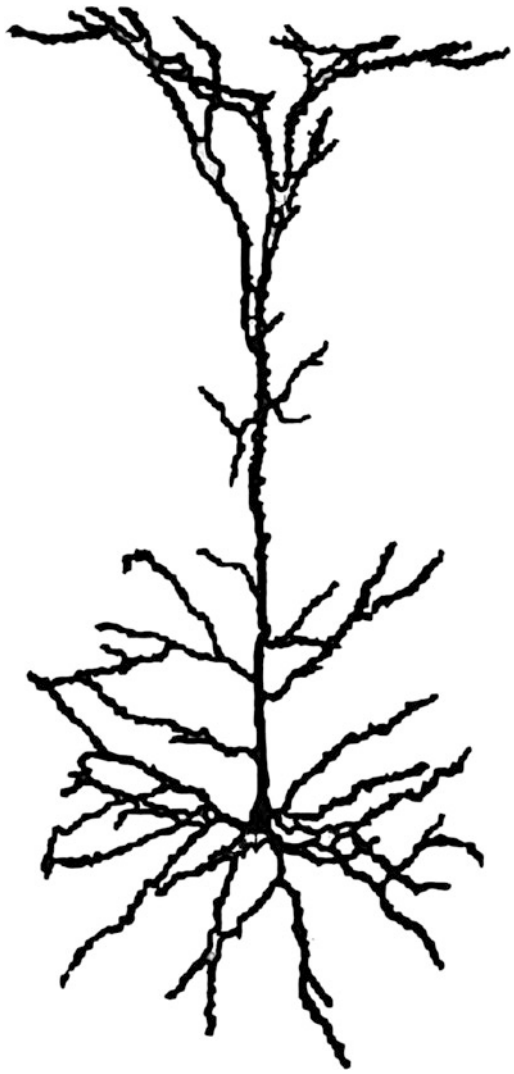

Fig. 2.1 Pyramidal neuron

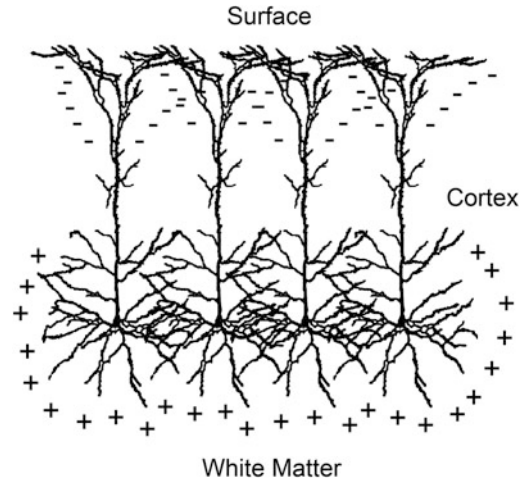

Fig. 2.2 Parallel arrangement of the pyramidal neurons allows for summation of the individual potentials

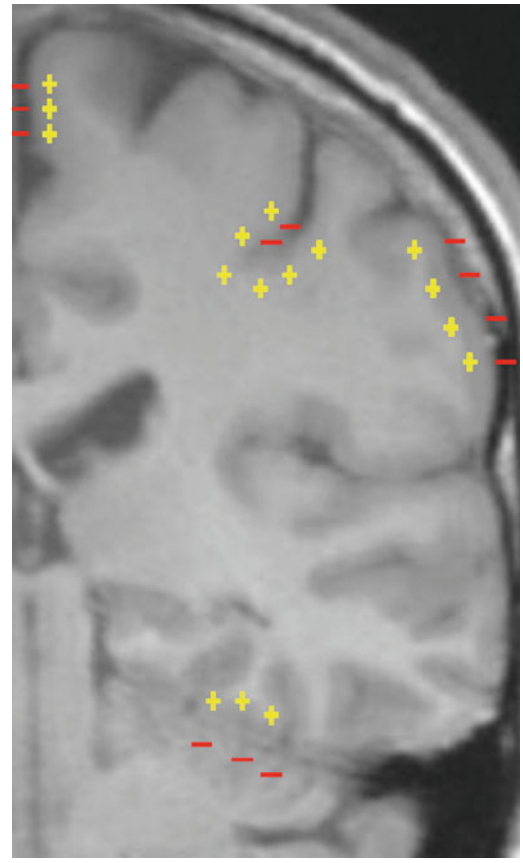

Fig. 2.3 Orientation of the sulci and therefore the dipoles determine what potential is recorded from the scalp

Montages

The 10–20 system employs 21 electrodes. Differences in potentials between these electrodes constitute channels. Combinations of different channels are called montages. The two main montage types are the bipolar and the referential.

In a bipolar montage, channels are arranged in chains that follow an anterior-to-posterior or a transverse arrangement (Figs. 2.5 and 2.6). The chains imply that the second lead in the first

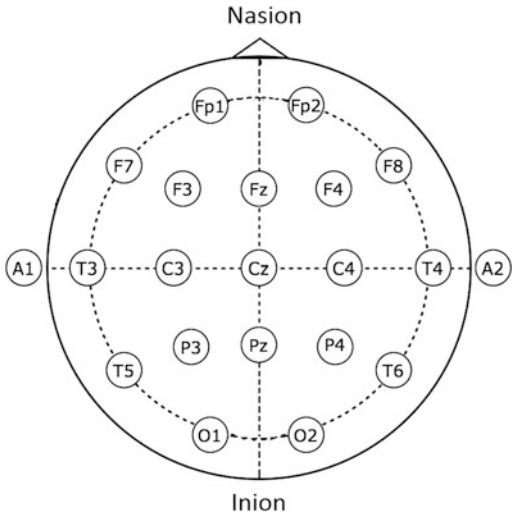

Fig. 2.4 International 10–20 system for electrode placement

channel is the first lead in the second channel, and so forth until the end of the chain. In a referential montage, each channel represents the difference of the potential of any given electrode with a single chosen electrode (Fig. 2.7).

Each configuration has its advantages and disadvantages. In a bipolar montage, external noise can easily be canceled out as it measures the difference in potential between contiguous electrodes, hence amplifying local potentials. Visual detection of differences in local potentials is easier on a bipolar montage particularly when "phase reversal" is seen, signifying a negative event taking place in the region of the electrode that is common to the two channels where polarity changes (Fig. 2.8).

A referential montage on the other hand would be highly susceptible to external noise but it would be able to detect both local (near field) and distant (far field) potentials. The amplitude of the deflection on a referential montage would be a closer representation of the absolute potential at an electrode.

Acquiring, Filtering, and Displaying the EEG Signal

Electrocerebral potentials are in the microvolt range and contaminated by significant ambient electrical noise. In order to record, isolate, and represent an interpretable tracing, certain processing of the signals is required.

Differential amplifiers and common mode rejection: Each electrode records potentials

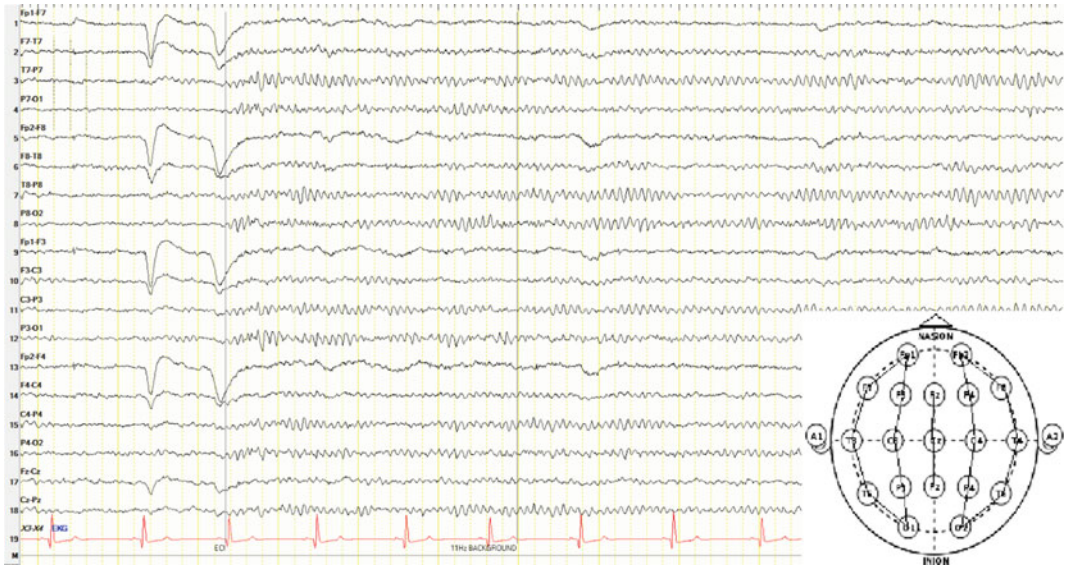

Fig. 2.5 Bipolar montage with anterior-to-posterior chains (longitudinal bipolar or double-banana montage)

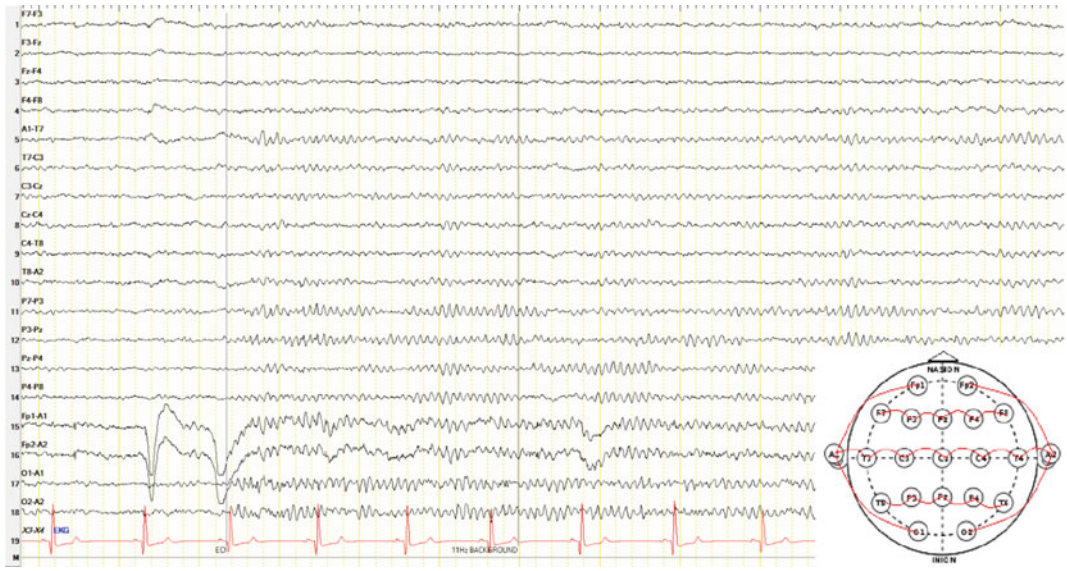

Fig. 2.6 Bipolar montage with transverse chains

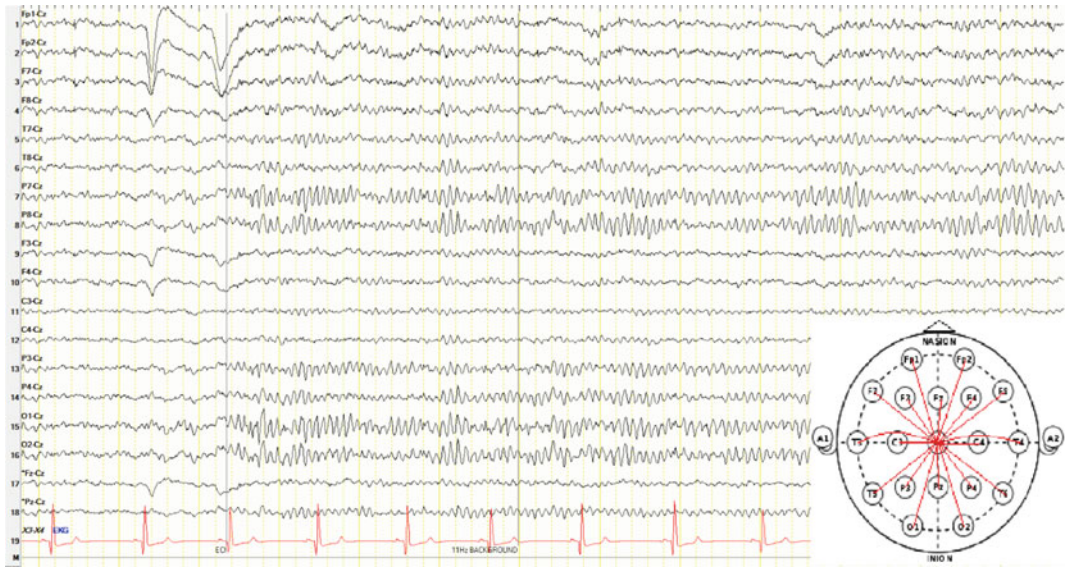

Fig. 2.7 Referential montage using Cz as the common reference

generated by both the brain and the environment. Filtering out the surrounding noise is done with a differential amplifier, which excludes the signals recorded by both electrodes in a channel and amplifies the differences in between. This function is also known as common mode rejection.

Filtering the EEG signal: Conventional EEG interpretation requires the exclusion of very low frequencies using a high-pass (or low frequency) filter, very high frequencies using a low-pass (or high-frequency filter) filter, or a specific band of frequencies using a high-pass filter.

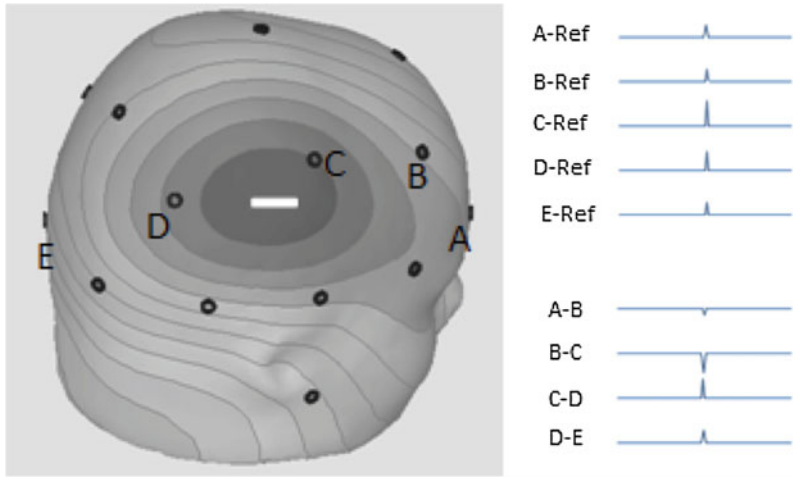

Fig. 2.8 To the *left* is a representation of a negative potential and its field as recorded from the scalp. *Right upper* is a representation of that potential as represented on a referential montage. Note that the amplitude of the spike corresponds to the proximity of the recording electrode to the negative filed maximum. *Right lower* is the same potential as recorded from the same electrodes but arranged in a longitudinal bipolar montage. Each channel represents the difference in potential between two adjacent electrodes in the same chain. The highest negative potential is recorded from contact C; this would lead to B–C to have a positive value (down-going tracing on EEG), while C–D will have a negative value (up-going). This would result in the so-called phase reversal on a bipolar montage, where the common electrode is closest to the maximum negative potential as recorded from the scalp and within that chain

A signal-filtering device is made from a circuit containing a capacitor and a resistor. A capacitor contains two conducting surfaces separated by non-conducting material. When placed as a part of a circuit, opposing charges will accumulate on each plate until each plate is "crowded" and the current stops (Fig. 2.9). If this is a part of a circuit with a direct current (DC), then no further current may pass once the capacitor is saturated. If, however, the circuit has an alternating current (AC) source, then once the polarity of the source is reversed a new current may pass in the circuit until the plates of the capacitor are once more saturated, though with opposite polarity. Increasing the frequency of the AC current above the limit of the saturation of a capacitor will allow for a current to pass continuously through the circuit.

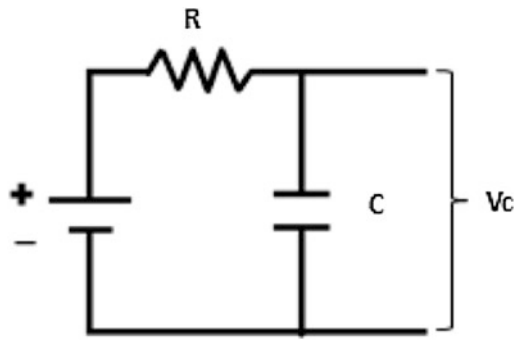

Fig. 2.9 Resistor–capacitor circuit

In the past, EEGs were obtained using analog recorders. Frequency filtering in these machines was done with devices that utilize resistor/capacitor circuits. Such filters are characterized by their time constant, which determines what frequencies will pass through.

The time constant is determined by the amount of resistance and capacitance in the circuit. It is defined as the time needed to discharge the capacitor in the circuit to 36.8% of its initial full charge. Its value is inversely related to the frequency that will pass through the filter. For example, using a filter with a higher time constant will allow the lower frequencies to pass through. With the more recent digital machines,

the EEG signal from each electrode is digitized first and frequency filtering is done using software processing.

A low-pass filter (also known as high-frequency filter) allows frequencies lower than a certain value to pass. The low-pass filter is set to 70 Hz in the usual scalp EEG reading settings. Changing this to 35 Hz will allow only frequencies lower than 35 Hz to pass through. This will filter out a lot of the faster myogenic

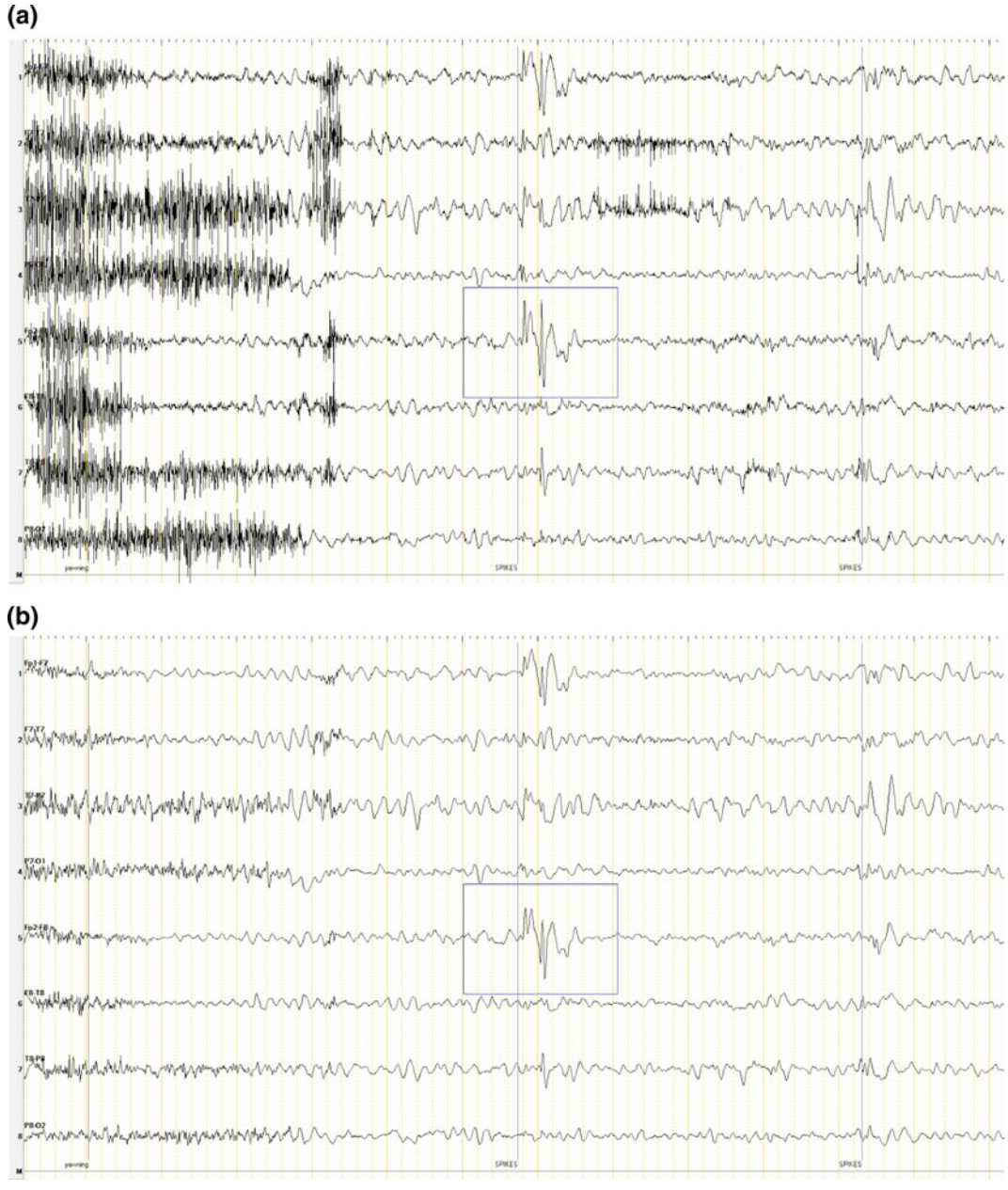

Fig. 2.10 **a** High-frequency filter set at 70 Hz. Note the abundant myogenic artifact in the first three seconds of the recording. A high-amplitude spike is also noted. **b** The high-frequency filter is changed to 15 Hz. Most of the myogenic artifacts are removed. There is a concurrent reduction in the amplitude of the spike

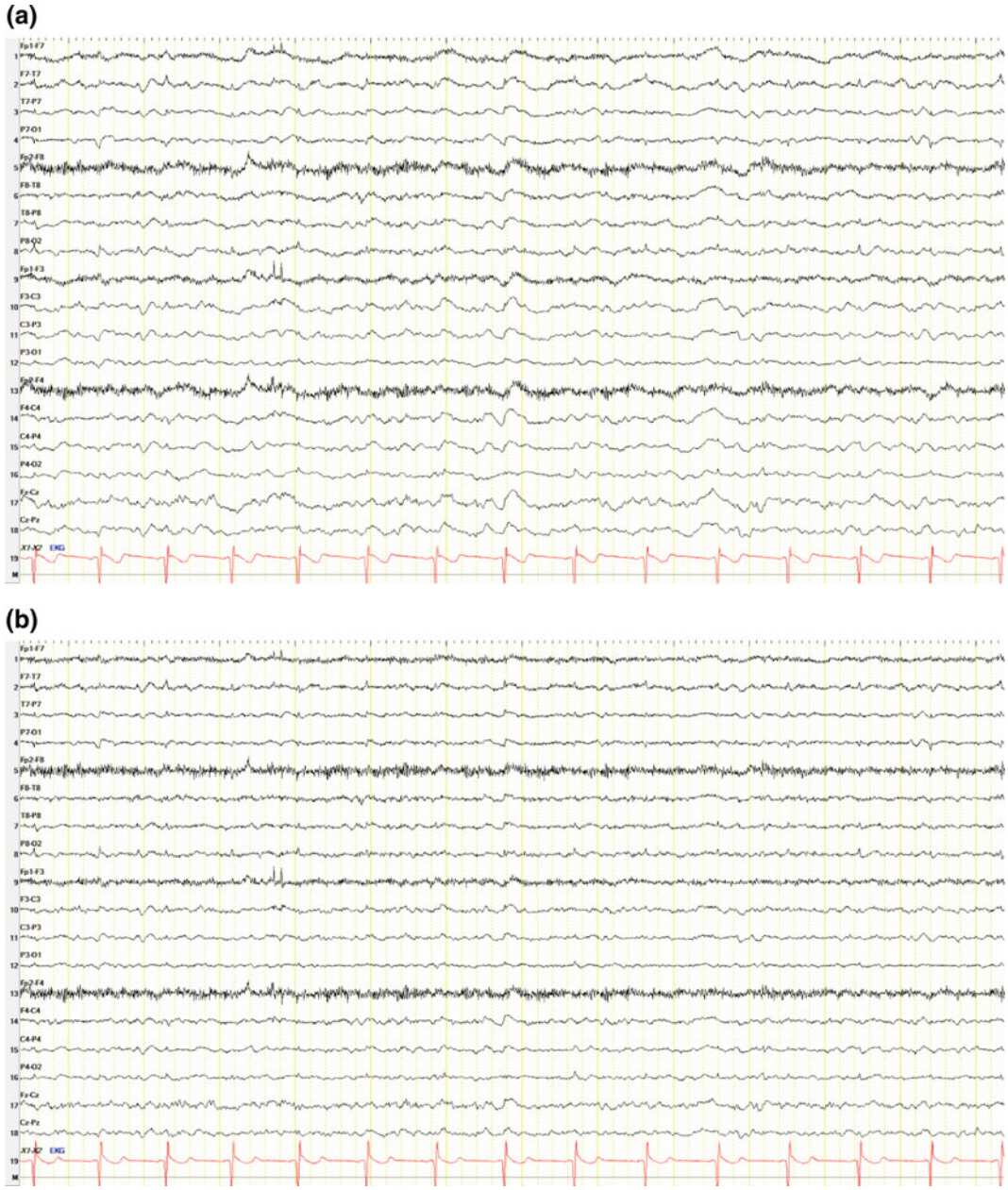

Fig. 2.11 **a** EEG with the low-frequency filter set to 1 Hz. **b** Same EEG with the low-frequency filter changed to 2 Hz. Note the reduction of the amplitude of the slow activity. **c** Low-frequency filter changed to 5 Hz. Only frequencies above 5 Hz pass. Note that there has been no effect on the fast frequency myogenic artifact

artifact and will also slightly reduce the *amplitude* of signals with a steep rise time, such as epileptiform spikes and sharp waves (Fig. 2.10).

A high-pass filter (also known as low-frequency filter) allows higher frequencies to pass, usually set to about 1 Hz (corresponds to a time constant of about 0.16 s) for routine scalp

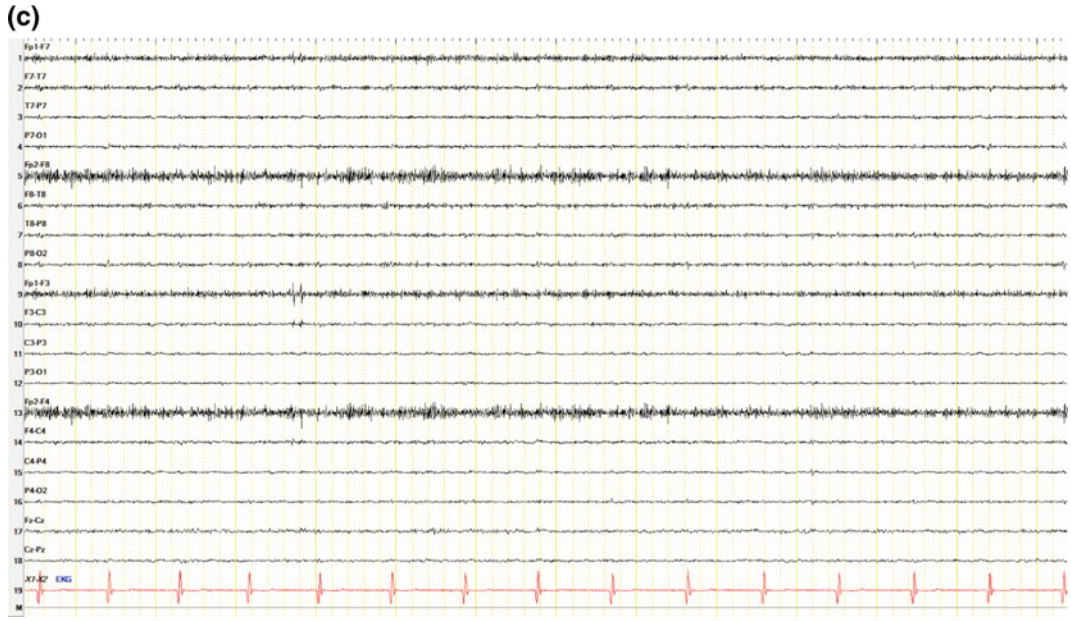

Fig. 2.11 (continued)

EEG reading. Raising this to 2 Hz, for example, will filter out some of the lower frequencies giving a more flat look to the EEG. This will also reduce the *amplitude* of the slower waveforms (Fig. 2.11).

A band pass or a band stop filter is also used. Commonly used such filters are notch filters, which stop a very narrow band around the 50 or 60 Hz noise generated from alternating current sources such as city power lines.

Filtering in intracranial recording: Subdural and depth electrodes allow the recording of frequencies that fall outside the usual range of the scalp EEG. These include high frequencies ranging from 80 to 500 Hz known as high-frequency oscillations (HFOs) and very slow frequencies appearing as slow baseline shifts. Specialized systems are needed to acquire these activities. High-pass and low-pass filters are manipulated to facilitate viewing the required range (Fig. 2.12).

Digital EEG Acquisition, Processing, and Display

In digital EEG machines, an additional electrode used as the machine reference is also needed. The signal from each electrode is recorded as the difference in potential between that electrode and the machine reference, which is then stored as digital data (bits). The signal from each channel is recorded and stored at regular intervals. This is reflected in the sampling rate of the EEG machine. Most current commercially available machines have a sampling rate that ranges between 256 and 1024 Hz. Higher sampling rates allow more accurate recording of brain signals and smoother appearance of the waveforms, but require higher data storage capacity.

Sampling rates determine what EEG frequencies can accurately be represented. If the

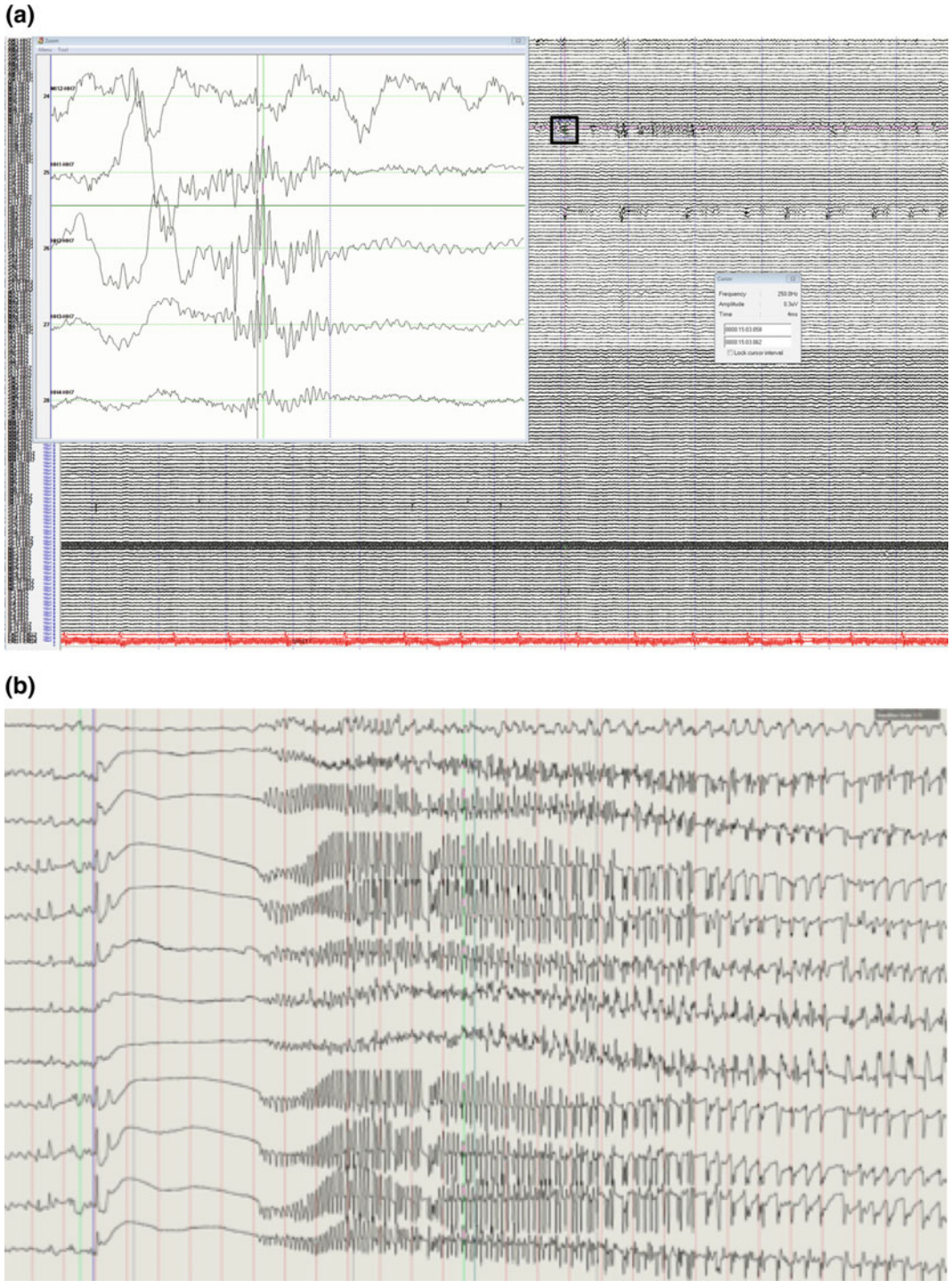

Fig. 2.12 **a** High-frequency oscillations at 250 Hz—the onset represents magnification of the boxed area. **b** Slow baseline shift at the beginning of a seizure recorded with grid electrodes

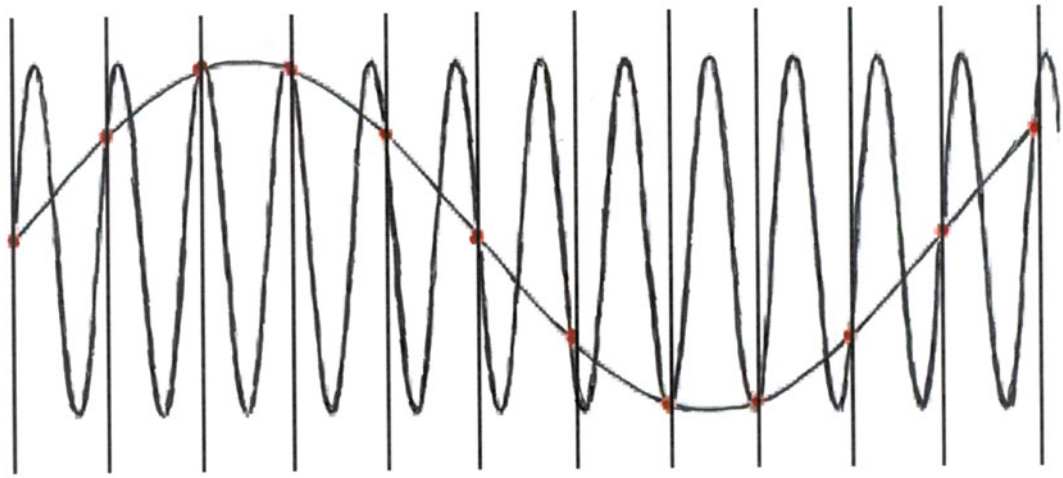

Fig. 2.13 High-frequency signal is sampled at a rate below the Nyquist rate. The resulting waveform remarkably misrepresents the original waveform, resulting in aliasing

sampling rate falls below a certain point, then the resulting waveform would no longer represent the original one. This erroneous representation is called aliasing. The Nyquist sampling theorem determines that the sampling rate should be at least twice the frequency of the original signal to avoid aliasing, or distortion of waveforms. The ACNS guidelines recommend a sampling rate at 3 times or more the frequency of the original signal (Fig. 2.13). A filter is used on the signal prior to digitizing to exclude all frequencies above a certain frequency determined by the Nyquist theorem (anti-aliasing filter).

Another important aspect is the monitor display. Most LCD monitors can display 1920 dots (pixels) horizontally. The sampling rate on the EEG machine may actually exceed the capacity of the monitor display. Low-definition monitors will give a "grainy" tracing, and this could be a particular concern with high-frequency activity (Fig. 2.14).

EEG and Patient Safety

Proper grounding during EEG is an important patient safety issue. The EEG machine should be connected to a three-pronged hospital grade outlet. The third prong ensures shunting of excess current from the EEG machine to the earth ground. All electrical devices in the EEG room should be connected to a common earth ground.

A single ground electrode is placed anywhere on the patient and connects to the appropriate jack in the input jackbox of the EEG machine. The patient should not be connected to the earth ground. In ICU setting, a patient may be connected to another electrical device with a ground connection. Double grounding should be avoided in these situations [2].

EEG Artifacts

Artifacts will be discussed in Chap. 3, but in the remaining part of this chapter we will provide some EEG examples with the purpose of further training of the reader's artifact pattern recognition. Artifacts may arise from the electrical environment as well as bioelectrical sources originating from the patient (Figs. 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23 and 2.24).

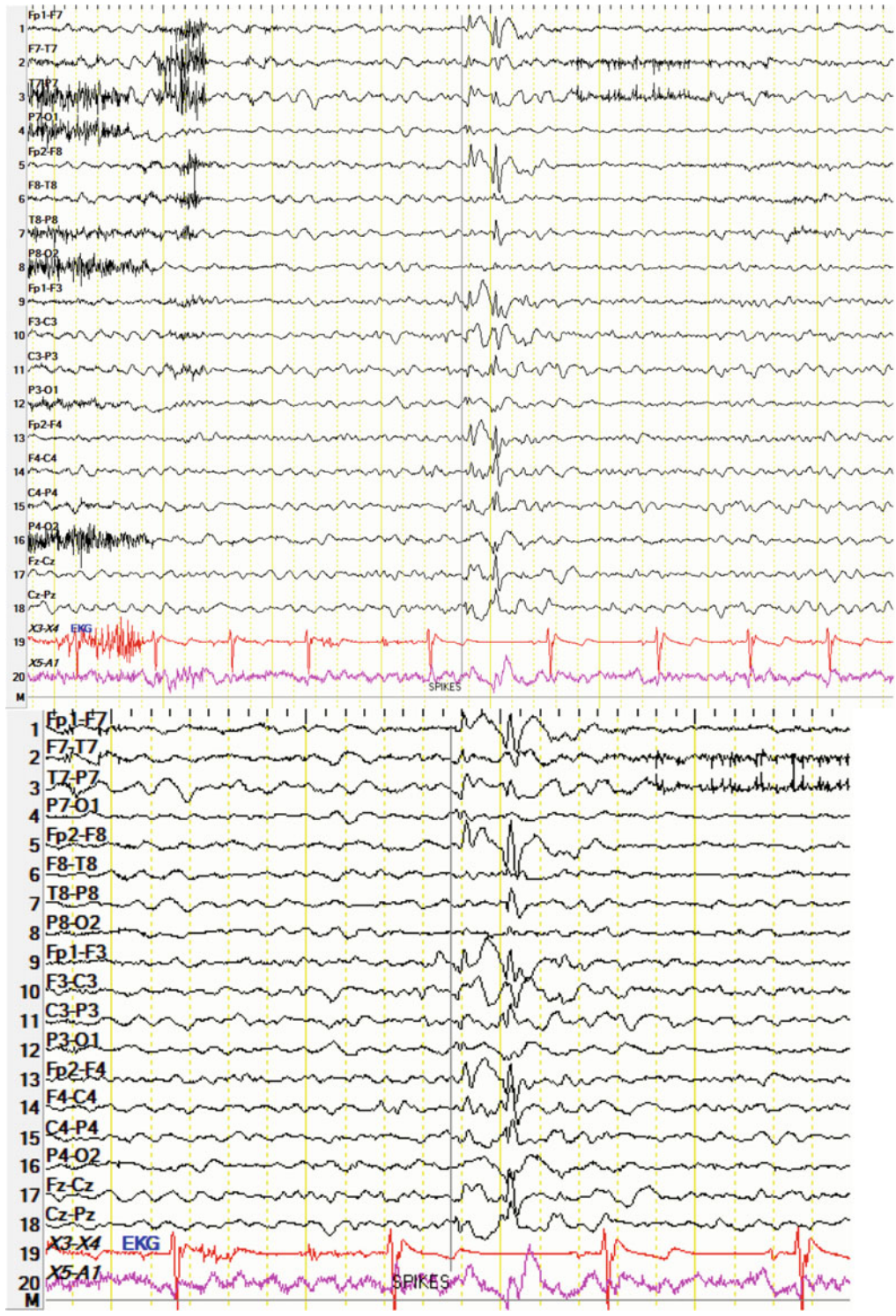

Fig. 2.14 Effect of reducing the display resolution from 1920 × by 1080 pixels (*top record*) to 1280 × by 1024 pixels (*bottom record*)

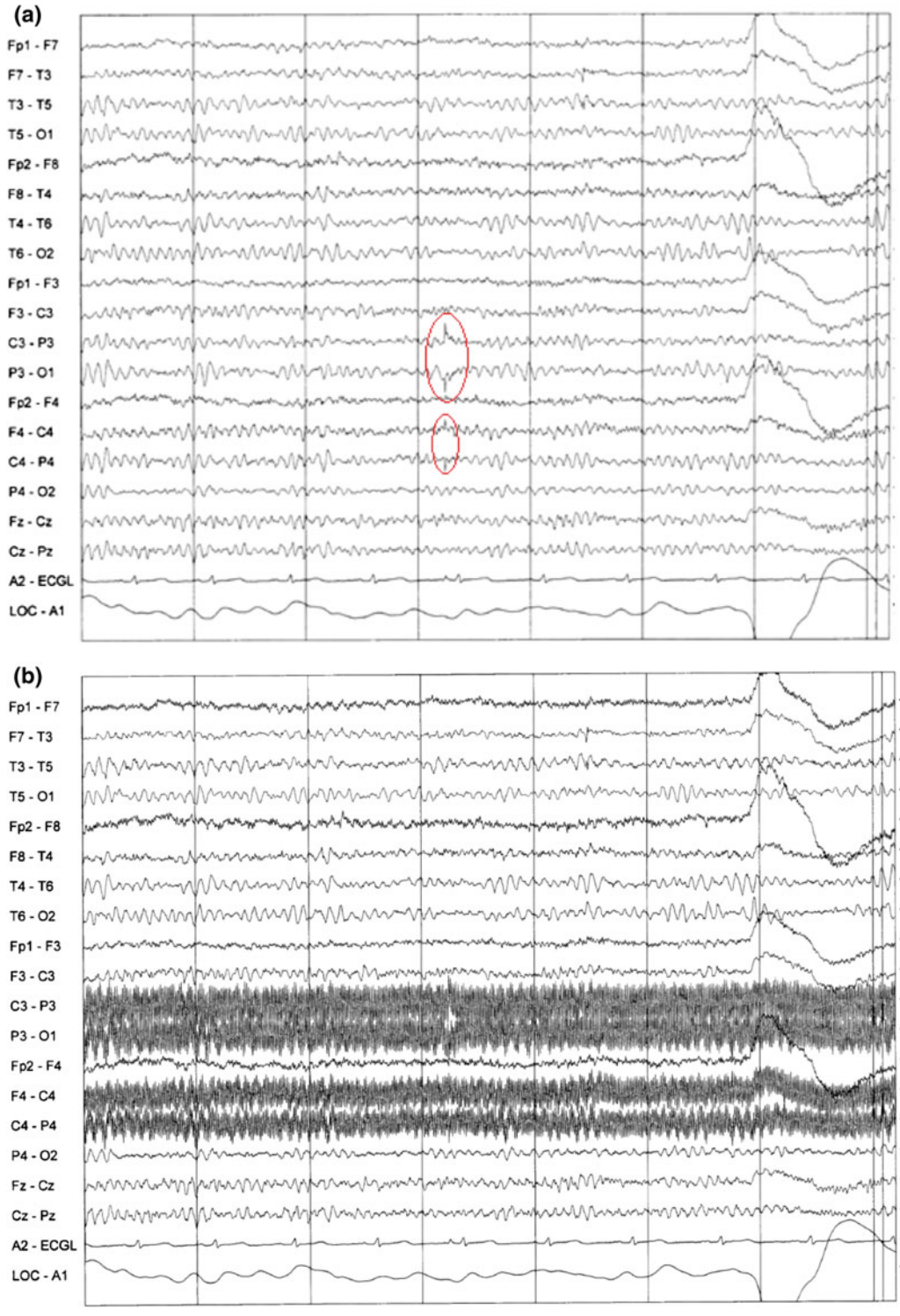

Fig. 2.15 **a** Electrode pop artifact. Poor contact at the P3 and C4 electrodes resulted in an isolated potential at these two contacts (60-Hz notch filter on). **b** The notch filter is removed and the 60-Hz artifact is now seen at the P3 and C4 electrodes, which have higher impedance due to poor contact with the scalp. The difference in impedance compared with the other electrodes interferes with the ability of the differential amplifier to reject the 60 cycle noise which actually gets amplified [3]

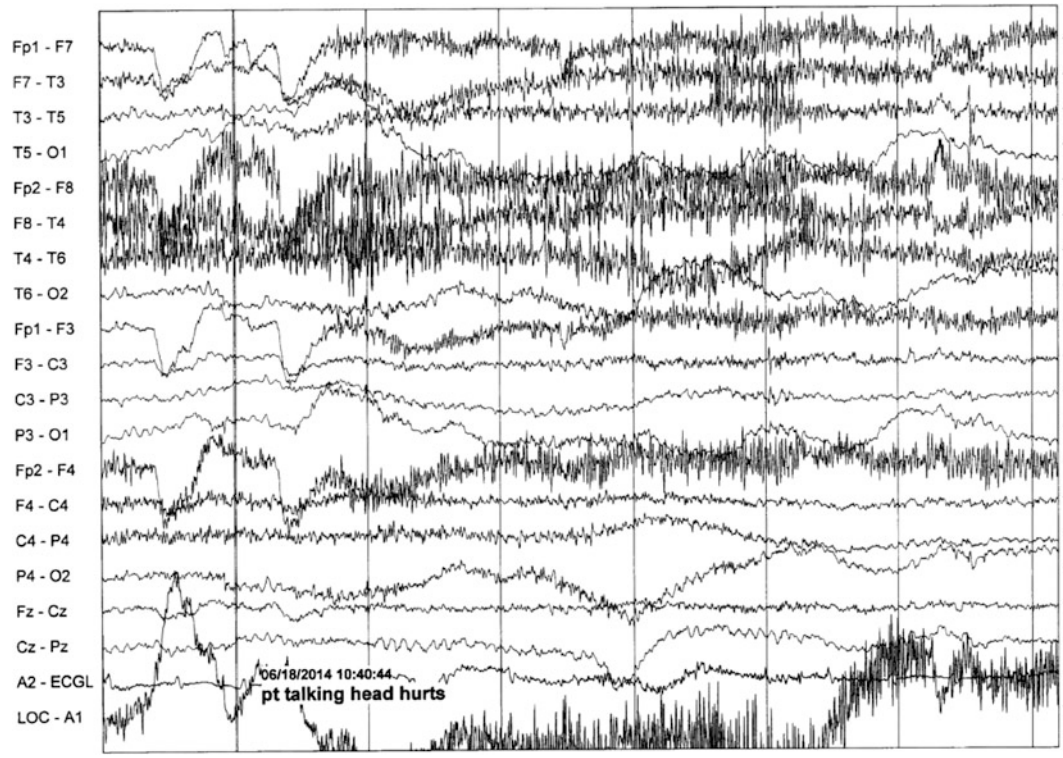

Fig. 2.16 Movement artifact. The disorganized EEG potentials do not have the typical field seen in brain-generated waveforms

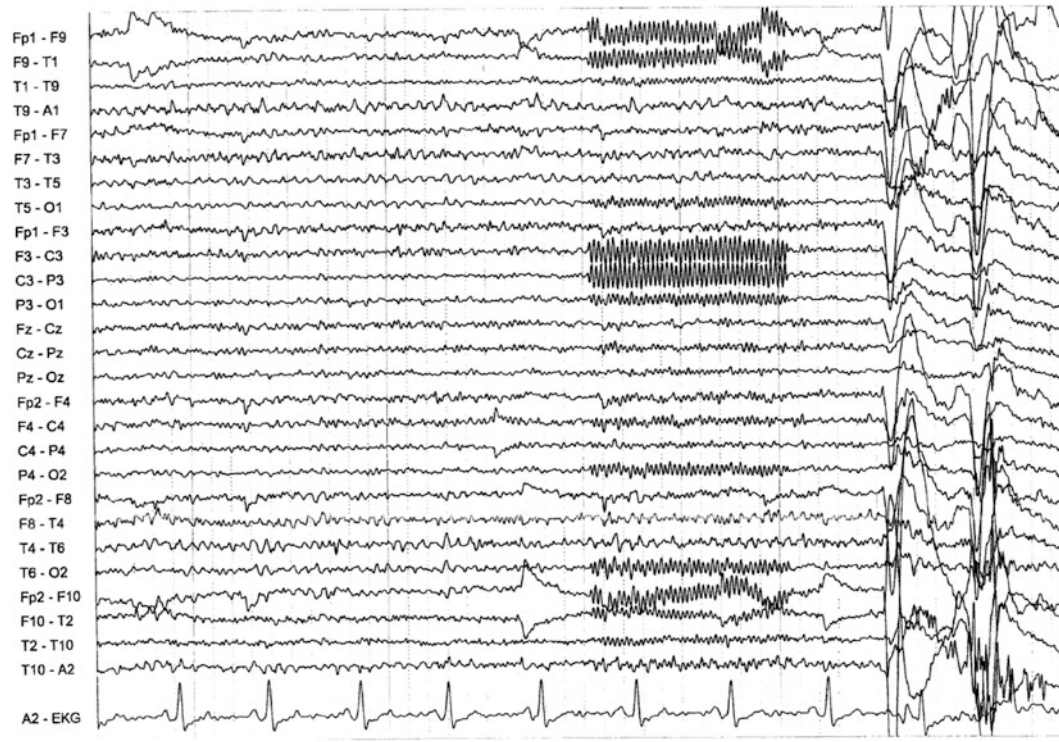

Fig. 2.17 Phone ringing artifact

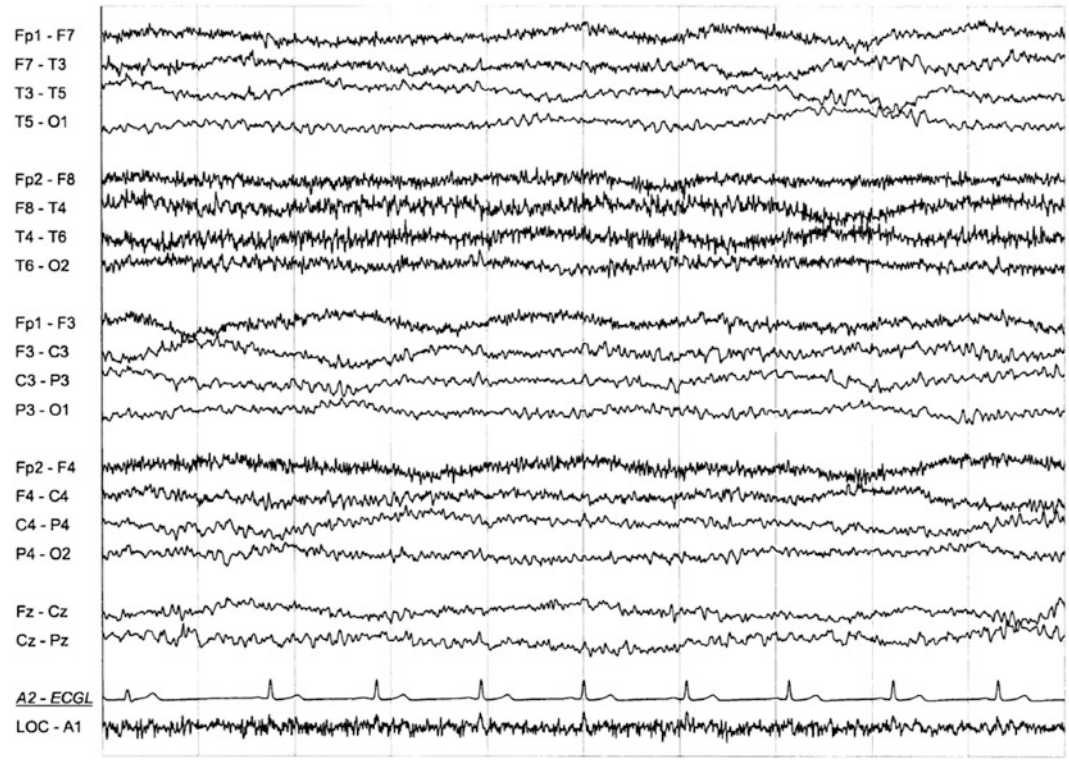

Fig. 2.18 Sweat artifact. Slow undulation (less than 1 Hz) of the EEG tracing is seen in a diaphoretic patient

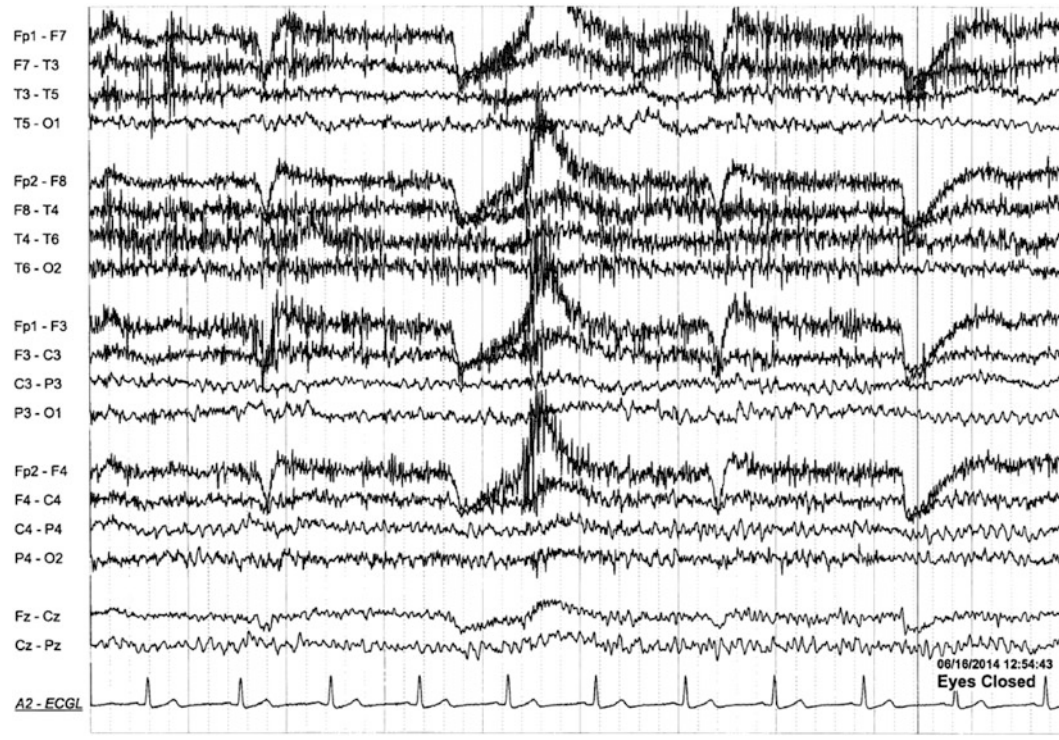

Fig. 2.19 Myogenic artifact. These high-frequency activities are generated by the frontalis and temporalis muscles; therefore, these are seen maximally in the anterior midline and temporal chains

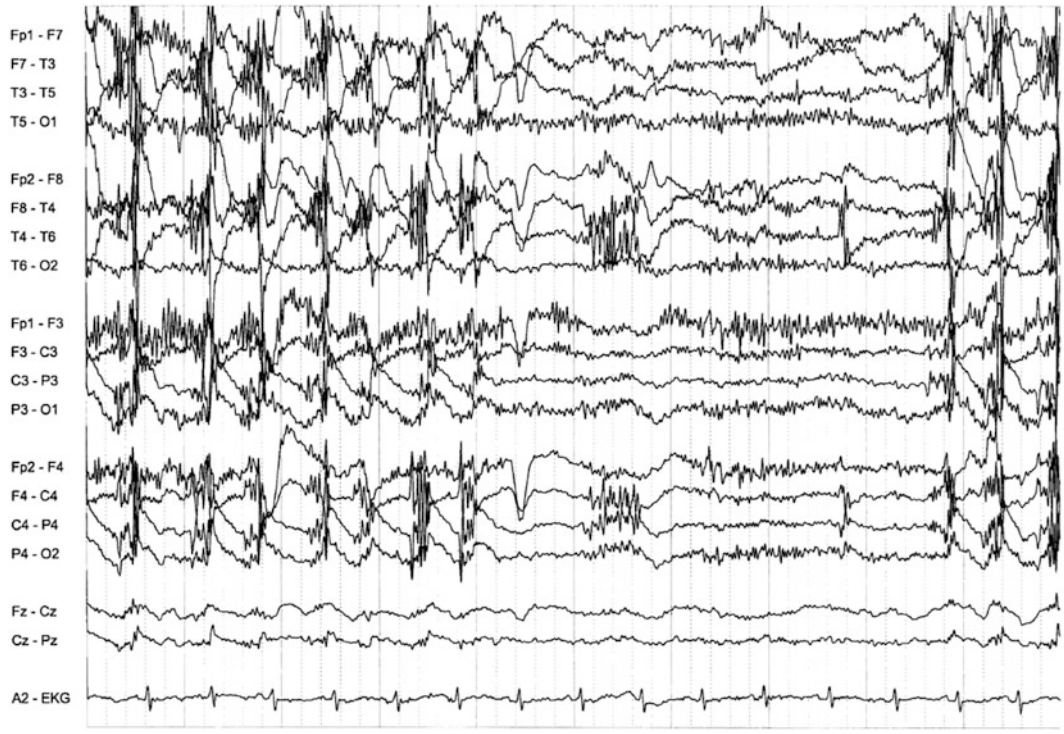

Fig. 2.20 Rhythmic myogenic artifact is seen during chewing

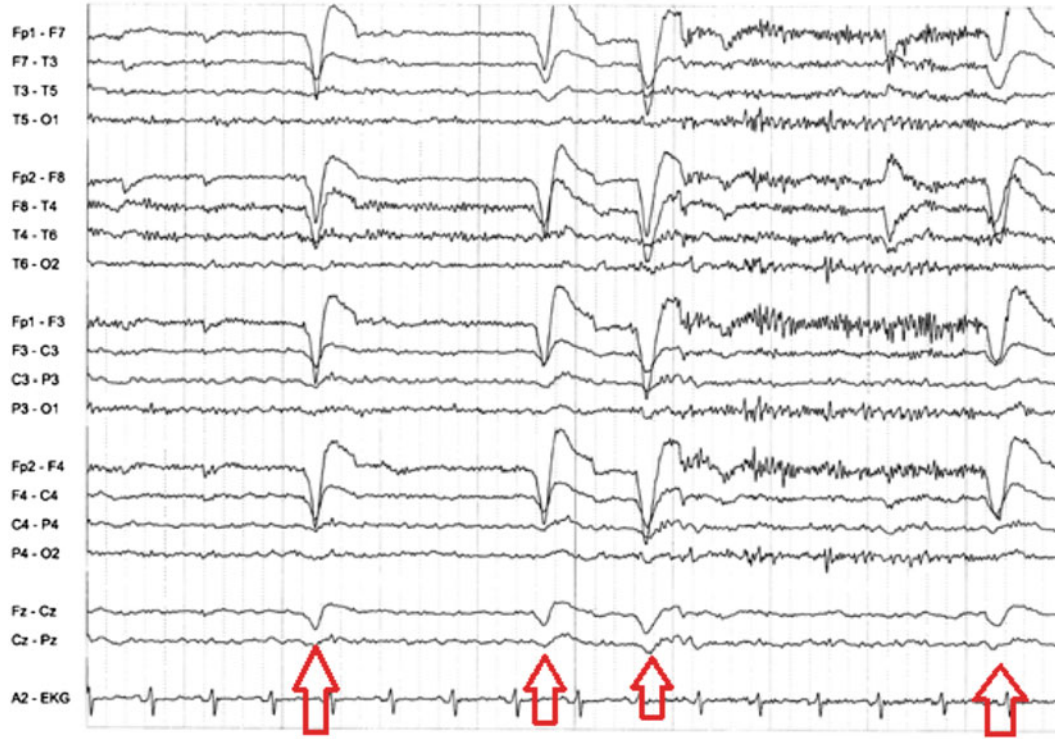

Fig. 2.21 Blink artifact. The cornea has a slightly positive potential compared to the retina. During a blink, the eyelid makes contact with cornea allowing for that positive potential to be recorded from the anterior frontal electrodes. This is represented as a *down-going* waveform, which falls in amplitude exponentially from the front to the back

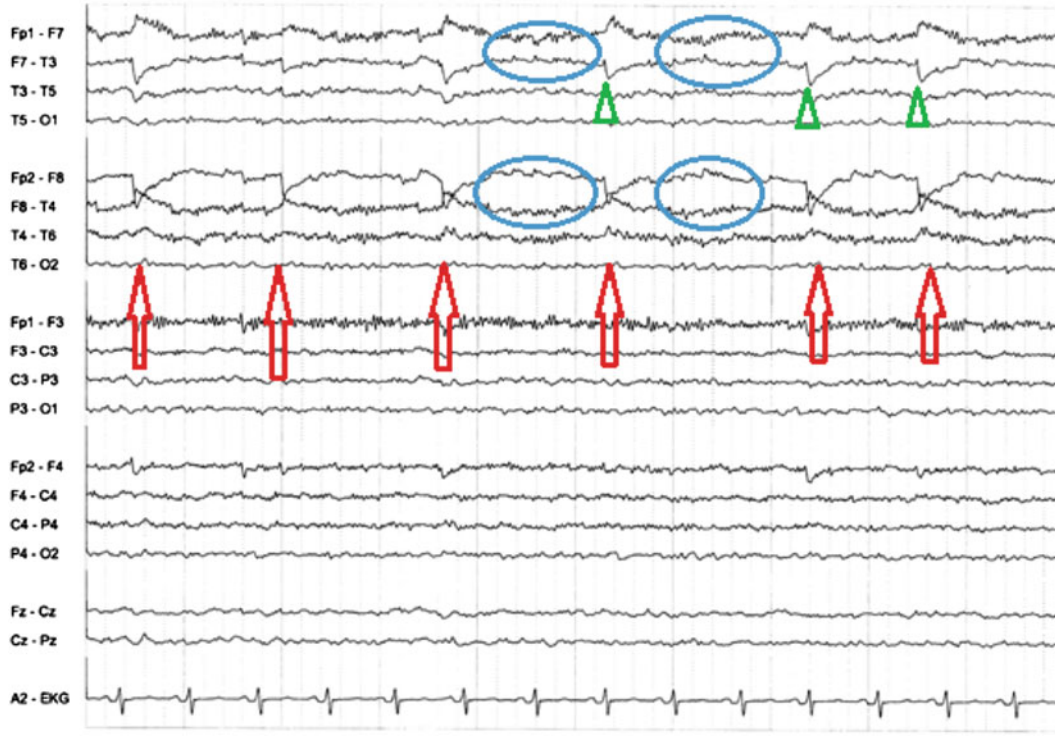

Fig. 2.22 Lateral eye movement artifact and lateral rectus spike. In this example, the patient is reading a book, the rapid saccade to the left brings the positive potential of the cornea closer to the left frontal channels producing a positive phase reversal at F7 and away from the right with a resulting negative phase reversal at F8 (*arrows*). This is followed by a slow rightward movement of the eyes with the potentials slowly shifting to the opposite direction (*ovals*). A small spike preceding the saccade is noted which is generated from the left lateral rectus muscle (*arrowhead*)

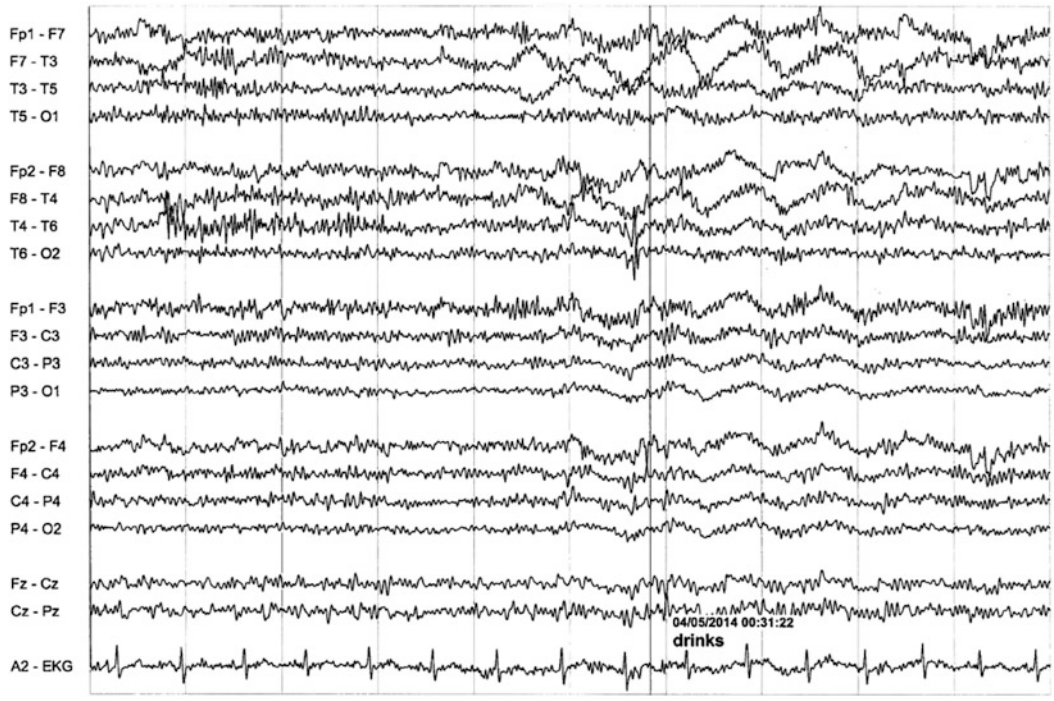

Fig. 2.23 Glossokinetic artifact. The difference in potential between the tip and the base of the tongue produces diffuse, slow waves with a frontal maximum

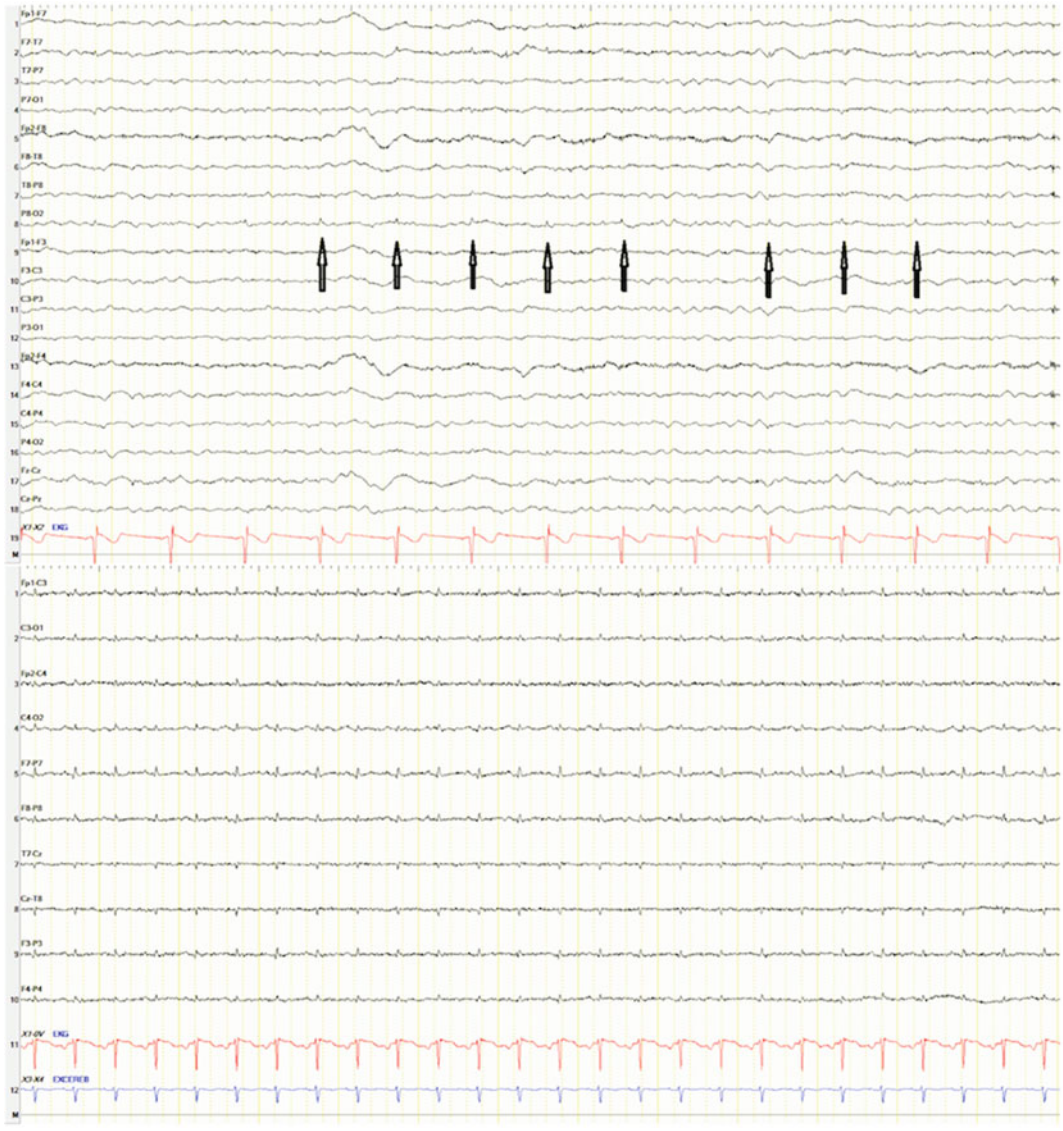

Fig. 2.24 ECG artifact. Small sharp transient can be seen time locked to the ECG QRS potentials. The lower tracing shows this ECG contamination during an EEG performed for the evaluation of electrocerebral inactivity

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Normal EEG Variants and Artifacts

3

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Accurate EEG interpretation greatly relies on pattern recognition of normal EEG variants and artifacts. Several of these normal patterns may mimic pathologic EEG findings, leading to potential misinterpretation of normal EEG tracings. Some of these normal patterns may even mimic ictal discharges, leading to overtreatment. This chapter covers the electrographic features of common normal EEG variants and artifacts [1–3].

Normal EEG variants often present with distinctive electrographic features that include morphology, distribution, and occurrence in specific stages (wakefulness, drowsiness, or sleep). Some benign EEG variants are better visualized when using a preferred EEG montage.

Fast Alpha (Fig. 3.1) and Slow Alpha Variants (Fig. 3.2):

- Harmonics of the posterior background rhythm: twice as fast (fast alpha variant) or half as fast (slow alpha variant).
- Notched appearance can resemble Rhythmic Mid-Temporal Theta Bursts of Drowsiness (RMTTBD) except that it occurs over the posterior head regions.
- Reactive to eye opening and closure.
- Fast alpha variant is similar to beta rhythms except that it is located in occipital rather than in frontal, central, and parietal regions.
- Slow alpha variant is more difficult to discern without clear reactivity to eye closure and opening.

Alpha Squeak (Fig. 3.3):

- Transient increase in frequency immediately after eye closure.
- Assessment of the frequency of the posterior background rhythm should not include the first 0.5–1 s after eye closure in order to avoid overestimation.

Rhythmic Mid-Temporal Theta Bursts of Drowsiness (RMTTBD) (Fig. 3.4):

- Also known as Rhythmic Mid-Temporal Discharges (RMTD) and psychomotor variant.
- Composed of rhythmic bursts or trains of theta waves (5–7 Hz) usually with a notched appearance that is maximal in mid-temporal regions.
- Occurs bilaterally with a shifting emphasis from side to side.
- It is monomorphic and monorhythmic and does not evolve into other waveforms or frequencies.
- Occurs during relaxed wakefulness and drowsiness.

Midline Theta Rhythm (Fig. 3.5):

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DOI 10.1007/978-1-4939-6774-2_3

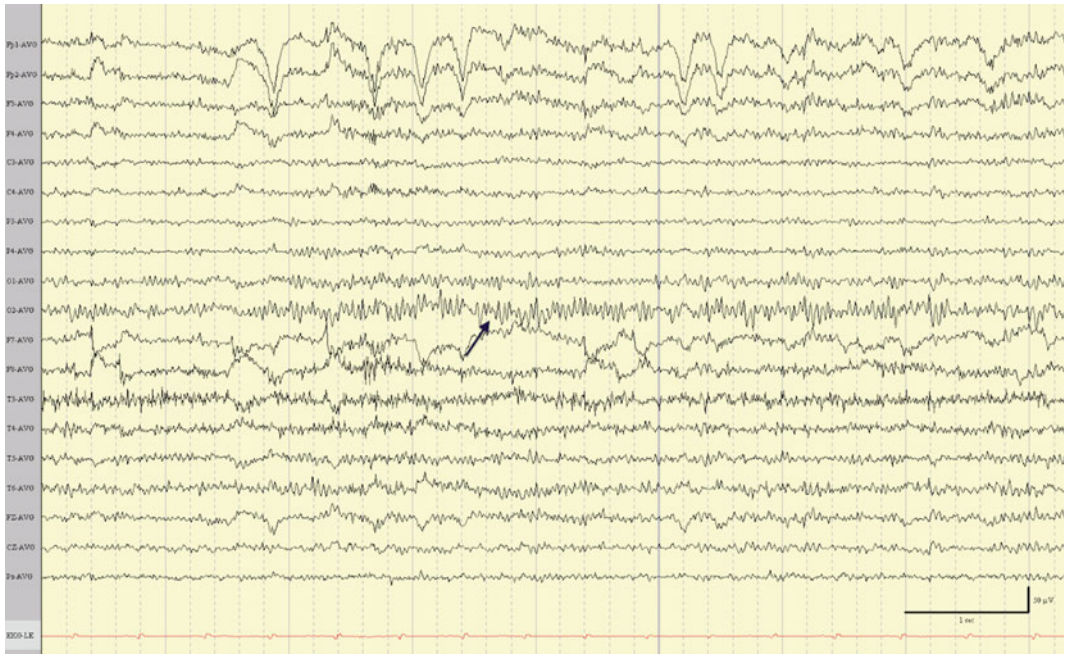

Fig. 3.1 Fast alpha variant (*arrow*); *sensitivity* 7 μV/mm, *low frequency filter (LFF)* 1 Hz, *high-frequency filter (HFF)* 70 Hz

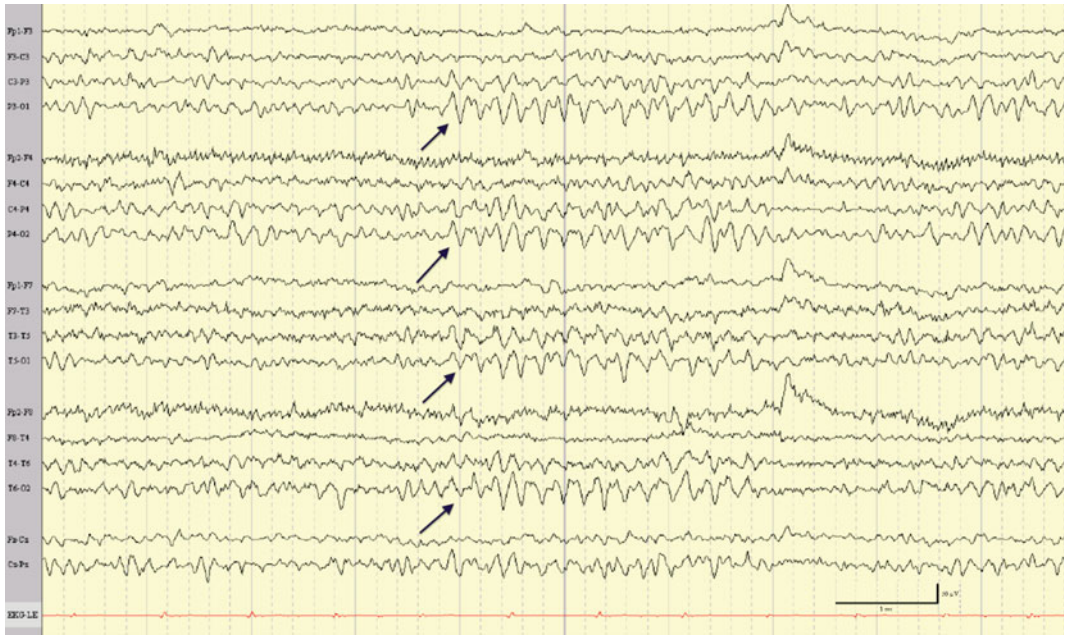

Fig. 3.2 Slow alpha variant (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

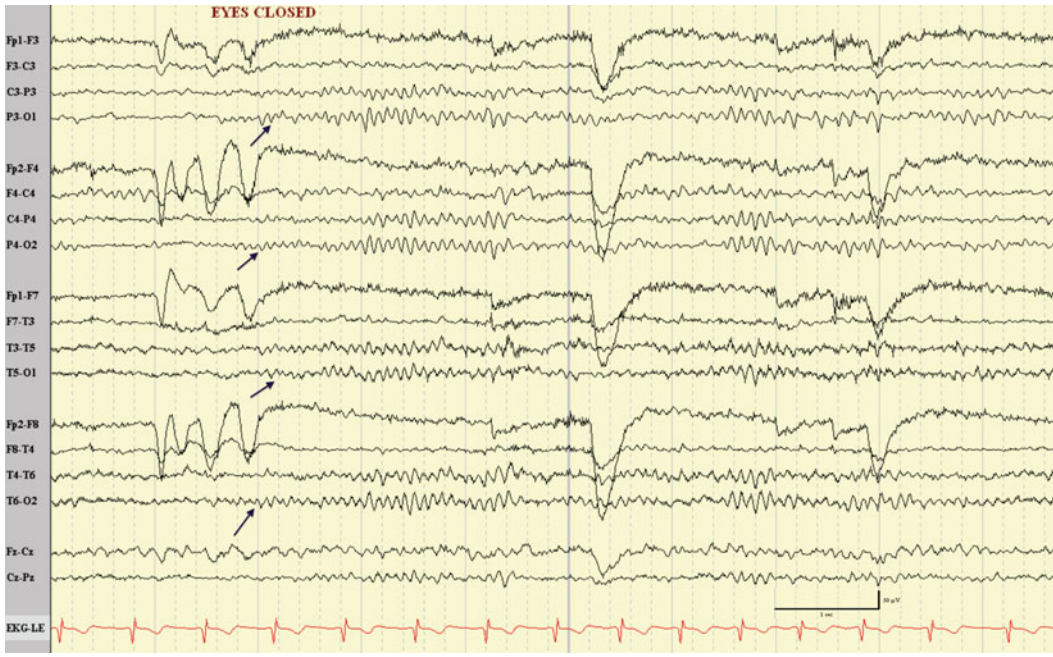

Fig. 3.3 Alpha squeak (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

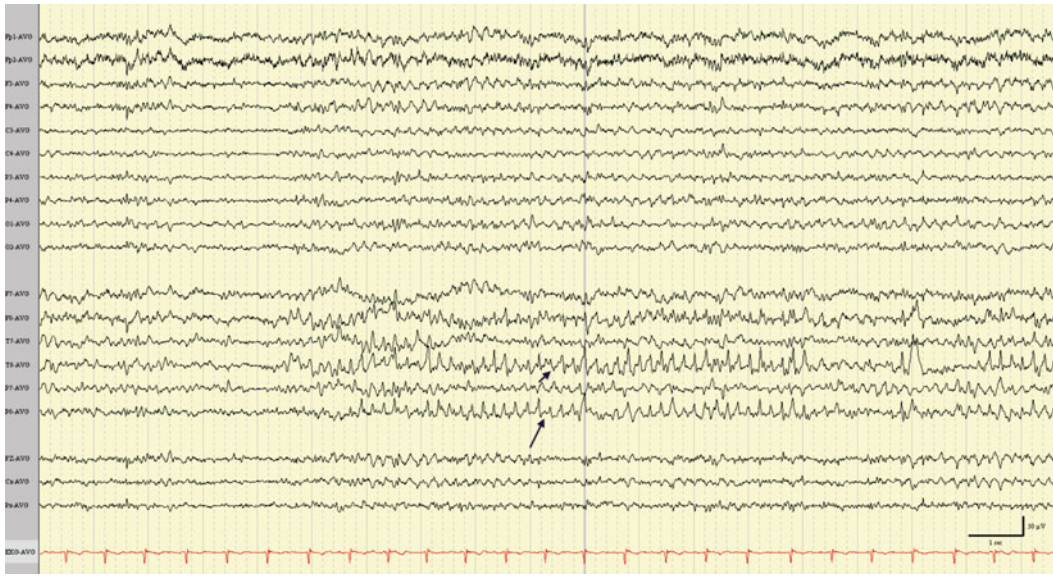

Fig. 3.4 Rhythmic Mid-Temporal Theta Bursts of Drowsiness (RMTTBD) (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

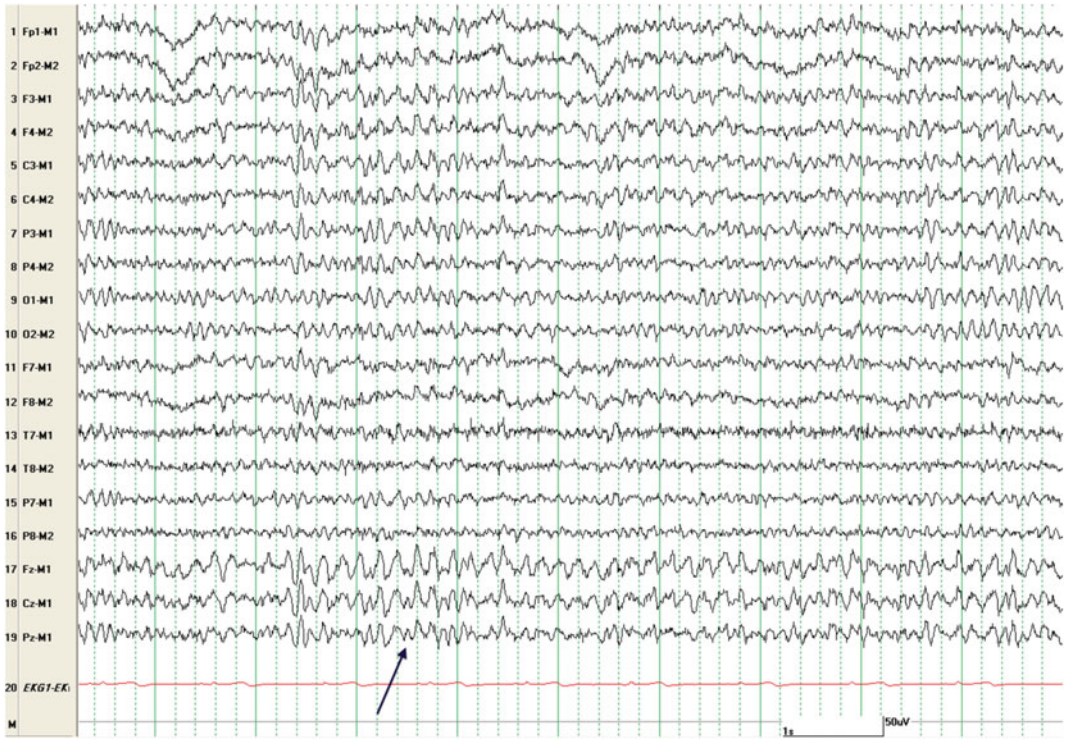

Fig. 3.5 Midline theta rhythm (*arrow*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

- Also known as Ciganek rhythm.
- Most prominent in the central vertex lead.
- Consists of a rhythmic train of 5–7 Hz smooth, sinusoidal, arciform, spiky, or mu-like activity.
- Occurs during wakefulness and drowsiness.
- Variable reactivity to eye opening and alerting.

Subclinical Rhythmic Electrographic Discharge in Adults (SREDA) (Fig. 3.6a–d):

- Uncommon pattern.
- Seen in people older than 50 years.
- Occurs at rest or drowsiness or during hyperventilation.
- Abrupt onset of mixed frequencies in the delta and theta ranges that evolve into a rhythmic pattern consisting of sharp-contoured components 5–7 Hz lasting from 20 s to a few minutes.
- Widespread distribution with maximal amplitude over parietal-posterior temporal head regions.
- Usually bilateral but may be asymmetric.
- May resemble a subclinical EEG seizure discharge but typically does not correlate with clinical seizures (this is however controversial).

14- and 6-Hz Positive Bursts (Fig. 3.7):

- Also known as ctenoids.
- Occur during drowsiness and light sleep.
- Consist of short trains of arch-shaped waveforms with alternating positive spiky components and a negative, smooth, rounded waveform that resembles a sleep spindle with a sharp positive phase.
- Mostly asynchronous and occurs bilaterally with shifting predominance.

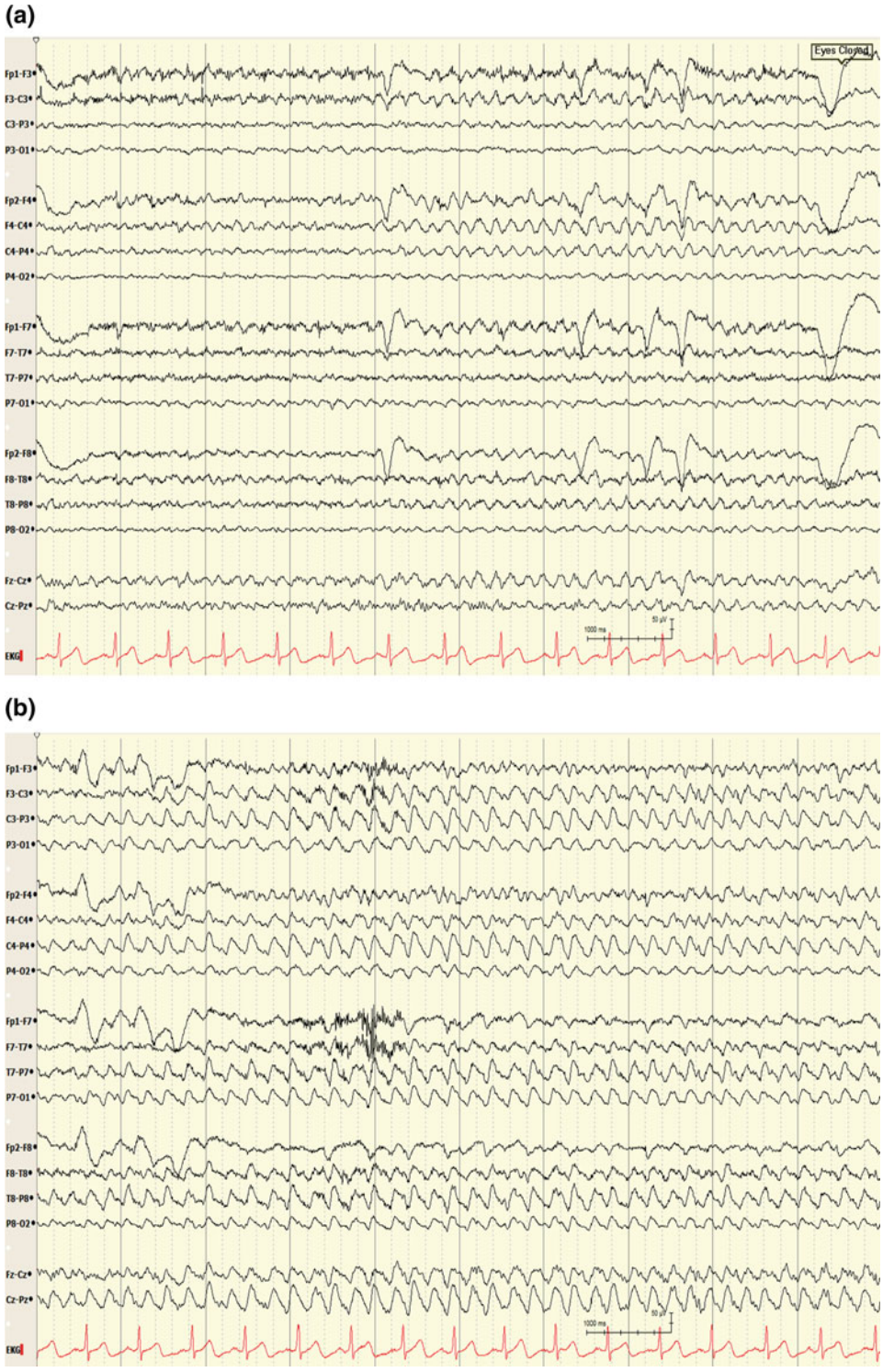

Fig. 3.6 Consecutive EEGs showing subclinical rhythmic electrographic discharge in adults (SREDA)

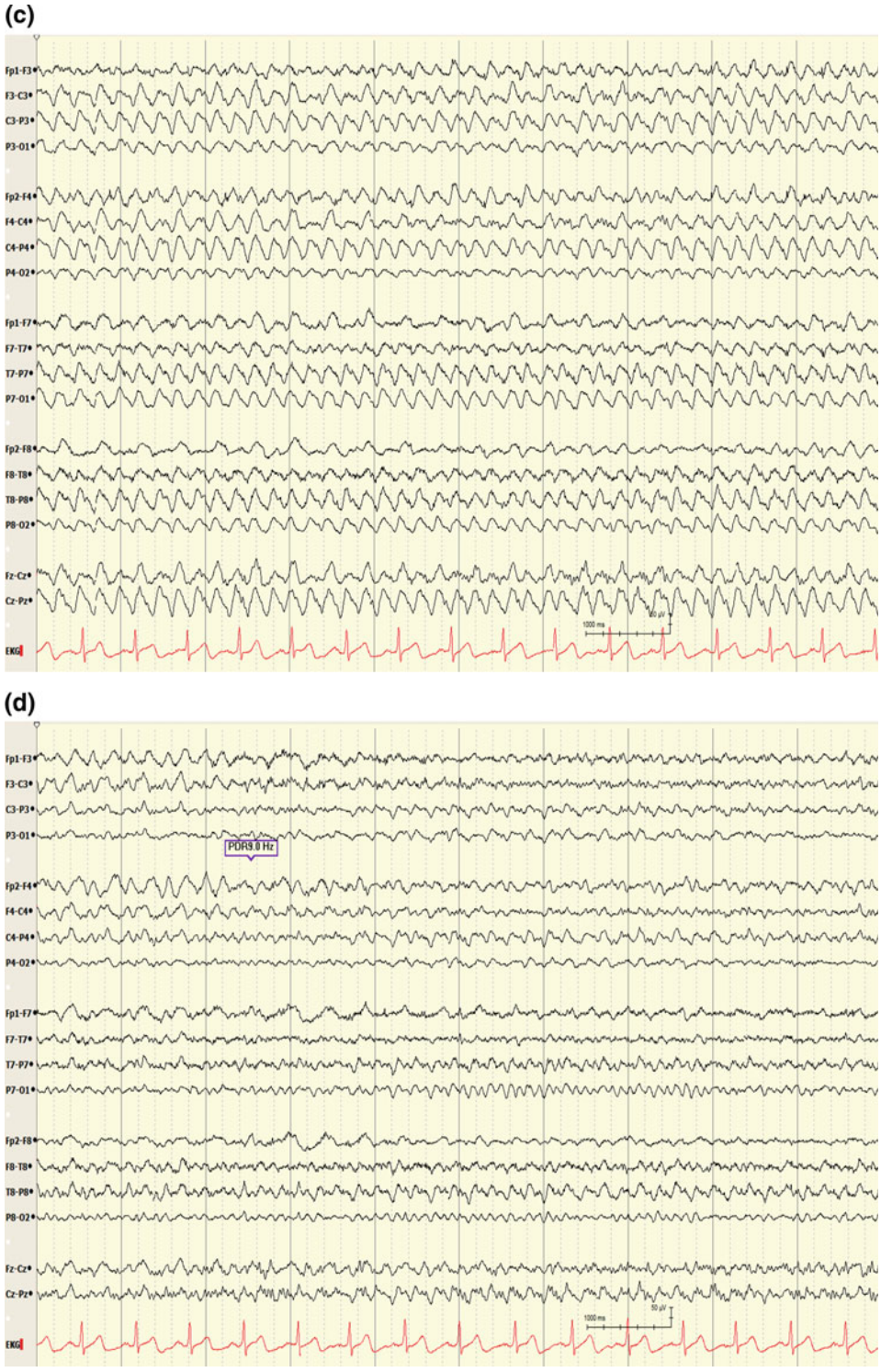

Fig. 3.6 (continued)

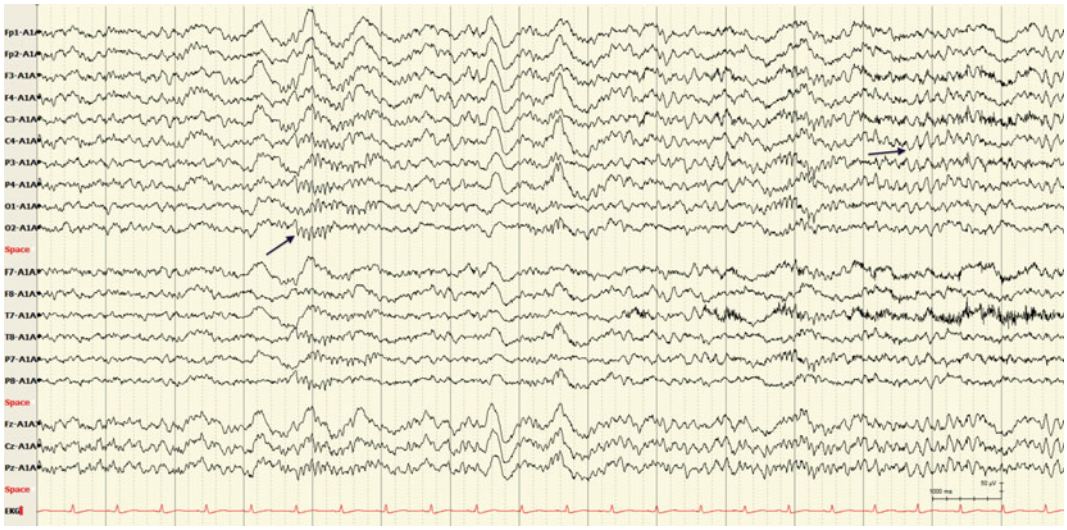

Fig. 3.7 14- and 6-Hz positive bursts (*arrow*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

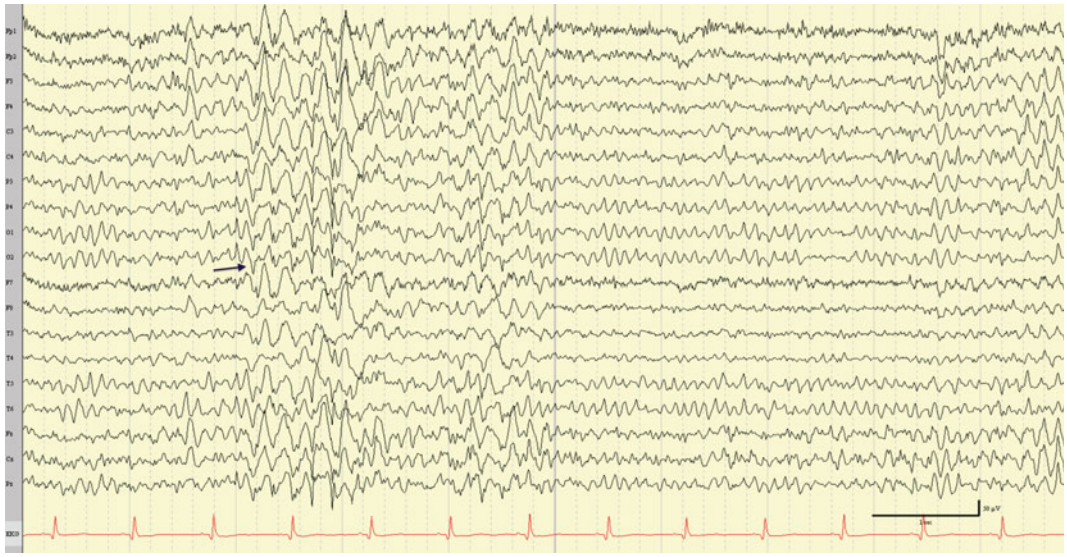

Fig. 3.8 6-Hz spike-and-wave bursts (*arrow*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

- Predominantly 14 Hz and the 6 Hz can occur either independently or in association with 14 Hz.
- Maximal amplitude over the posterior temporal region.
- Better seen in a referential montage (ear references).
- Peak at the age of 13–14 and decrease in incidence with increasing age.
- May be enhanced in Reye's syndrome.

6-Hz spike-and-wave bursts (Fig. 3.8):

- Also known as phantom spike-and-wave.
- Consist of 5–7 Hz brief bursts of a subtle low-amplitude spikes followed by a more prominent slow wave.

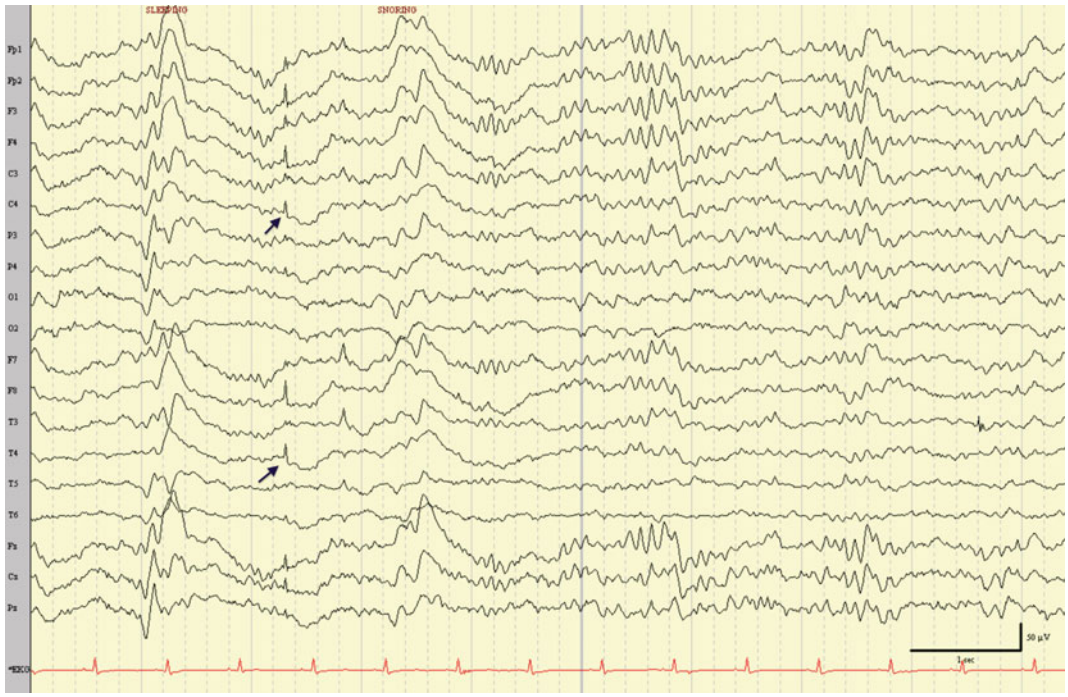

Fig. 3.9 Benign sporadic sleep spikes (BSSS) (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

- Occurs during relaxed wakefulness and drowsiness disappearing with deep sleep (unlike spike-and-wave discharges which persist during sleep).
- Usually occurs bilaterally and synchronously.
- Two types have been described: FOLD (Female Occipital Low-amplitude and Drowsiness) and WHAM (Wake High-amplitude Anterior and Male).
- FOLD is considered to be benign, whereas WHAM is more likely to be associated with seizures.

Benign Sporadic Sleep Spikes or (BSSS) (Fig. 3.9):

- Also known as small sharp spikes (SSS) or benign epileptiform transients of sleep (BETS).
- Seen in adults during drowsiness and light sleep and disappear with deeper sleep.
- Low-voltage (<50 μV) and short-duration (<50 ms) monophasic or diphasic spike with abrupt ascending limb and a steep descending limb.
- Usually do not have a slow-wave component and do not occur in repetitive trains.
- Commonly occur unilaterally but can independently involve the opposite hemisphere.

Wickets (Fig. 3.10):

- Intermittent trains of monophasic arciform waveforms or single spike-like waveforms.
- Occur exclusively on one side (left > right) or bilaterally with shifting predominance.
- Frequency of 6–11 Hz and possibly represent fragments of temporal alpha activity or the third rhythm.
- Seen during wakefulness, drowsiness, and light sleep, and disappear in deeper sleep.
- Should not be mistaken for a temporal seizure discharge or spikes; if a single spike is found, it should be compared with a train of wicket spikes on other pages.
- Not associated with a slow wave and do not distort the background.

The Third Rhythm (Fig. 3.11):

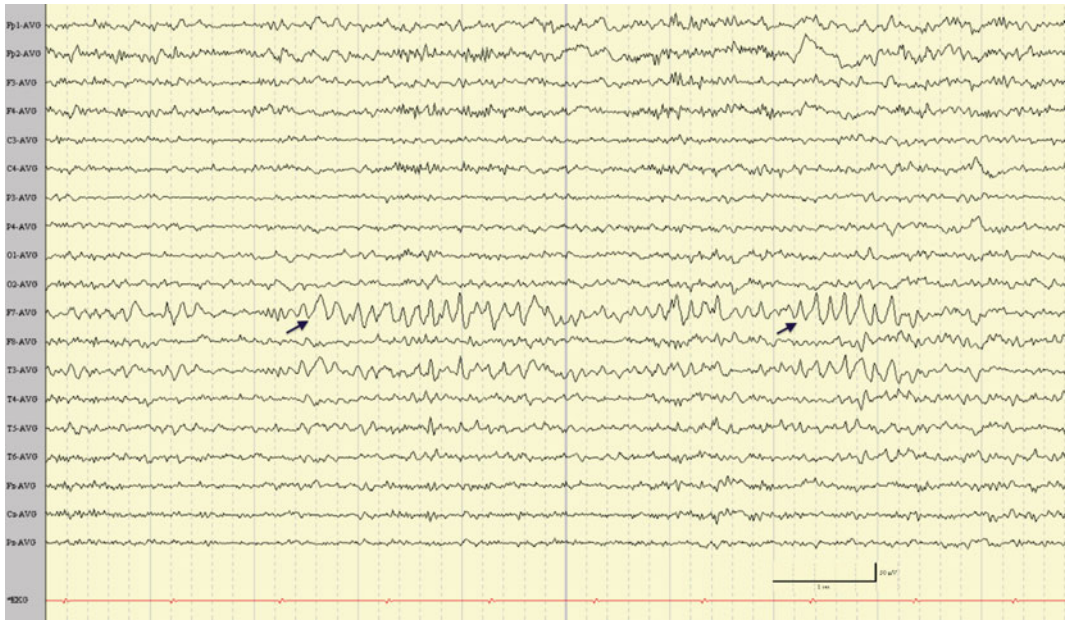

Fig. 3.10 Left wicket rhythm (*arrows*); *sensitivity* 7 μV/mm, *LFF* 0.5 Hz, *HFF* 70 Hz

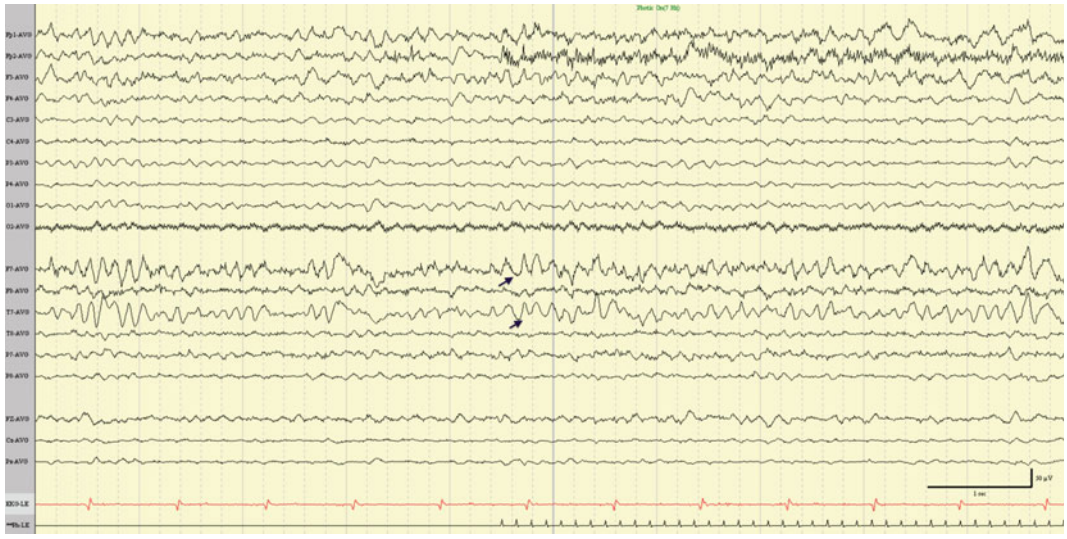

Fig. 3.11 The third rhythm (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

- Also called temporal alphoid rhythm.
- Rhythmic activity in the alpha and upper theta range over the mid-temporal region.
- Rarely detected in the scalp EEG and more commonly seen when there is a local bone defect or recorded from epidural electrodes.
- The origin and function remain debatable, with some related it to cortical auditory function.

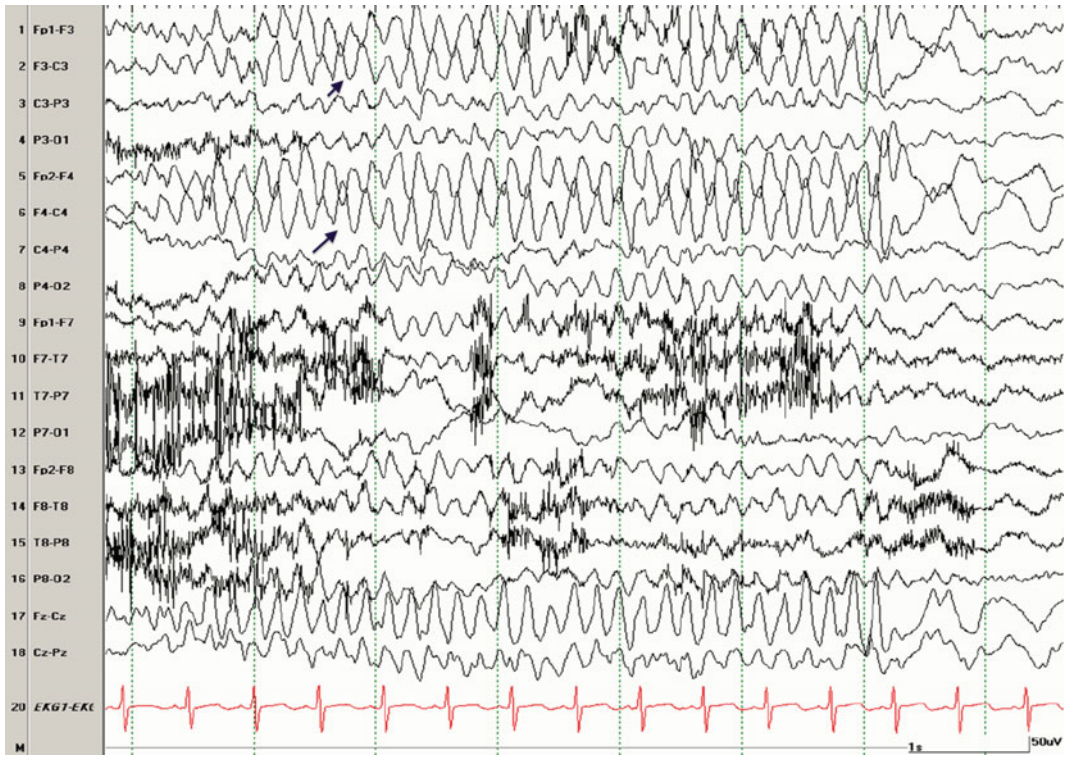

Fig. 3.12 Frontal arousal rhythm (FAR) (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

Frontal Arousal Rhythm (FAR) (Fig. 3.12):

- Trains of 7–20 Hz waveforms that occur predominantly over the frontal regions lasting up to 20 s.
- May be notched in appearance with varying harmonics.
- Seen mainly in children following arousal from sleep and disappears with full wakefulness.

Mu-Rhythm (Fig. 3.13):

- Archiform 7–11 Hz waveforms occurring independently over the central head regions.
- Functionally related to the sensorimotor cortex and is attenuated by touch, active, or passive movement of the extremities, or thought of such movement.

Lambda Waves (Fig. 3.14):

- Resemble the Greek letter λ with monophasic or diphasic waveforms with prominent surface-positive waveform.
- Occurs over the occipital regions when subject is visually scanning.
- Bilateral and synchronous but may be asymmetric.
- Possibly represent an evoked cerebral response to visual stimuli.

Positive Occipital Sharp Transients (POSTs) (Fig. 3.15):

- Sharp-contoured, positive transients over the occipital regions.
- Bilateral synchronous but may be asymmetric.
- Occur during light sleep.

Mitten Pattern (Fig. 3.16):

- Seen during sleep.

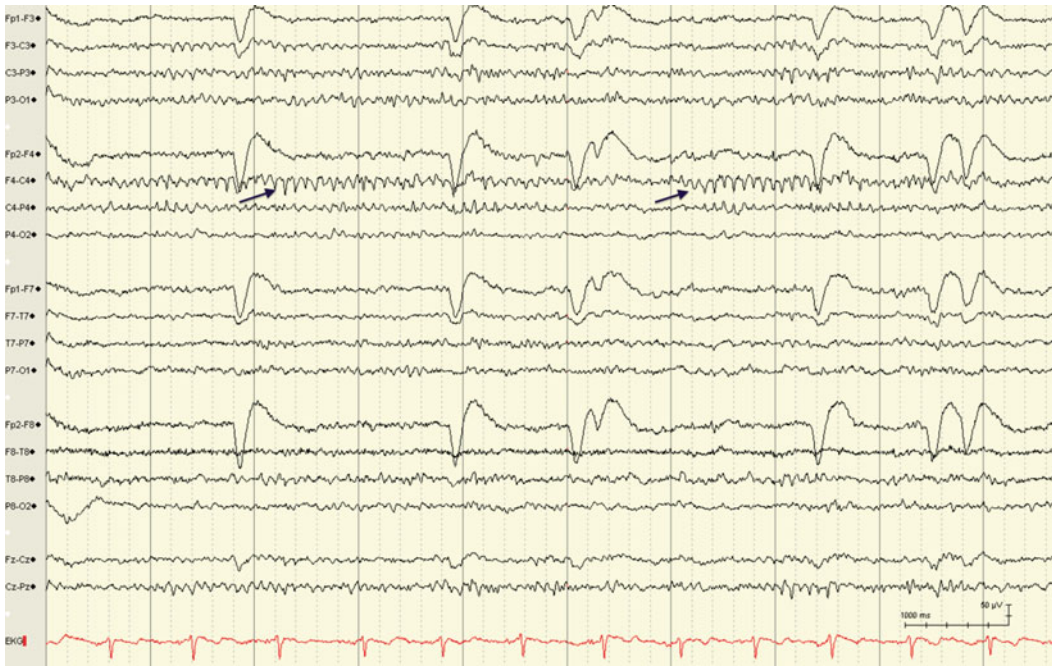

Fig. 3.13 Mu-rhythm (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

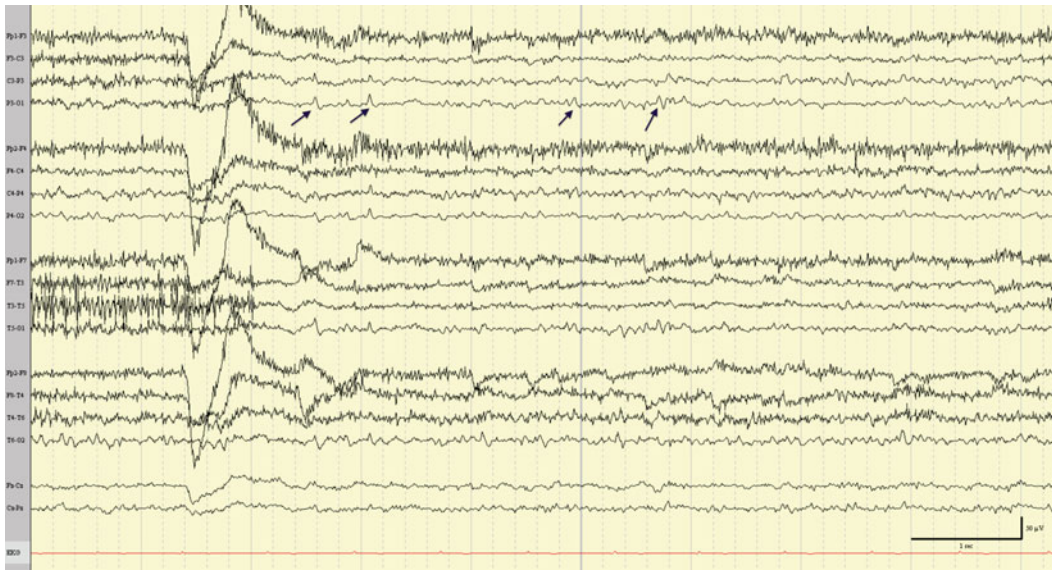

Fig. 3.14 Lambda waves (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

- Consists of fast-wave and slow-wave components and resembles a mitten with the thumb of the mitten formed by the last wave of a spindle and the hand portion by the slower wave component.
- Variant of a vertex wave or K-complex.

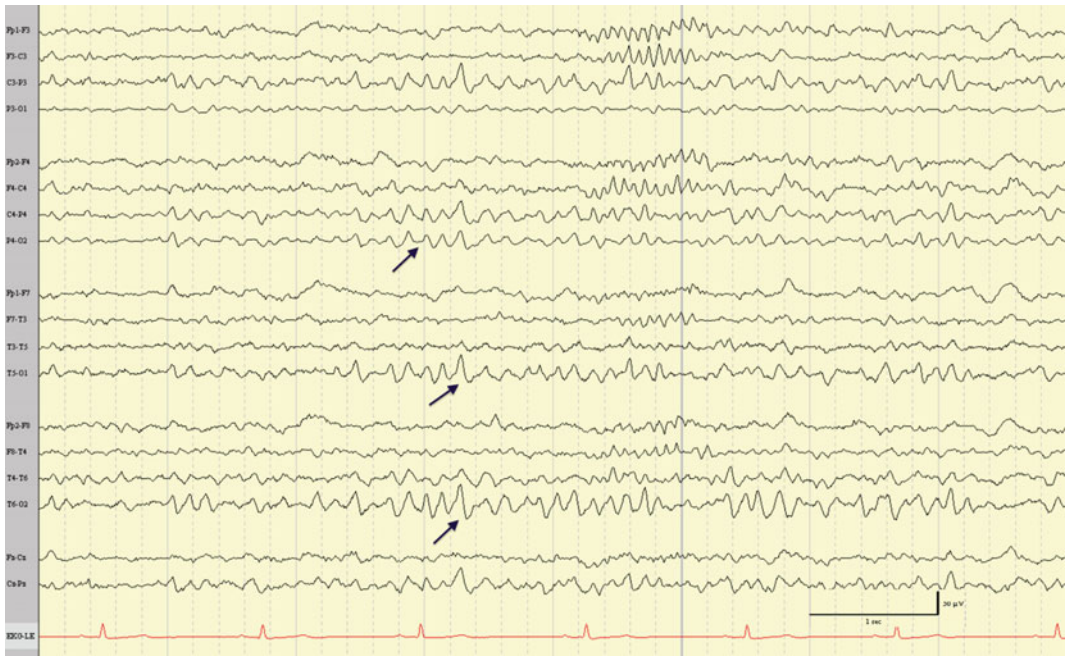

Fig. 3.15 Positive occipital sharp transients (POSTs) (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

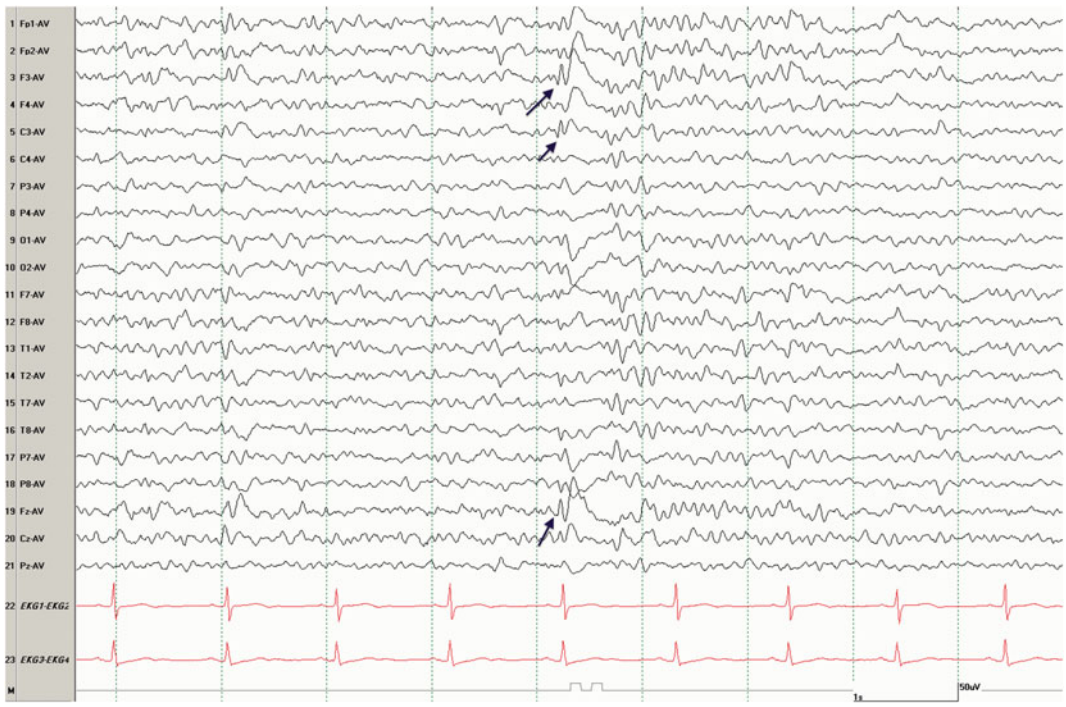

Fig. 3.16 Frontal mitten pattern (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

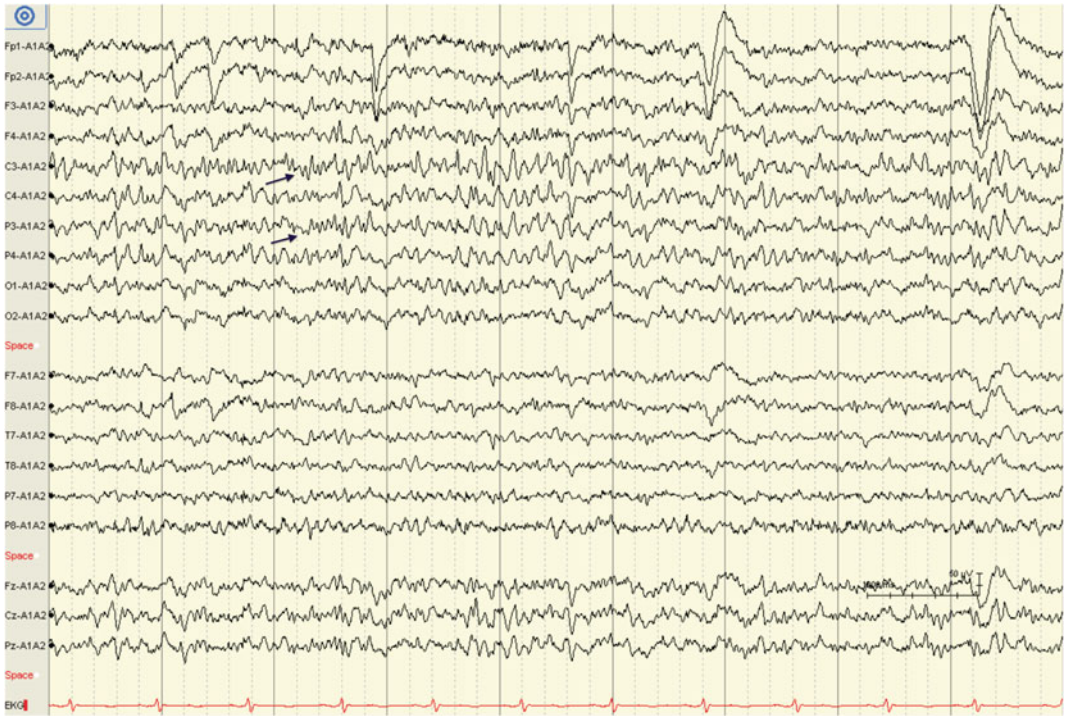

Fig. 3.17 Breach rhythm in the left centro-parietal region (*arrows*); *sensitivity* 7 μV/mm, *LFF* 1 Hz, *HFF* 70 Hz

Breach Rhythm (Fig. 3.17):

- High-voltage activity over a skull defect.
- Consists of a spiky appearance and sharply contoured arciform 6–11 Hz waveforms.
- Most prominent in temporal and central regions and can usually represent wickets and mu-rhythms depending on the location of the skull defect.

EEG artifacts are activity recorded by the EEG that is usually not cerebral in origin. Several sources of artifacts exist and can be divided into physiologic and non-physiologic.

Physiologic EEG Artifacts

Eye movements—vertical (Fig. 3.18), horizontal (Fig. 3.19), oblique (Fig. 3.20), flutter, and nystagmus:

- All eye movements are generated by corneal and retinal potentials.
- It is a direct current represented by a dipole whose positive pole localizes to the cornea and negative pole localizes to the retina.
- The electrodes involved are closest to the eyeball: Fp1, Fp2, F7, and F8.
- The electrodes surrounding the eyeball detect a positive potential which voltage is usually greater than the cerebral potential.
- For example, when the eyes are closed, the eyeballs move upward to their natural position (Bell's phenomenon) and this upward movement is detected by a positive potential recorded at Fp1 and Fp2 (Fig. 3.21). This activity is then followed by a falloff recorded at the next electrodes: F3 and F4. When the eyes are open again, the inverse occurs. If these movements happen repetitively, they will result in a blink artifact.

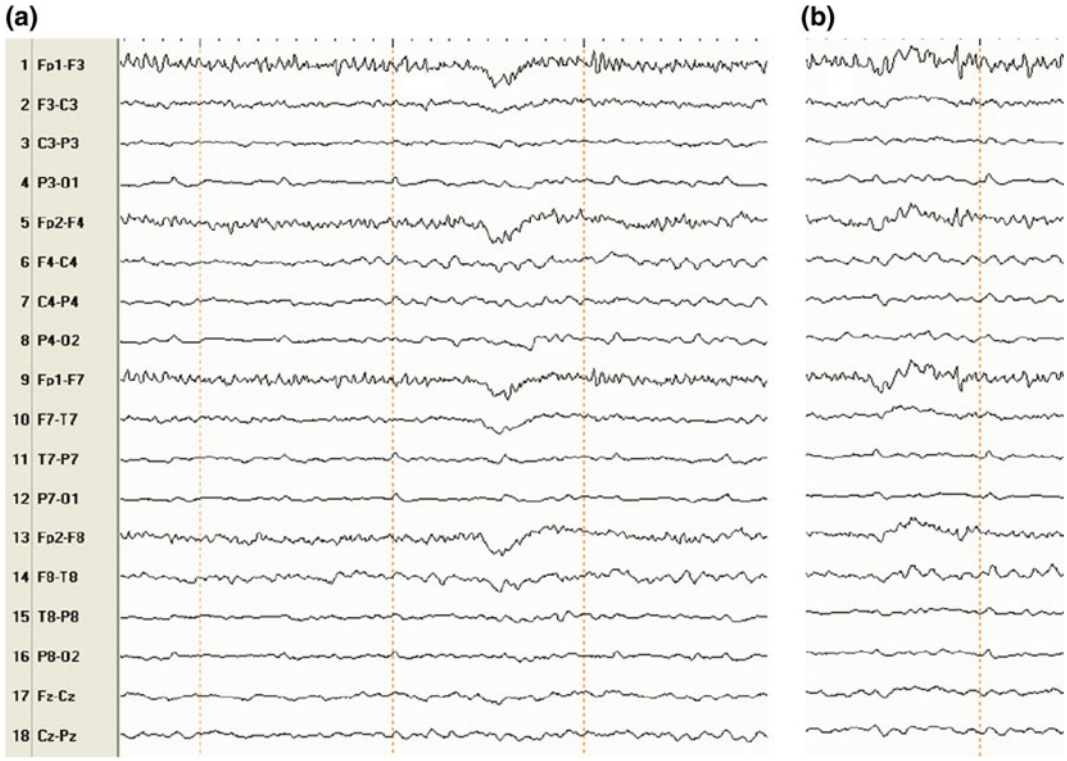

Fig. 3.18 Vertical eye movements: **(a)** up gaze, **(b)** down gaze; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

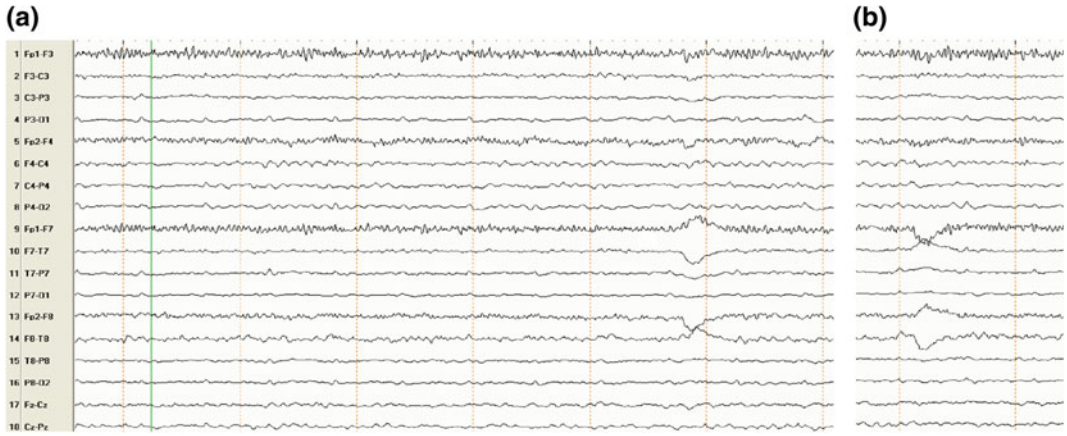

Fig. 3.19 Horizontal eye movements: **(a)** left gaze, **(b)** right gaze; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

- Another example is when eyes move to the left, the activity at Fp1 and Fp2 remains steady, with no change in potential. However, the positive potential is detected by the electrode F7 and it becomes more positive than other electrodes. Because the eyes move conjugately, the cornea is moving away from F8 and it becomes less positive, or more

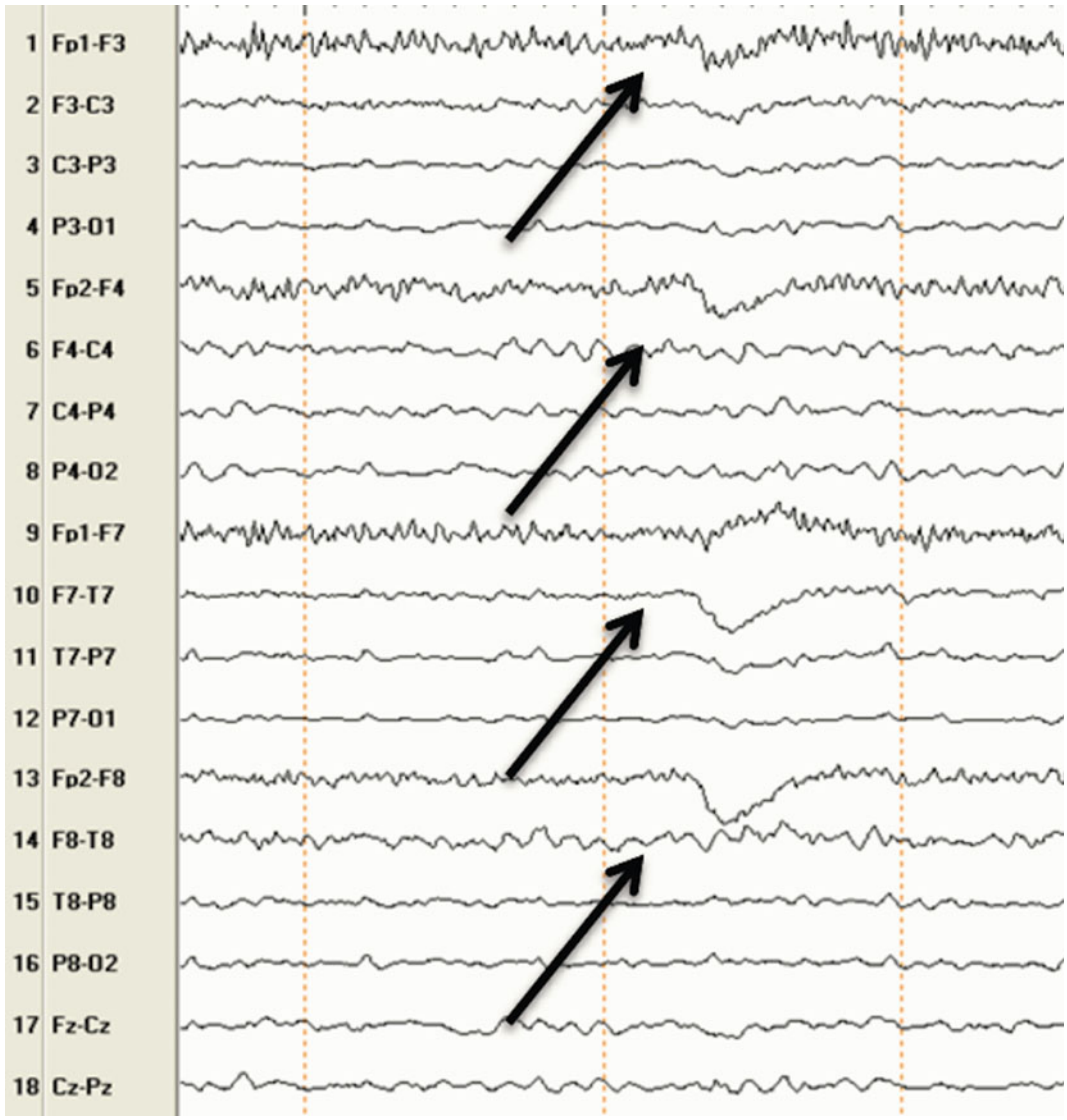

Fig. 3.20 Oblique eye movement: up and to the left (*arrow*); *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

negative, because the retina is now closer to this electrode. This horizontal movement to the left produces a positive phase reversal with a maximal positive potential at F7 and a negative phase reversal with a maximal negative potential recorded at F8.

- Oblique eye movements are more difficult to interpret and constitute a combination of both vertical and horizontal movements. An eye movement upward and to the left would generate an equal positive potential recorded in a bipolar montage recording from electrodes Fp1–F7 and a large upward deflection on the channel recording Fp2–F8. This occurs because the positive potential involves both Fp1 and F7 relatively equally, and the potential difference recorded with the differential amplifier approximates to zero. The potential difference recorded from Fp2–F8 is negative at Fp2 and positive at

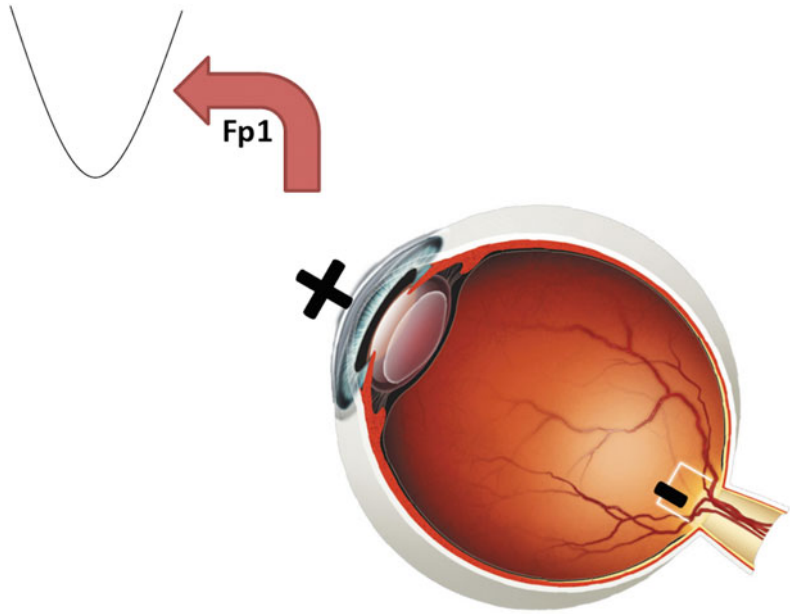

Fig. 3.21 Upward movement of the eyeball brings the positively charged cornea closer to Fp1 and the negatively charged retina farther from Fp1, resulting in a positive or downward deflection

F8, creating an upward deflection in that channel. This is due to the rules of localization (if input 1 is more negative than input 2, an upward deflection will be recorded).

- Eyelid flutter produces low-voltage slow activity and is often limited to Fp1 and Fp2 electrodes.
- Horizontal nystagmus is usually detected unilaterally, and the movement is recorded by the electrode on the side of the fast phase of the nystagmus because of the larger positive voltage of the cornea near that electrode. Vertical nystagmus is rarely detected because of the low voltage and the distance of these electrodes from the eyeball.

Electromyographic—lateral rectus, single motor units, frontalis, temporalis, swallowing, and chewing:

- The lateral rectus artifact (Fig. 3.22) is a low-voltage motor unit potential recorded from the F7 and F8 electrodes. It appears as a sharp positive deflection of very short duration with a slow falloff as the muscle relaxes.
- Single motor units appear as repetitive or single negative or positive deflections that have a comb-like appearance.
- The frontalis electromyogram (EMG) is seen in frontal electrodes, as when tightly closing eyes. This can also be seen during photic stimulation, a photomyoclonic response. The temporalis EMG is recorded from F7, F8, T7, T8, P7, and P8. This is typically seen with jaw clenching or chewing.
- High-frequency filters should not be used to eliminate the EMG artifact because they alter its appearance from a sharp wave to a more sinusoidal frequency that resembles cerebral beta activity.

Electrocardiographic—QRS complex (Fig. 3.23), pulse, cardioballistic:

- The QRS complex is easily monitored by applying electrodes to the chest. The generated signal is high voltage generated by the heart. This activity when recorded at the scalp constitutes a far-field potential. It is often picked up by montages using ear electrodes as a reference. It is prevalent in obese

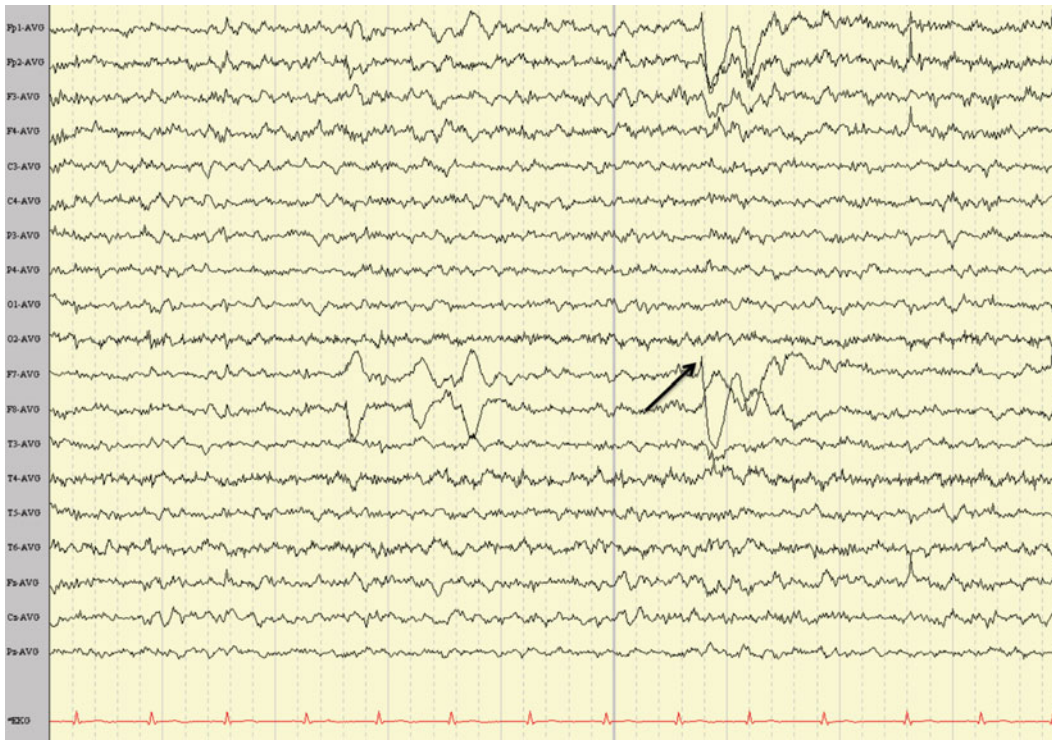

Fig. 3.22 Lateral rectus spike (*arrow*); *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

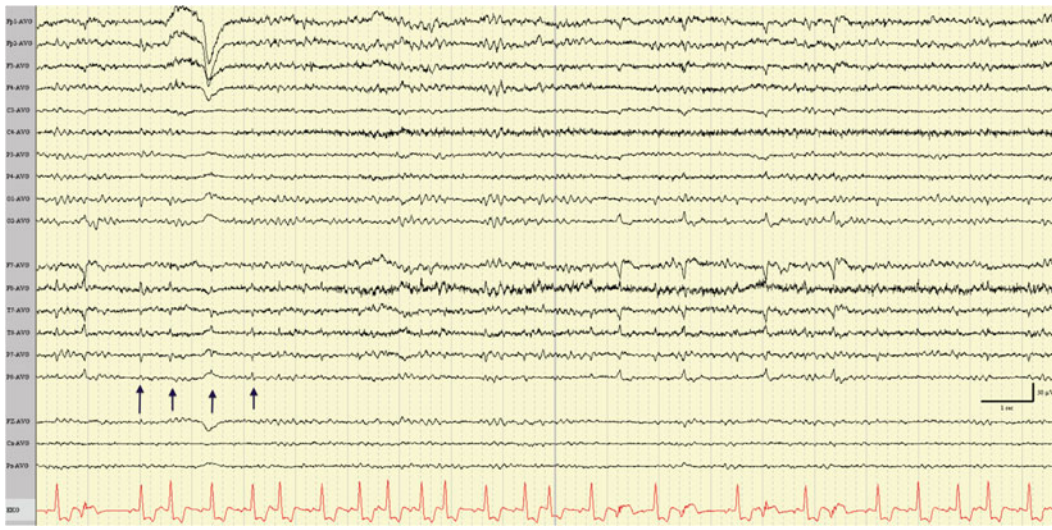

Fig. 3.23 Electrocardiographic artifact (*arrows*); *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

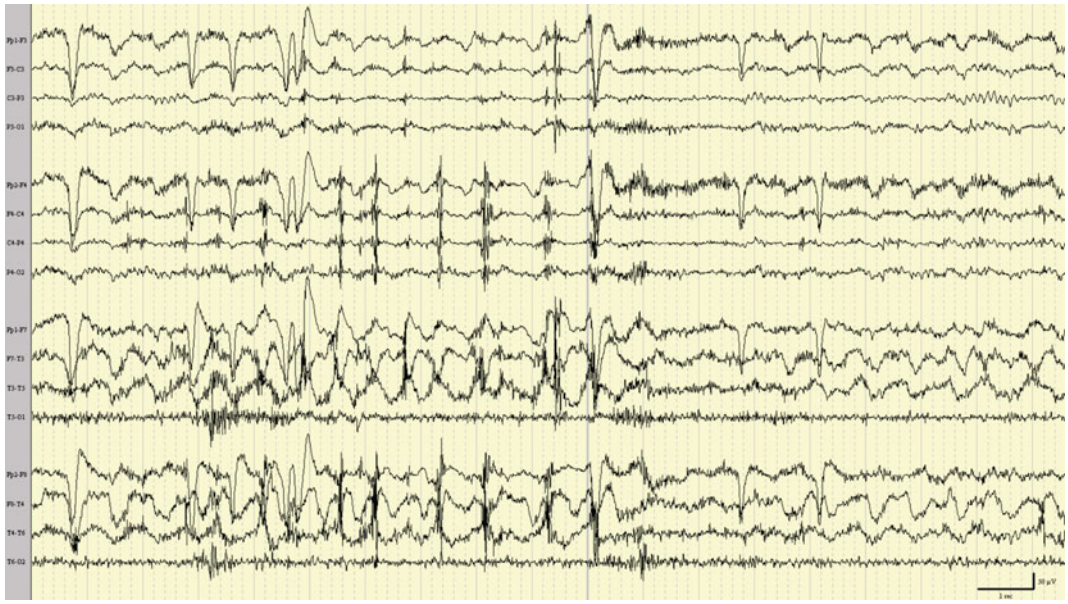

Fig. 3.24 Glossokinetic and chewing artifacts; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 35 Hz

patients, and patients with short necks and babies.

- Pulse artifact is usually confined to a single electrode and appears as a slow-wave potential. It occurs when an electrode is placed over a surface artery. The electrocardiogram signal will be time locked to the slow wave and always occurs at the same location.
- A cardioballistic artifact is rhythmic delta activity, usually widespread in distribution, which represents head movement with each pulse. The relationship between the cardiac signal and these pulsations is not always time locked to any particular phase of the signal.

Glossokinetic (Fig. 3.24):

- Movement of the tongue creates a direct current potential where the tip of the tongue is negative with respect to its base. They are frequently recorded as slow activity from the temporal electrodes. This can be reproduced by having the patient repeat words or phrases that produce active tongue movements, such as la-la-la or ta-ta-ta. This artifact may resemble generalized spike-and-wave discharges when filtered.

Galvanic (Fig. 3.25):

- This artifact is secondary to perspiration and results in high-amplitude slow-wave potentials.
- Standard low-frequency filters reduce this artifact.
- A salt bridge may be formed shorting two electrodes contacting the perspiration.

Physiologic movements—tremor (Fig. 3.26) and jerks:

- Tremor is often between 4 and 6 Hz and localized to the body region involved. It is often seen in the head and upper limbs.
- Jerks produce enough body movement to move the electrodes or the head creating a potential in the recording.

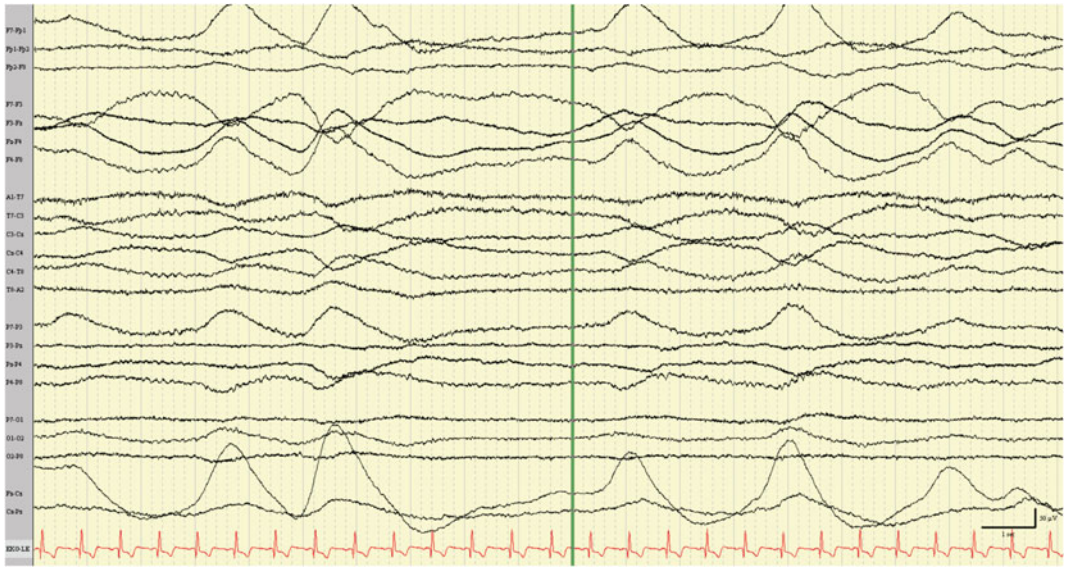

Fig. 3.25 Diffuse sweat artifact; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

Non-physiologic Artifacts

Instrumental artifacts:

- Sixty-cycle interference results from poor electrode application. It is produced by high-impedance electrodes that affect the input circuitry of the amplifier and also common-mode rejection when impedances are not equal (Fig. 3.27).
- Capacitative and electrostatic artifacts are related to movement of wires. An example is when someone steps on the input cable. The cable acts as a capacitor because of multiple insulated wires enclosed in the cable. Moving or stepping on the cable causes the capacitor to discharge and results in high-voltage transient recorded on the EEG.

Electrode artifacts:

- These are mostly related to poorly attached electrodes, high resistance, a broken wire, or changes in the lead–scalp interface (change in the gel used to complete this interface). They are usually restricted to one electrode (Fig. 3.28). These may resemble repetitive discharges in a longitudinal montage.
- An electrode pop is a high-voltage deflection that exceeds the limits of the individual channel sensitivity and blocks or squares off at the top.
- Repetitive and rhythmic electrode artifact can be produced by tapping the electrodes when the mother of the patient pats the baby's back.

Environmental artifacts:

- Radiofrequency waves are high-frequency signals that may be continuous or intermittent and affect some or all recording channels. This often results from being in the vicinity of machines such as microwaves or the operating room.

Digitization:

- This often results from failure in the components used to acquire the EEG data.

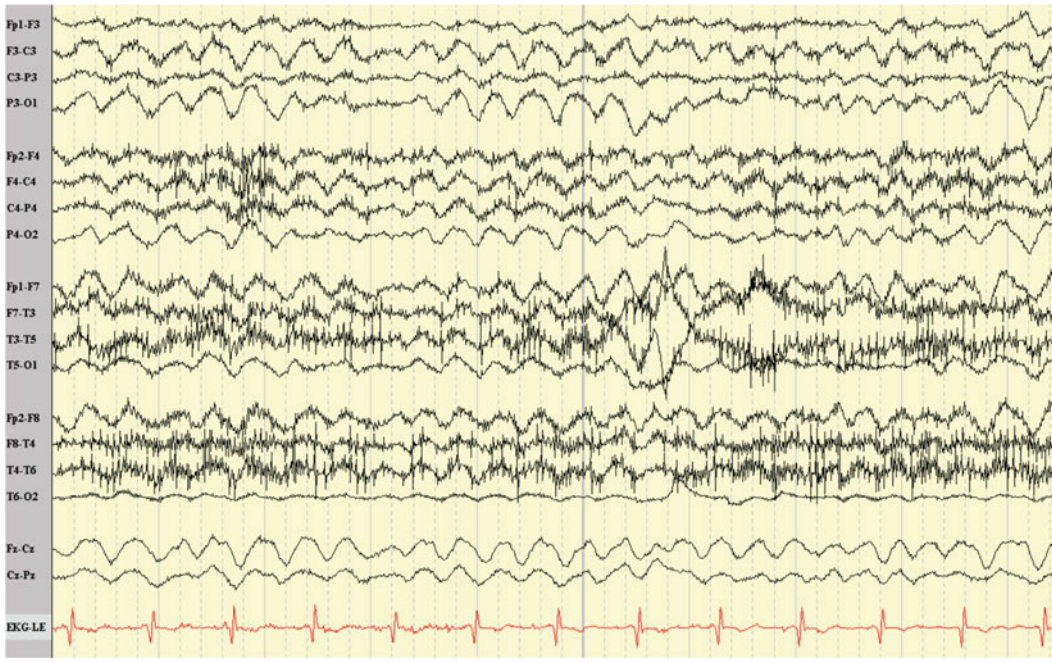

Fig. 3.26 Tremor artifact; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

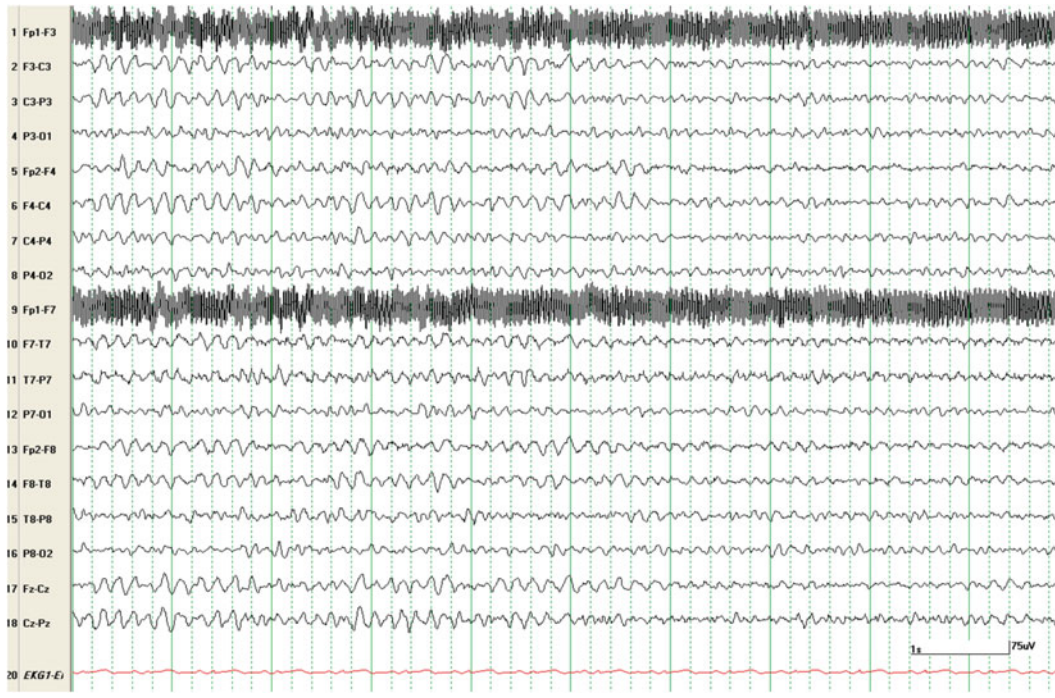

Fig. 3.27 60-Hz artifact; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

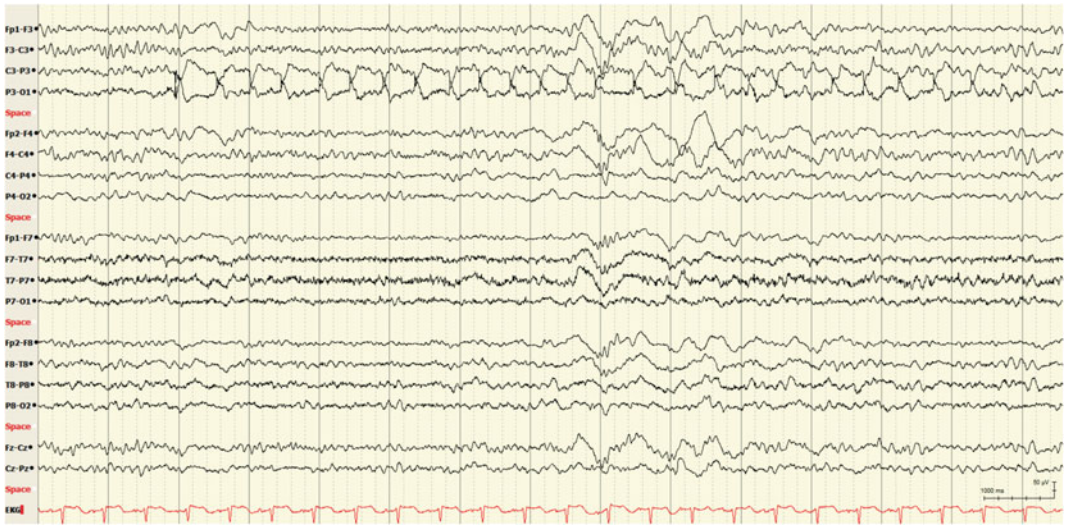

Fig. 3.28 Electrode artifact; *sensitivity* 7 μV, *LFF* 1 Hz, *HFF* 70 Hz

- One example is related to aliasing, which is sampling at a rate that is less than twice the frequency of the high-frequency filter. This is uncommon since most EEG instruments sample at a rate of at least 200 samples per channel per second.
- With the ability to make changes in sensitivity, filtering, and montages, many artifacts can be created where the EEG may appear very different from the true signal. This often results in misinterpretation of the EEG as possibly ictal in nature.

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Neonatal EEG and Neonatal Seizures

4

Kohilavani Velayudam and Ahsan N.V. Moosa

Neonatal EEG

- Neonatal EEG assists in studying the functional integrity of immature neonatal cortex and its connections. The exact generators are unknown for these activities. Neonatal EEG helps to assess the prognosis for the neonates who are at risk for neurological sequelae following a CNS insult.
- Rapid rate of cerebral development happens during the neonatal period. Recognizing and identifying age-dependent findings from conceptional age less than 28 weeks through 44 weeks is very critical.
- EEG findings in a newborn rapidly change with brain maturity and hence need to be carefully correlated with the age of the baby. Postconceptional age is frequently used as the reference.
  - Postconceptional age (PCA) = gestational age (prenatal) + chronological age (postnatal)
  - Postmenstrual age is also used (usually postmenstrual age = PCA + 2 weeks)
- Quick clinical behavioral state change happens and parallel EEG changes also happen.

Technical Information that is Unique in Neonatal EEG and that May Affect Interpretation

- First step is identifying the postconceptional age.
- Behavioral state of the infant: Whether the infant is awake or asleep.
- Medications like benzodiazepines, neuromuscular blocking, sedatives, hypnotics, anxiolytics, general anesthesia, and antiepileptic drugs.
- Temperature and depth of hypothermia in babies being cooled.
- Topographic—caput or cephalohematoma, scalp IV placement, VP shunt.

Neonatal Montage

- Newborn typical montages use both longitudinal and transverse chains to record term and preterm neonates with head circumference <35 cm.
- It is modified 10–20 system with a minimum of 9 electrodes. Cz electrode plays an important role because abnormal positive sharp waves (and sometimes seizures) can be

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M.Z. Koubeissi and N.J. Azar (eds.), *Epilepsy Board Review*,
DOI 10.1007/978-1-4939-6774-2_4

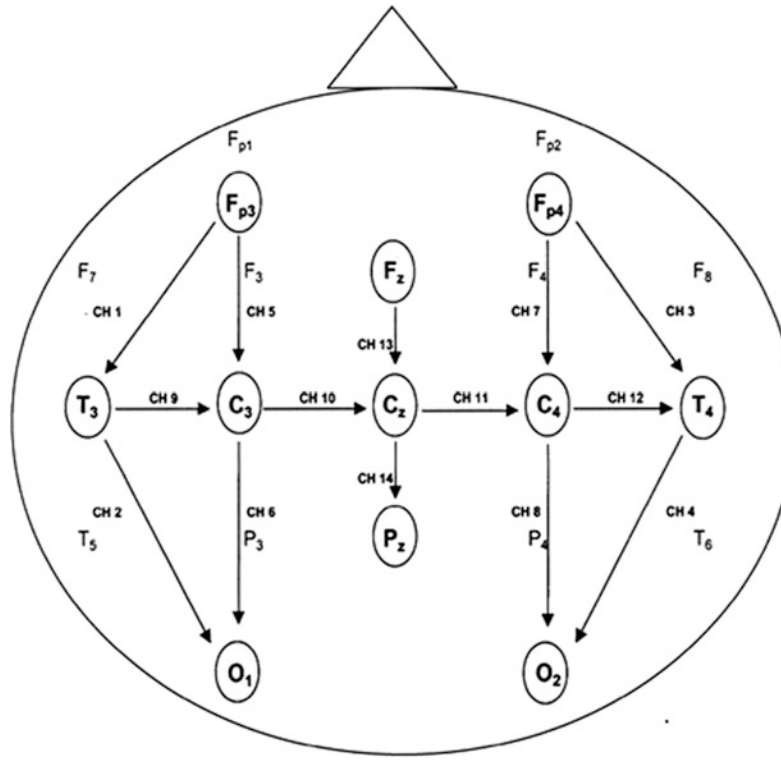

Fig. 4.1 Neonatal montage. Special montage —preterm or newborn with head circumference <35 cm

confined to this single electrode without involving or spreading to nearby regions (Fig. 4.1).

- Usually, 16 channels recording are done, which should include 2 or more non-cerebral channels.
- Non-cerebral electrodes include EKG, EMG, ocular, and respiratory belt. It helps in staging the sleep cycle, abnormal body movements, and also to identify the artifacts.
- Duration of the recording: 60-min recording is mandatory in an attempt to capture EEG in various behavioral states. EEG abnormalities are usually the most prominent in quiet sleep. In a term neonate, the total sleep cycle lasts anywhere between 45 and 60 min (active sleep: ~25 min; quiet sleep: ~20 min; transitional sleep: ~15 min).

Timing of the Neonatal EEG

- EEG is ideally done within 24 h following the insult.
- EEG changes are very dynamic, and significant changes in background activity may happen rapidly (in hours). Serial EEGs provide valuable information for therapy and prognostication.

Normal Developmental Landmarks

Normal developmental landmarks on a newborn's EEG provide information regarding the functional maturity and reflect the PCA of the baby. EEG findings in acute encephalopathy in

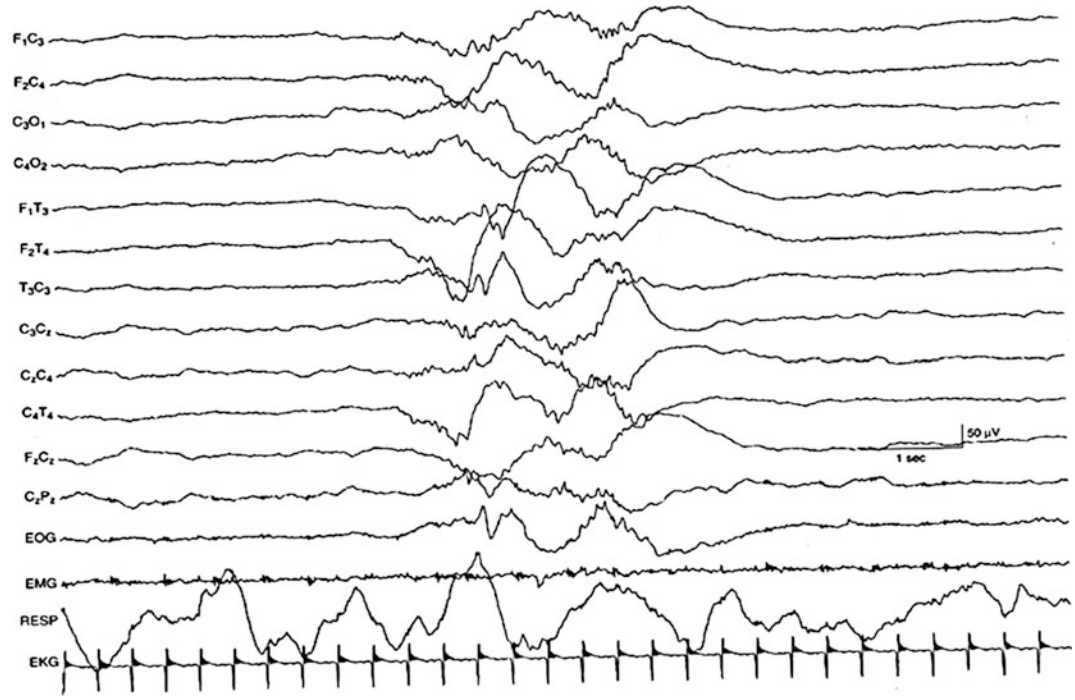

Fig. 4.2 Trace discontinue. Trace discontinue pattern seen in 26–28 weeks of PCA (*Picture source* Atlas of neonatal encephalography—Third Edition Lippincott Williams and Wilkins A Wolters Kluwer Company)

newborns frequently show the patterns that may be normal for a baby of a lesser PCA. Such patterns are described as dysmature patterns and indicate encephalopathy in the appropriate setting. This may improve rapidly with the improvement in encephalopathy. Developmental landmarks are best categorized in 3 phases: <30 weeks, 30–37 weeks, and >37 weeks.

PCA <30 Weeks of Gestation

EEG may be indistinguishable from awake and sleep in extremely premature infants of PCA <30 weeks. A discontinuous EEG pattern termed trace discontinue is noted in all behavioral states.

Trace Discontinue

- Tracé discontinue pattern is a predominant pattern seen in preterm neonates with PCA <30 weeks. It is characterized by high-amplitude (50–300 μV) bursts of mixed frequency (theta and alpha riding over delta) which are seen simultaneously on both the hemispheres followed by low-amplitude periods of quiescence (<25 μV) which can last anywhere between few seconds and 1 min (inter-burst interval—IBI) (Fig. 4.2).

Inter-burst interval (IBI)

- The key factor that determines the IBI in healthy babies is the postconceptional age. As the PCA increases, the IBI decreases.
- Approximately 30 weeks or older, median IBI of 8 s or less has higher survival than those with longer median IBI.
- Approximately IBI lasts anywhere between 20 and 35 for neonates with PMA <30–33 weeks with <25 μV. After 34 weeks, it significantly reduces, and closer to the term, it

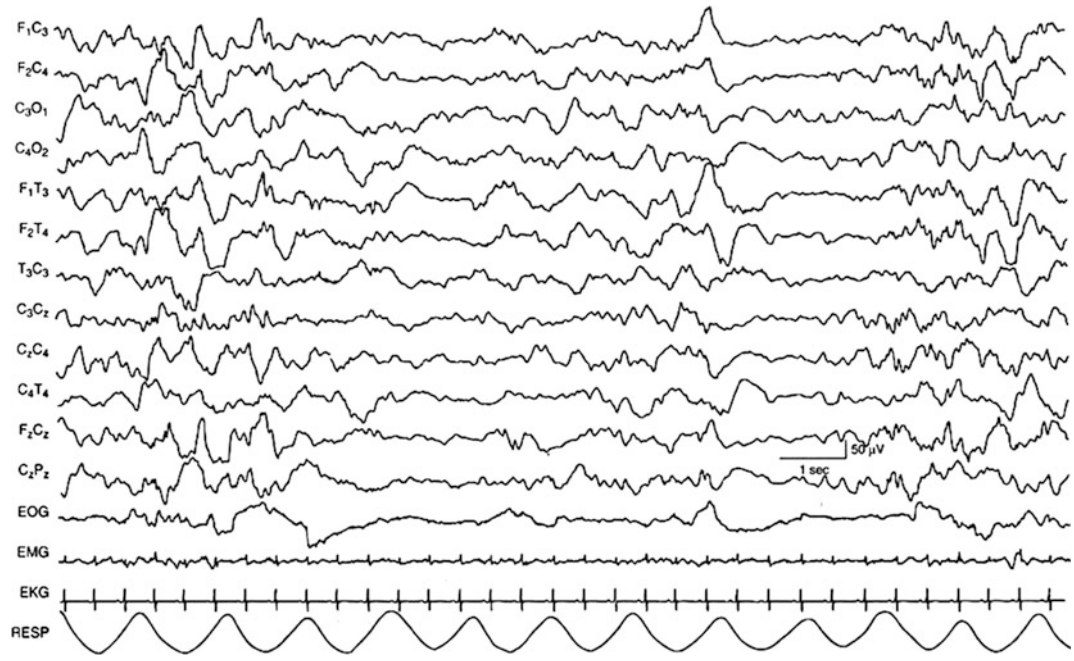

Fig. 4.3 Trace alternant. Trace alternant pattern seen in quiet sleep in 38–30 weeks of PCA (*Picture source* Atlas of neonatal encephalography—Third Edition Lippincott Williams and Wilkins A Wolters Kluwer Company)

ranges anywhere between 6 and 10 s and has higher voltage >25 μV.

- Prolonged IBI is seen in acute encephalopathy secondary to any type of brain injury, but is also commonly seen in moderate-to-severe hypoxic ischemic encephalopathy.

PCA Between 30 and 37 Weeks

EEG starts showing variation in different behavioral states around 35 weeks of PCA. Identifying different sleep stages in a newborn's EEG is critical for optimal interpretation. EEG maturational changes occur first in active sleep; after a lag of about 2 weeks, the awake periods start showing more mature patterns. Quiet sleep is the last stage to show more mature changes. For these reasons, the abnormalities are most frequently seen in the quiet sleep phase.

Trace alternant: These are characterized by high-amplitude (50–150 μV) synchronous burst of mixed frequencies predominantly delta activity for 3–10 s followed by 3–5 s of low-amplitude burst (25–50 μV) of predominant theta activity. This patterns replaces the trace discontinue with advanced PCA. This pattern is seen only in quiet sleep in neonates between PCA of 36 and 38 weeks (Fig. 4.3).

- TA usually starts appearing in neonates >35 weeks and can be seen until 42 weeks but no longer than 44 weeks of PCA.
- In active sleep (and later in wakefulness), TA is replaced by more continuous pattern characterized by uninterrupted, low-to-medium amplitude, mixed EEG activity with <2 s of

EEG maturation happens in the following order

Active sleep → Awake → Quiet sleep

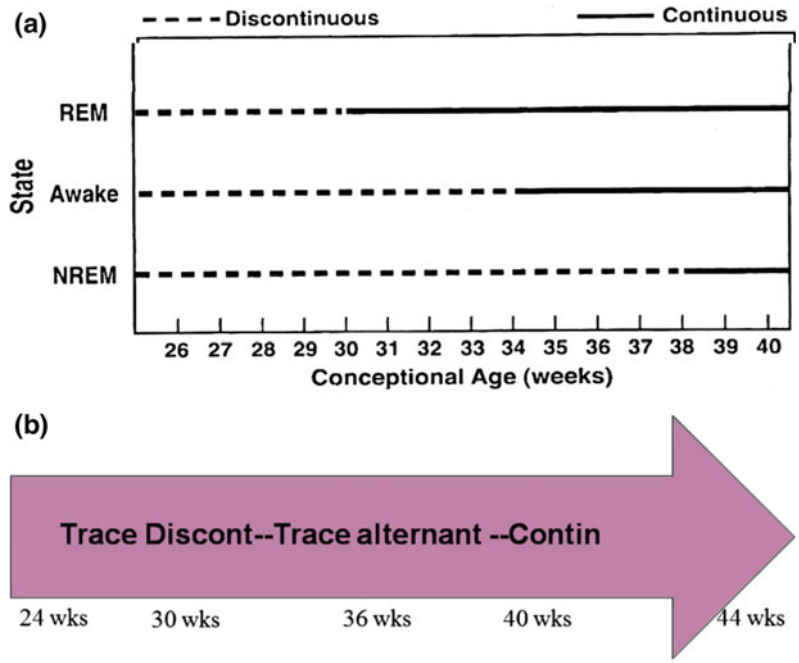

Fig. 4.4 **a** Development of continuous activity (*Picture source* Levin and Luders Comprehensive Clinical Neurophysiology W.B. Saunders Company). **b** Evolution of the background activity

voltage attenuation (<25 μV), and seen in mostly neonates with PCA >30 weeks.

- TA pattern is replaced by medium-to-high voltage delta slow wave sleep after PCA of 44–48 weeks (Fig. 4.4a, b).

Abnormalities in Voltage

Excessive discontinuity: Abnormal discontinuous tracing separated by prolonged IBI for PCA. This is usually seen in neonates with severe hypoxic ischemic encephalopathy, meningitis, encephalitis, and severe intraventricular hemorrhage.

Burst suppression: Burst suppression pattern is a pattern with high-amplitude burst (50–300 μV) of delta and theta frequency with sharp waves and spikes followed by severe background suppression (<5 μV). Usually, the background shows no reactivity to stimuli.

In certain conditions like non-ketotic hyperglycinemia, the EEG bursts may be accompanied by myoclonic jerks (Fig. 4.5).

Synchrony: Burst of morphological similar activity in the homologous head regions is separated by <1.5 s.

- <28 weeks: no asynchrony
- 28–32 weeks: 70% synchrony
- >37 weeks: mostly synchronous
- Abnormal finding: Asynchrony of >1.5 s may be significant if in excess for the PCA (Fig. 4.6).

Normal Graphoelements

Delta brushes: Delta brush is characterized by 0.3–1.5 Hz delta activity superimposed with beta or fast activity (18–22 Hz).

- Other names are beta-delta complexes, ripples of prematurity, spindles/delta bursts.

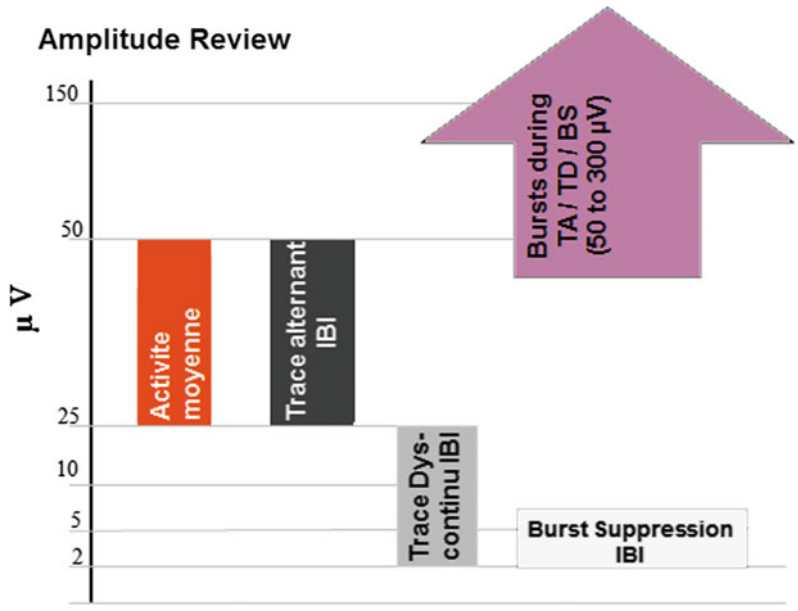

Fig. 4.5 Amplitude review

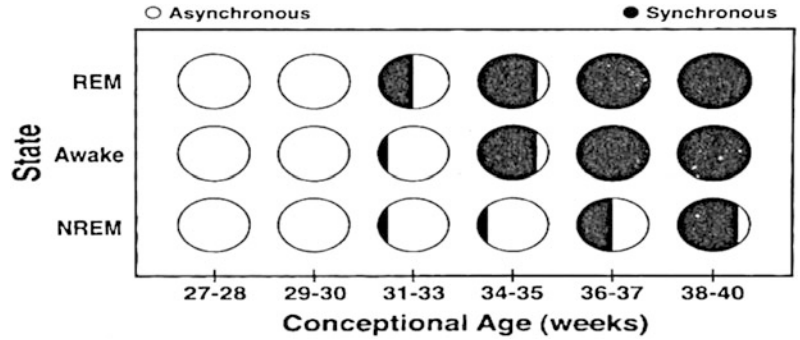

Fig. 4.6 Synchrony (*Picture source* Levin and Luders Comprehensive Clinical Neurophysiology W.B. Saunders Company)

- They usually appear in the central region first followed by temporal and occipital and also disappear in the same order.
- Most commonly seen during 24–34 weeks and starts to disappear first in the active sleep after 30 weeks. They can be present in the quiet sleep up to 38 weeks.
- Abnormal findings: Delta brushes are often asynchronous, but when consistently absent on one side, a concern for some cerebral dysfunction is raised; if it is persistently present beyond 44 weeks then it is consistent with dysmaturity (Fig. 4.7).

Frontal sharps (*Encoches Frontales*): These are blunt isolated biphasic broad sharp transients (0.5–0.75 s) seen in the frontal region with initial smaller negativity followed by prominent positivity phase.

- They are usually symmetric and synchronous;
- Frequently seen in the transitional stage of sleep;
- Usually seen between 33 and 46 weeks of PCA with peak around 35 weeks;
- Mostly associated with rhythmic bi-frontal delta; and

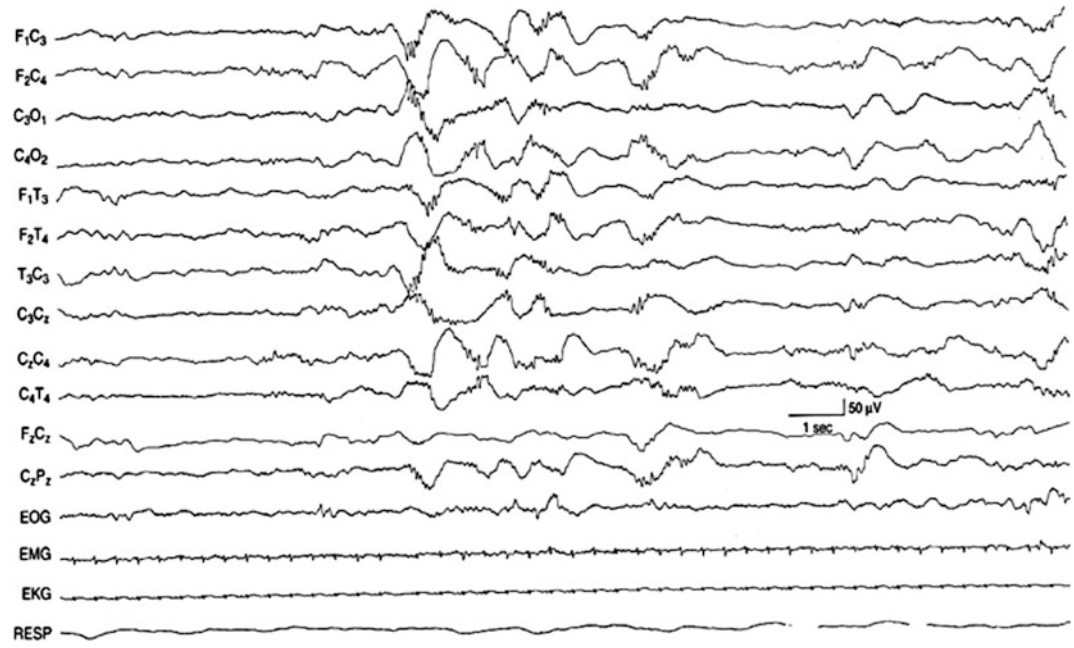

Fig. 4.7 Delta brushes in 29–30 weeks of PCA: Delta brushes seen in the bilateral central regions in a discontinuous background (*Picture source* Atlas of neonatal encephalography—Third Edition Lippincott Williams and Wilkins—A Wolters Kluwer Company)

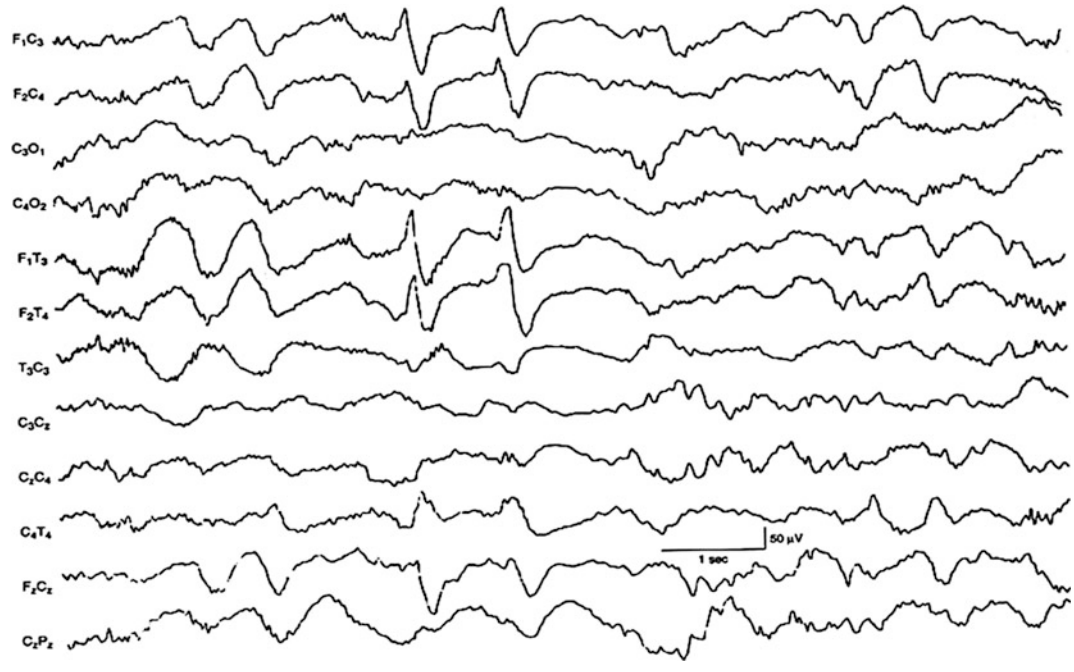

Fig. 4.8 Frontal sharps in 34–35 weeks of PCA (*Picture source* Atlas of neonatal encephalography—Third Edition Lippincott Williams and Wilkins—A Wolters Kluwer Company)

- Abnormal findings: Consistently absent on one side or any asymmetry raises concern for structural lesion on the other side (Fig. 4.8).

Temporal Theta

- This graphoelement is a developmental marker that appears as a 2-s burst of 25–120 μV theta burst over the temporal region;
- Typically present between 25 and 32 weeks and disappears by 34 weeks

PCA between 38 and 44 weeks.

- Awake and sleep contains continuous, low-to-medium voltage, mixed frequency predominantly theta and delta with overriding beta activity (activite moyenne);
- Rudimentary spindles starts appearing in sleep state; and
- Sleep–wake cycling is more distinctive in terms of neonates after 37 weeks. Fig. 4.9—Developmental Landmarks.

Other Abnormal EEG Findings

Abnormalities in a newborn EEG can be in various aspects of the EEG such as continuity, symmetry, synchrony, and amplitude, excess of sharp waves, reactivity, seizures, and abnormal representation of normal graphoelements. Some of the abnormalities related to graphoelements and dysmature patterns were already discussed in earlier sections.

Asymmetry: Asymmetry is defined as a persistent difference in amplitude/voltage of >50% between homologous regions of right and left hemispheres. It should be interpreted with cautions as extracranial factors such a caput succedaneum, cephalhematoma, and subgaleal hemorrhage may result in similar findings.

Positive sharp waves: These are abnormal positive polarity sharp waves seen mostly in the rolandic and central vertex regions around the 5th–8th postnatal day in preterm neonates with severe intraventricular hemorrhages.

- Examples seen in neonates with interventricular hemorrhage, hydrocephalus, and periventricular leukomalacia.
- It is an electrographic marker often linked to parenchymal white matter injury and usually disappears in 3–4 weeks.

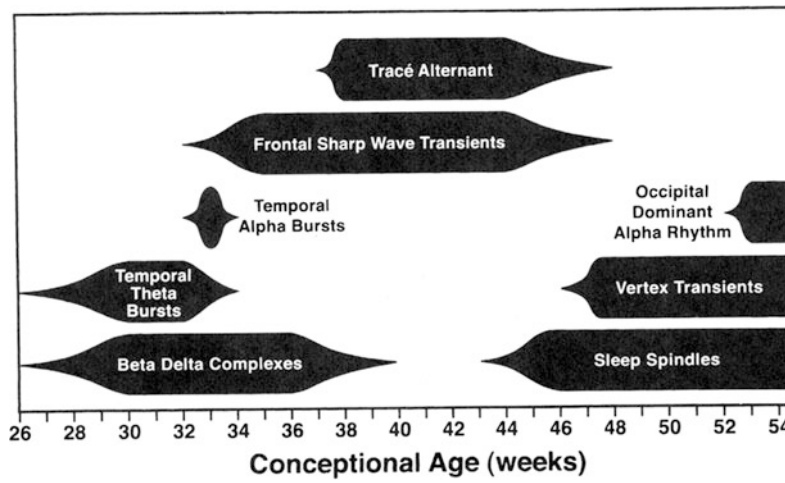

Fig. 4.9 Developmental landmarks (*Picture source* Levin and Luders Comprehensive Clinical Neurophysiology W.B. Saunders Company)

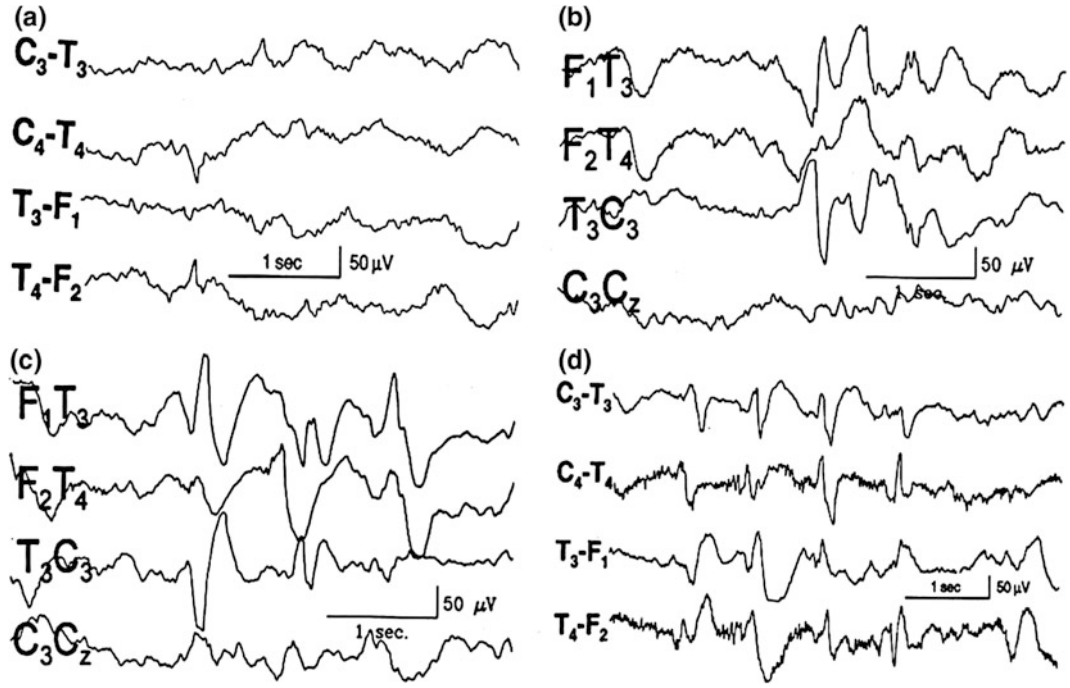

Fig. 4.10 Sharp electrographic transients (*Picture source* Levin and Luders Comprehensive Clinical Neurophysiology W.B. Saunders Company)

Table 4.1 Normal and abnormal sharp electrographic transients

Normal sharp transients	Abnormal sharp transients
Bitemporal, central	One persistent location
Monophasic or diphasic	Variable and polyphasic
Polarity: negative	Polarity: negative or positive
Amplitude usually <75 μV	Amplitude usually >150 μV
Duration <100 ms	Duration >150 ms
Sharp waves seen synchronously and asynchronously	Spikes, occurs in long runs
Normal background	Abnormal background
Quiet sleep	Awake and quiet sleep

Sharp transients: These are frequently seen in temporal, central, and frontal regions, and less frequently in vertex and occipital regions.

Abnormal sharp transients are differentiated from the Encoches Frontales by the presence of associated frontal slowing, usually asymmetric and seen mostly in active sleep and awake state (Fig. 4.10 and Table 4.1).

Dyschronism/dysmature: Dyschronism is defined as any discrepancy between clinically determined conceptional age and EEG-derived conceptional age. Discrepancy of 2 weeks or less indicates transient CNS dysfunction, and of 3 weeks or more indicates higher likelihood of persistent impairment of CNS function.

Neonatal Seizures

- Incidence is ~1.5–5.5/1000 live births;
- It is the sign of acute brain injury and mostly happens within the first week of life; and
- Early recognition and initiation of treatment is very important to prevent brain damage.

Risk factors: There are two main specific risk factors:

Conceptional age:
- <30 weeks—higher incidence ~3.9%
- 30 weeks—1.5%

Birth weight:
- <1500 gm → 57/1000 live birth
- 1500–2499 gm → 5/1000 live birth
- 2500 gm → 3/1000 live birth.

Table 4.2 Etiology—neonatal seizures. Modified from Chapter Neonatal seizures in Volpe J Neurology of Newborn. 5th ed

Etiology		Key features	% Patients with normal development
Hypoxic ischemic encephalopathy (~32%)	Prenatal: toxemia, fetal distress, abruptio placentae, cord compression Perinatal: iatrogenic, maternal hemorrhage, fetal distress Postnatal: hyaline membrane disease, congenital heart disease, Pulmonary hypertension	– Common cause both in term and preterm infants – Usually within 4 days of life – Focal clonic or multifocal clonic seizures – Severity of seizures parallel with grade of the encephalopathy.	50%
Intracranial hemorrhage (~17%)	Intraventricular, intraparenchymal subarachnoid subdural hemorrhage	Tonic seizures are common	IVH: 10% SAH: 90%
Stroke (~7%)	Arterial stroke, venous infarction due to venous sinus thrombosis	Focal clonic seizures in the setting of hemiparesis	–
Trauma	Subdural and subarachnoid hemorrhage	–	SAH: 90%
Infections (~14%)	Beta-hemolytic streptococci, *E. coli*, Herpes simplex, HIV, coxsackievirus B, torch mycoplasma infection	HSV infections—PLEDS seen in temporal regions HSV DNA PCR—more sensitive test	~50%
Cerebral malformations	Migration disorders, neurocutaneous disorders	Usually occur within 1 week Peroxisomal disorders—polymicrogyria. Early myoclonic epileptic Encephalopathy—burst suppression pattern Poor prognosis	0%
Metabolic disorders (~9%)	Transient: hypoglycemia, hypocalcemia hyponatremia, hypernatremia Persistent: inborn errors of metabolism	Usually occur within first 2 days Seizures common with late onset hypocalcemia, hypomagnesemia with hypocalcemia in premature infants Good prognosis IEM—Infantile spasms, tonic spasms, myoclonic seizures Poor prognosis	Transient: 50–100%
Unknown (~10%)	–	–	–

Clinical Manifestations

Semiology:

- Focal and multifocal clonic (25%)
- Focal and generalized tonic (5%)
- Myoclonic (20%)
- Subtle seizure pattern (50%)
  - Apnea
  - Tonic deviation of the eyes
  - Eyelid fluttering
  - Drooling, sucking, and chewing
  - Swimming movements of the arm
  - Pedaling movements of the legs
  - Paroxysmal laughing.

Etiology:

See Table 4.2.

Treatable Causes of Inborn Errors of Metabolism Presenting with Seizures and Encephalopathy

Pyridoxine-Dependent and Folinic Acid Responsive Seizures

Age of onset:

- Neonatal type—presents soon after birth;
- Atypical type: Late onset between 1 and 3 years in pyridoxine-dependent seizures.
- Seizure features: intractable seizures not controlled with antiepileptic medications which respond both clinically and electrographically to daily pyridoxine or folinic acid.
- Variable seizure semiology seen.
- Prolonged seizures and status epilepticus common.

Testing:

- Elevated—α-aminoadipic semialdehyde (α-AASA) in urine and plasma.

Table 4.3 Benign neonatal seizure syndromes

	Benign familial neonatal seizures	Benign idiopathic neonatal seizures
Age of onset	Usually present within first few weeks of life	Within first week "Fifth-day fits"
Genetics	AD inheritance potassium channelopathy; KCNQ2 and KCNQ3; chromosome 20, 8	None
History	Multiple family members positive for neonatal seizures	No family history
Clinical features	Tonic seizures with apnea Unilateral focal, multifocal manifestation—later part Multiple times/day	Focal clonic, multifocal clonic seizures and usually happens every few hours to days
Status epilepticus	None	Very common
Neuro-examination	Normal	Normal
MRI brain and metabolic evaluation	Normal	Normal
Interictal EEG	Normal	Normal ("Theta point alternant"—seen for 2 weeks)
Treatment	Phenobarbital levetiracetam	Phenobarbital, levetiracetam
Remission	– ~6 weeks of age	Good
Prognosis	Usually good except 8–16% has tendency to develop epilepsy as adult	

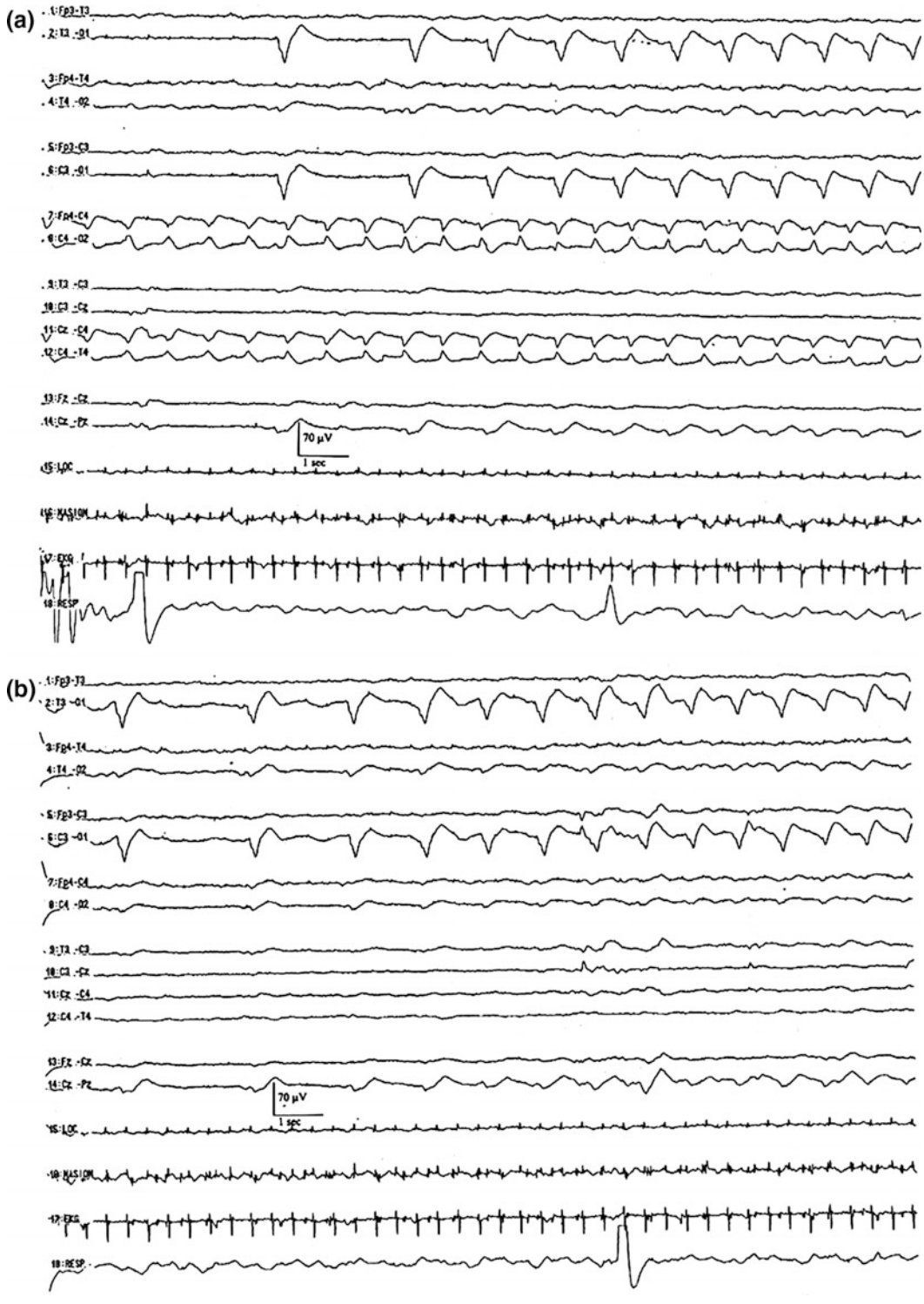

Fig. 4.11 Various neonatal ictal patterns

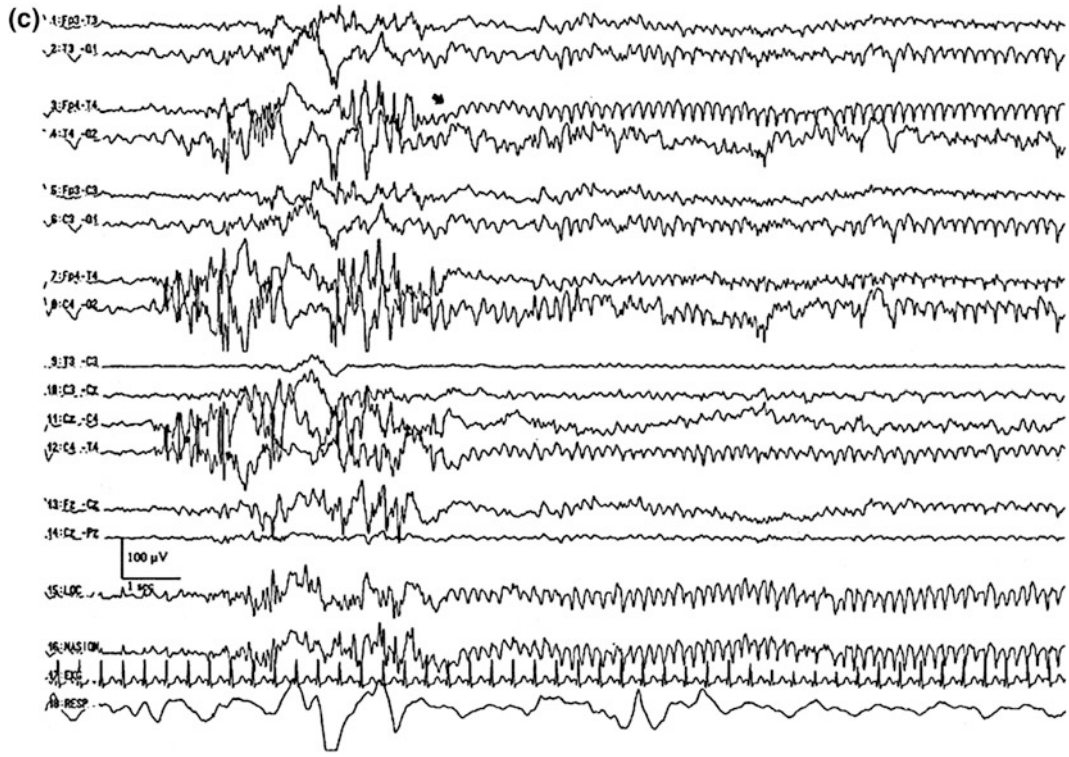

Fig. 4.11 (continued)

- Elevated—pipecolic acid in plasma and cerebrospinal fluid.
- Mutations in ALDH7A1 cause pyridoxine-dependent epilepsy.

Management:

- Response seen with IV pyridoxine 100–500 mg or daily PO pyridoxine 30 mg/kg/d for at least 2 weeks
- Prior to the administration of folinic acid, CSF neurotransmitters studies are obtained
- Response seen within 24 h with folinic acid started at 4 mg/k/D divided BID.

Benign Neonatal Seizure Syndromes

Benign neonatal seizures represent two rare genetically mediated syndromes with seizures in the newborn period. The long-term outcome for both seizures and development is generally good. In this, they resemble the spectrum of benign focal epilepsies of childhood. However, interictal EEGs are not helpful. These disorders are often a diagnosis of exclusion in the acute setting. The two well-characterized benign neonatal seizure syndromes are described in Table 4.3.

Neonatal Non-epileptic Events

- Benign nocturnal myoclonus
- Jitteriness
- Opisthotonus
- Pathological myoclonus
- Apneic spells

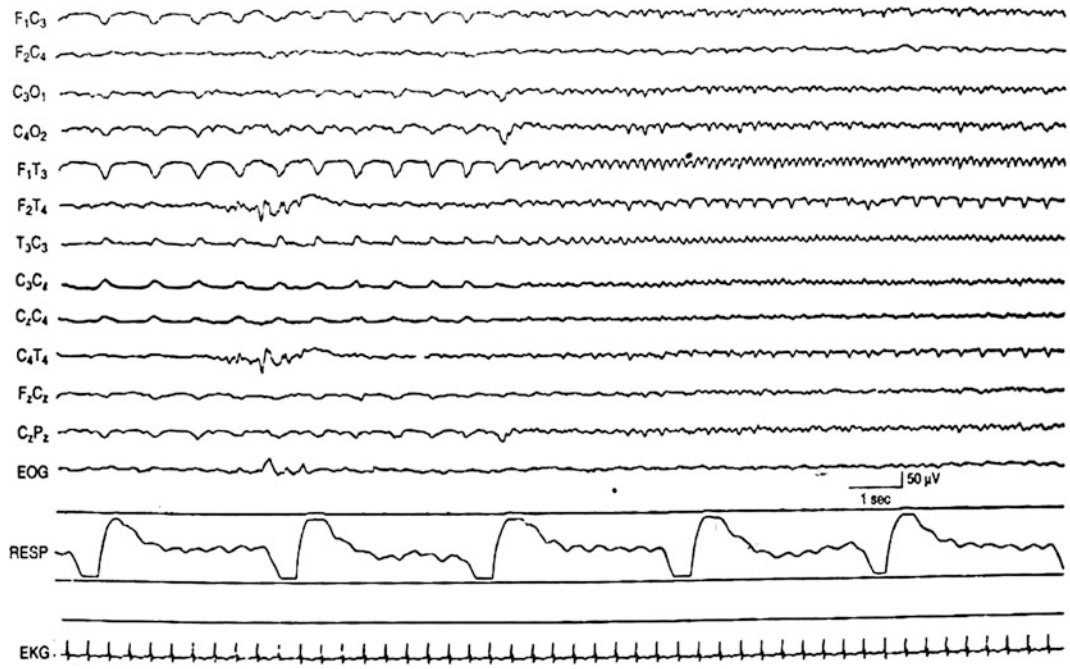

Fig. 4.12 Alpha seizures (*Picture source* Atlas of neonatal encephalography—Third Edition Lippincott Williams and Wilkins—A Wolters Kluwer Company)

Special Features—Neonatal Ictal EEG Pattern

- Ictal patterns—vary significantly within a same neonate EEG recording. Within a same recording, focal or multifocal ictal discharges can be seen simultaneously and independently from different locations of brain.
- Electrical seizure activity—rare before 34 weeks;
- Generalized EEG activity—infantile spasm and myoclonic jerks;
- BIRDS—brief ictal rhythmic discharges of unclear significance;
- Special ictal patterns—burst suppression is seen in metabolic diseases and has poor prognosis; and
- Alpha seizures—seen in severe HIE and has poor prognosis (Figs. 4.11a–c and 4.12).

Neonatal Seizures Management

- Neonatal seizures always require urgent treatment.
- First-line phenobarbital—82% → lorazepam —9% → phenytoin—2%
- Second-line therapy: lorazepam 50% → phenytoin (39%) → phenobarbital (20%)
- ~58% continued to have EEG seizures after the administration of AED and cessation of clinical seizures.

Long-term Outcome

- ~20% neonatal seizures survivors develop postnatal epilepsy.
- Neonates with seizures due to perinatal asphyxia and cerebral dysgenesis develop postnatal epilepsy about ~30 and 80%, respectively.

- Neonatal seizures due to acute encephalopathy usually improve in 7–14 days.

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Multiple Choice Questions for Part I

1. Neurons in the cerebral cortex are organized in:

   A. Three horizontal layers
   B. Four horizontal layers
   C. Six horizontal layers with layer IV receiving inputs from thalamus
   D. Six horizontal layers with layer VI being the most superficial
   E. Six vertical layers

2. What is the predominant pattern seen in a <30 weeks PCA preterm infants?

   A. Trace discontinue
   B. Trace alternant
   C. Trace continue
   D. Electrocerebral silence
   E. Burst-suppression pattern

3. Which of the following is true about GLUT1 deficiency?

   A. High CSF glucose levels
   B. Ketogenic acid is the treatment of choice
   C. Macrocephaly is common
   D. Responds fairly well to sodium channel blockers
   E. All of the above

4. Resting membrane potential of a neuron is around:

   A. +90 mV
   B. –70 mV
   C. +70 mV
   D. –70 μV
   E. –20 μV

5. Choose the one incorrect statement from the following:

   A. At least 6 cm^2 of synchronous cortical activation is necessary to detect an individual epileptic spike on scalp electrodes.
   B. Epileptic spikes are exclusively surface negative.
   C. EEG potentials recorded from the scalp are produced by the summation of the excitatory and inhibitory postsynaptic potentials of pyramidal neurons.
   D. At the cortical layers III, V, and VI, the pyramidal neurons are aligned in a perpendicular fashion to the cortex.
   E. EEG potentials are not mere representations of neuronal action potentials.

6. The EEG of 2-year-old male with Canavan disease will likely show:

   A. Multifocal epileptiform discharges
   B. LPDs
   C. Burst-suppression pattern
   D. Amplitude attenuation
   E. Polymorphic delta activity

7. Which of the following is false about myoclonic epilepsy of infancy?

   A. Males are more affected than females
   B. Valproate is the treatment of choice
   C. Positive family history of febrile seizures or epilepsy
   D. Developmental delay is seen in majority of patients
   E. EEG can show generalized polyspike-and-wave

8. Which of the following is incorrect about Dravet syndrome?

   A. Progressive neurological regression
   B. Overall poor prognosis
   C. SCN1A gene mutation
   D. Respond to lamotrigine
   E. All of the above is true

9. Resting membrane potential of a cell can be calculated by the following equation:

   A. Nernst equation
   B. Goldman–Hodgkin–Katz equation
   C. Henderson–Hasselbalch equation
   D. Both A and B
   E. None of the above

10. A 2-week-old boy is having daily seizures characterized by brief multifocal jerks, at times with apnea. The boy is alert and acting normal in between seizures. His father and paternal grandfather had similar seizures that resolved after several months from birth. The likely mutation is:

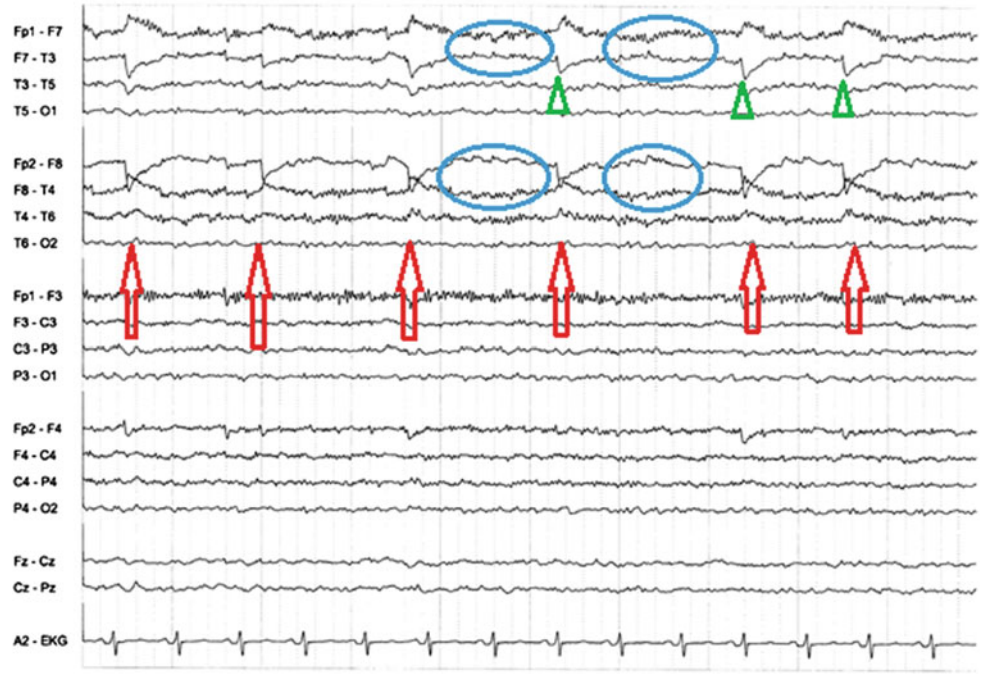
    A. SCN1A, encoding the sodium channel $\alpha 1$ subunit
    B. CACNA1G, encoding the T-type voltage-gated calcium channel
    C. CHRNA4, encoding the $\alpha 4$ subunit of the neuronal nicotinic acetylcholine receptor
    D. GABRG2, encoding the $\gamma 2$ subunit of the γ-aminobutyric acid A receptor
    E. KCNQ2, encoding a voltage-gated potassium channel

11. The recommended length of a neonatal EEG is:

    A. 20 min
    B. 30 min
    C. 60 min
    D. 90 min
    E. 120 min

12. In the following image which of the following represents the artifact generated from the left lateral rectus muscle:

    A. Long arrow
    B. Short arrowhead
    C. Circled area
    D. None of the above



13 In full-term infants, sleep spindles are seen at the age of:

A. Birth
B. 1–3 months
C. 6–12 months
D. 12–24 months
E. Not until adolescence

14. Choose the one incorrect statement from the following:

A. In the international 10–20 system of electrode arrangement the average inter-electrode distance is 4–6 cm.
B. The commonly used electrodes for scalp EEG have a contact made of chloride-treated silver, which if applied properly would show a resistance of a few hundred ohms.
C. If the difference in potential between two electrodes is negative this is represented by a downward deflection.
D. Each channel in an EEG recording represents the difference in potential between two electrodes.
E. None of the above

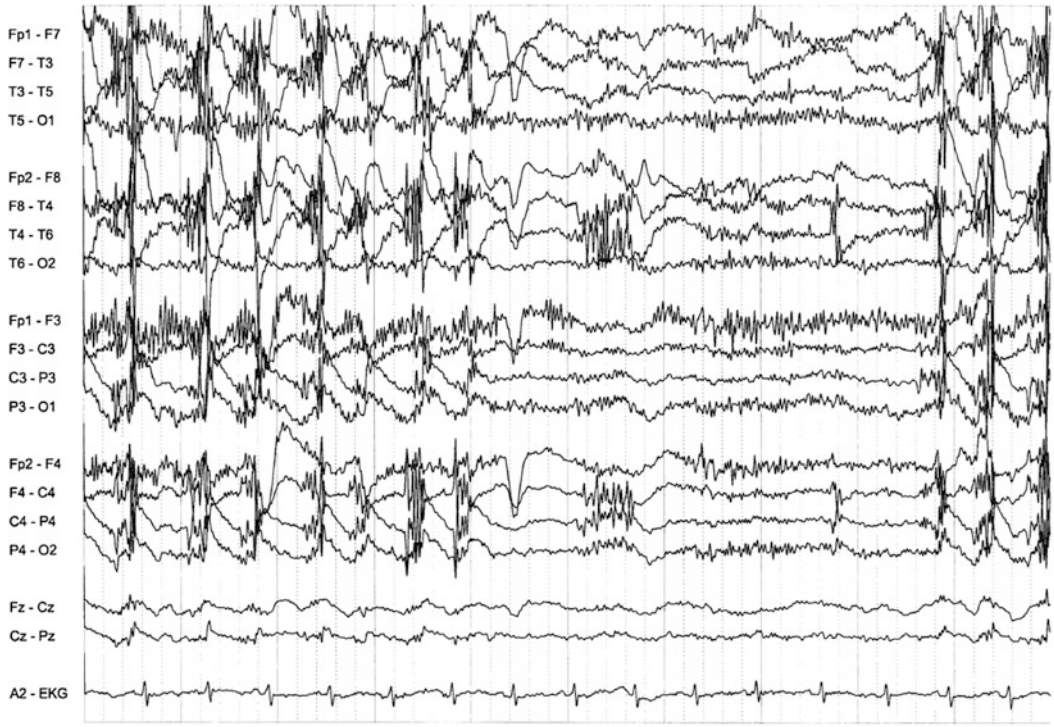
15. Which of the following is the correct order in which the maturational changes in neonatal EEG develop?

A. Awake → Quiet sleep → Active sleep
B. Active sleep → Awake → Quiet sleep
C. Quiet sleep → Active sleep → Awake
D. Active sleep → Quiet sleep → Awake
E. Quiet sleep → Awake → Active sleep

16. Which of the following statements is true regarding distribution of ions across the cell membrane of a neuron?

A. Potassium has a higher intracellular concentration
B. Sodium has a higher extracellular concentration
C. Chloride has a higher extracellular concentration
D. All of the above
E. None of the above

17. What artifacts can be seen in the following image?



A. Blink artifact
B. Chewing artifact
C. Myogenic artifact
D. Lateral eye movement
E. All of the above

18. The channels that play a major role in generation and propagation of action potential in neurons are:

A. Voltage-gated sodium channels
B. Voltage-gated potassium channels
C. Chloride channels
D. Potassium leak channels
E. A, B, and C

19. The major contribution to EEG potentials recorded from scalp comes from:

A. Action potentials
B. Excitatory postsynaptic potentials
C. Inhibitory postsynaptic potentials
D. B and C
E. A and B

20. Which one of the following feature is NOT true about Frontal sharps (also known as Encoches Frontales)?

A. Frequently seen during transitional stage of sleep
B. Initial Negative (200 ms) · Positive phase (longer)
C. Seen between 33 and 46 weeks
D. Usually Asymmetric and Asynchronous
E. Sometimes seen with mixed rhythmic bi-frontal delta

21. Infantile spasms are electrographically associated with:

    A. Burst-suppression pattern
    B. Ripples
    C. Electrodecremental pattern
    D. Electrocerebral silence
    E. RTTBD

22. What is true regarding the polarity of potentials recorded on a scalp electrode?

    A. Superficial EPSPs and deep IPSPs will show the same polarity (negative) on a surface recording electrode
    B. Superficial EPSPs and deep IPSPs will show the opposite polarity (negative and positive, respectively) on a surface recording electrode
    C. Superficial IPSPs and deep EPSPs will show the same polarity (negative) on a surface recording electrode
    D. Superficial IPSPs and deep EPSPs will show the opposite polarity (positive and negative, respectively) on a surface recording electrode
    E. None of the above

23. Which of the following statements is true about neonatal seizures?

    A. Most common etiology—Hypoxic ischemic encephalopathy
    B. Decoupling—Neonates treated with AED continued to have electrographic seizures and stopped clinical seizures
    C. Tonic seizures mostly seen in preterm with intraventricular hemorrhage
    D. Focal seizures with hemiparesis is seen with ischemic infarcts
    E. All of the above

24. Sleep spindles originate from:

    A. Cortex
    B. Midbrain
    C. Thalamus
    D. Any of the above
    E. None of the above

25. Cortical oscillations faster than beta-gamma frequency (ripples or fast ripples):

    A. Have been both described under normal conditions
    B. Have been both described during epileptic seizures
    C. Are always pathologic
    D. Are never associated with epileptic seizures
    E. A and B

26. The intracellular pathophysiological mechanism of an epileptiform discharge is:

    A. Action potential
    B. Depolarization
    C. Hyperpolarization
    D. Paroxysmal depolarizing shift
    E. Presynaptic excitation

27. Focal slow waves are due to:

    A. Thalamic synchronization
    B. Cortical partial deafferentation from subcortical structures
    C. Cortical hyperexcitability
    D. Paroxysmal depolarizing shift (PDS)
    E. Midbrain suppression

28. All of the following reduce the of electrocution except:

    A. Equipments with small leakage current
    B. Connecting people using appliances to the ground
    C. Using short connecting cords
    D. Using one ground per patient
    E. All of the above

29. Choose the incorrect statement regarding "common mode rejection":

    A. Helps to filter out the environmental electrical noise.
    B. Requires the use of a differential amplifier.
    C. Involves exclusion of the signals recorded by both electrodes and amplifying the differences in between.
    D. Is unable to reject the 60 Hz artifact since the latter is also recorded by the ground electrode.
    E. None of the above.

30. The minimal surface area of the postsynaptic action potential required for recording of a spike on scalp EEG is:

    A. 0.6 mm^2
    B. 6 mm^2
    C. 0.6 cm^2
    D. 6 cm^2
    E. None of the above

31. Which of the following statements concerning filter use in EEG is incorrect:

    A. A low-pass filter allows lower frequencies to pass. In usual scalp EEG reading settings, it is set to 70 Hz.
    B. A high-pass filter allows higher frequencies to pass. In usual scalp EEG reading settings, it is set to 1 Hz.
    C. A notch filter can be used to filter out the 50 or 60 Hz noise generated from the city power lines.
    D. Filters in analog EEG devices consist of a resistor–capacitor circuit.
    E. The time constant of a filter determines the half-life of its resistor.

32. Which of the following statements concerning digital EEG machines is incorrect:

    A. They require the use of an additional electrode used as the machine reference.
    B. The signal from each channel is sampled and stored at regular intervals. This sampling rate in most machines ranges from 256 to 1024 Hz.
    C. The Nyquist sampling theorem determines that the sampling rate should at least match double the frequency of the original signal to avoid aliasing.
    D. The ACNS guidelines recommend a sampling rate at 3 times or more the frequency of the original signal.
    E. All of the above are correct.

33. Which of the following statements concerning EEG grounding is correct:

    A. The EEG machine should be connected to a two-pronged hospital grade outlet.
    B. A single ground electrode is placed anywhere on the patient and connects to the appropriate jack in the input jackbox of the EEG machine.
    C. Connecting a grounding wire from the EEG machine to the patient's bed is required for patient safety.
    D. In an ICU patient, each electric device connected to the patient should have separate grounding.

34. A premature infant with apneic spells has an EEG showing frequent multifocal sharp waves. These findings are most consistent with:

    A. Normal finding in this age
    B. Multifocal potential epileptogenicity
    C. Non-specific generalized cerebral dysfunction
    D. Hypsarrythmia
    E. Status epilepticus

35. Changing the filter settings on the EEG allows for all of the following, except:

    A. Passing of signals above a certain frequency.
    B. Exclusion of signals below a certain frequency.
    C. Allowing viewing high-frequency oscillations in intracranial EEG.
    D. Stopping a narrow band of frequencies.
    E. Preferential amplification of epileptiform discharges.

36. If 60 Hz sine wave is sampled at 100 Hz, the result is:

    A. Electromagnetic gain
    B. Digital filtering
    C. Aliasing
    D. Sub-harmonic wave
    E. Amplification delay

37. West syndrome is characterized by:

    A. Myoclonic seizures
    B. Infantile spasms
    C. Absence seizures
    D. Dialeptic seizures
    E. All of the above

38. Which of these options represents an advantage of a bipolar montage over a referential montage:

    A. Ability to detect both local (near field) and distant (far field) potentials
    B. Provides a closer representation of the absolute potential at an electrode
    C. Makes the visual detection of differences in local potential easier
    D. Requires placement of fewer electrodes
    E. All of the above

39. Which of the following is true about neonatal seizures:

    A. Majority of ictal discharges originate in the central regions
    B. Ictal discharges are often generalized, due to immaturity of the brain
    C. Absence seizures are most common
    D. Urgent surgery is the treatment of choice
    E. VNS is usually helpful early-onset infantile spams

Answers

1. (C). The cerebral cortex is organized in six horizontal layers with layer I being the most superficial underneath the pial surface, and layer VI being the deepest overlying the subcortical white matter. Layer IV (Internal Granular Layer) receives input from thalamus.
2. (A). At a gestational age below 30 weeks, the EEG activity consists of burst of mixed frequency (mostly delta) in a discontinuous fashion interspaced with periods of EEG attenuation lasting for few seconds to 1–2 min. The higher amplitude of the bursts occurs in the posterior region This EEG pattern is referred as to trace discontinue. At this age, there is no distinction between sleep and awake states.
3. (B). GLUT1 deficiency syndrome is caused by impaired glucose transport across the blood–brain barrier and is linked to low CSF glucose levels. Clinically, patients present with acquired microcephaly, and early-onset epilepsy that is refractory to standard AEDs. Most patients carry mutations of the SLC2A1 gene. The ketogenic diet is the treatment of choice as conventional AEDs are not effective.
4. (B). The resting membrane potential of a neuron is typically −70 mV, the inside of the neuron being negative in relation to the outside. The resting membrane potential is determined by movement of potassium, sodium, and chloride ions along their electrochemical gradient across the cell membrane.
5. (B). Epileptic spikes are most commonly surface negative. However, on occasions

where the spike is generated in a sulcus perpendicular to the scalp, the dipole will be parallel to the scalp and surface positivity can be recorded. Positive epileptiform discharges are also seen after brain surgery and in infants with germinal matrix hemorrhage.

6. (E). Canavan disease like all leukodystrophies affects the white matter. Since Canavan disease affects diffusely the white matter, it typically produces diffuse EEG slow activity such as polymorphic delta activity.
7. (D). Benign myoclonic epilepsy of infancy is a rare disorder occurring in children between the age of 5 months to 5 years. Males are more affected than females, and a family history of febrile seizures or epilepsy is present in 30–40% of cases. Myoclonus is the most common seizure type followed by absence and generalized tonic–clonic seizures. EEG can be normal but most commonly show generalized polyspike-and-wave discharges and valproate is the treatment of choice. Overall development is usually normal except for some learning disability.
8. (D). Dravet syndrome is a form of severe infantile-onset epilepsy that usually presents between 5–15 months of age with generalized, hemiclonic convulsions, or status epilepticus. Common triggers include acute illness, fever, or vaccination. Development is initially normal but then regresses slowly afterward. Majority of patients (>70%) have de novo mutations in the voltage-gated sodium channel gene, SCN1A. Seizures are worsened by sodium channel modulating drugs such lamotrigine. The ketogenic diet is a common treatment modality but the overall outcome is typically poor. The term GEFS+ originally called generalized epilepsy with febrile seizures plus but now has been revised to genetic epilepsy with febrile seizures plus (as some patients also have partial seizures). The GEFS+ spectrum includes several entities ranging from typical febrile seizures at the mild end, patients with fever related seizures persisting beyond 5 years of age to myoclonic-astatic epilepsy, some cases of temporal lobe epilepsy to Dravet Syndrome at the severe end of this spectrum. Seizures include absence, myoclonic, atonic, and generalized tonic–clonic and tend to lessen by late childhood and adolescence. 10% of familial GEFS+ cases have mutations in the SCN1A gene; a few have GABA channel mutations in the GABRG2.
9. (C). Equilibrium potential for an ion is the membrane potential at which there is no net movement of that ion across the cell membrane. Equilibrium potential for an individual ion can be calculated using the Nernst equation. The membrane potential at which there is no net flow of ions across the cell membrane is the resting membrane potential which can be calculated using the Goldman–Hodgkin–Katz equation which takes multiple ions into account. The Henderson–Hasselbalch equation describes the derivation of pH as a measure of acidity.
10. (E). The clinical picture is typical of benign familial neonatal seizures. This condition has been linked to mutations of the KCNQ2 or KCNQ3 gene, encoding for a voltage-gated potassium channel that has a major role in regulating neuronal excitability.
11. (C). The recommended length of a neonatal EEG recording is 60 min. In a full-term neonate, this will allow the sampling of all the neonatal sleep stages that approximately include 25 min of active sleep, 20 min of quiet sleep, and 15 min of intermediate sleep. Neonatal EEG recording during wakefulness has a low yield due to excessive artifacts. Unlike neonates, adults have a typical sleep cycle of 80–120 min.
12. (B). The short spike at F7 from the lateral rectus muscle is immediately followed by a positive phase reversal resulting from the positive charge of the cornea moving closer to the electrodes on the left.
13. (B). Sleep spindles are formed at the age of 1–3 months in term infants, maximal in the

central regions. They are initially bilateral but asynchronous until the age of 2 years when they become synchronous.

14. (C). By convention, if the difference in potential between two electrodes is negative, then it is represented by an upward deflection.
15. (B). EEG maturational changes occur first in active sleep, EEG maturational changes occur first in active sleep; after a lag of about 2 weeks the awake periods start showing more mature patterns. Quiet sleep is the last stage to show more mature changes. For this reasons, the abnormalities are most frequently seen in the quiet sleep phase.
16. (D). Sodium and chloride ions have a higher extracellular concentration while potassium concentration is higher in the intracellular compartment.
17. (E). The rhythmic myogenic artifact in the first four and last one-second represent chewing artifact. In addition, isolated myogenic artifact can be seen in seconds 7–8–9, blink artifact can be seen in second 5, and lateral eye movement to the left on second 7 of this epoch.
18. (A). The voltage-gated sodium channels play a major role in generation and propagation of action potential by allowing sodium to enter into the soma.
19. (D) A large number of EPSPs and IPSPs generated in a complex network of neurons generate an extracellular field potential that changes over time which is believed to be the basis of potentials recorded on EEG.
20. (D). Frontal sharps (or Encoches Frontales) are blunt isolated biphasic broad sharp transients (0.5–0.75 s) seen in the frontal region. They are usually symmetric and synchronous, frequently seen in transitional stage of sleep, between 33 weeks–46 weeks PCA with peak around 35 weeks. If consistently absent or asymmetrical on one side, structural lesion on the that side will be highly suspected.
21. (C). Infantile spasms are brief epileptic tonic contractions affecting infants and children, seen in West syndrome. The interictal correlate of infantile spasm is the chaotic hypsarrhythmia with seizures consisting of electrodecremental pattern.
22. (A). The polarity of extracellular field potentials recorded by surface electrodes on EEG depends on the direction of the current flow as well as on the position of the electrode relative to the location of the generator. Thus, superficial EPSPs and deep IPSPs will show the same polarity (negative) on a surface recording electrode. Likewise, superficial IPSPs and deep EPSPs will show the same polarity (positive) on a surface recording electrode. Therefore, orientation of neurons and their processes as well as location of synaptic contacts with respect to the cortical surface are important determinants of extracellular field potentials recorded by EEG electrodes.
23. (E). Most common etiology of neonatal seizures is hypoxic ischemic encephalopathy. Tonic seizures are typically seen in preterm neonates with intraventricular hemorrhage and focal seizures with hemiparesis are typically seen in neonates with ischemic infarcts.
24. (C). Sleep spindles (7–14 Hz) originate from the thalamus and are considered to be the first signs of EEG synchronization during early stages of sleep. The reticular nucleus of the thalamus is regarded as the pacemaker of the spindles.
25. (E). Episodes of cortical oscillations (100–600 Hz) called ripples (100–200 Hz) or fast ripples (>200 Hz) have been described both under normal conditions and epileptic seizures. Ripples probably reflect synchronized IPSPs whereas fast ripples appear to represent bursts of population spikes.
26. (D). The paroxysmal depolarizing shift (PDS) is an intracellular mechanism that is not recorded by scalp EEG. It represents the intracellular electrophysiological correlate of focal epileptiform discharges such as sharp waves and spikes. It consists of abnormal synchronous activation of multiple neurons at the cellular level causing a wave of depolarization. It is primarily due

to the activation of high-frequency fast sodium channel potentials.

27. (B). Slow activity (slowing) is a function of white matter disturbance while voltage or amplitude reduction (attenuation) is a function of cortical disturbance. The mechanism of focal slowing is likely due to partial cortical deafferentation from subcortical structures. This could be due to functional or anatomic deafferentation of the cortex as may be seen in toxic-metabolic encephalopathies or structural brain lesions.
28. (B). Small leakage currents, short cord connections, people not connected to the ground, high-resistant contacts (dry skin), and one common ground are all measures that minimize the risk of electrocution.
29. (D). The differential amplifier can reject the 60 Hz artifact as long as it is recorded equally by both electrodes in each channel. If there is significant difference in the impedance between two electrodes, then the 60 cycle signal will be recorded unequally and the artifact will appear on the EEG.
30. (D). The postsynaptic action potential should involve at least 6 cm^2 of cortex to be detected as an epileptiform discharge on scalp EEG.
31. (E). The time constant equals the time needed to discharge the capacitor in the circuit to 36.8% of its initial full charge. Its value is inversely related to the frequency that will pass through the filter.
32. (C). If the sampling rate falls below a certain point, the resulting waveform would no longer represent the original one (aliasing). Per the Nyquist sampling theorem the sampling rate should be at least twice the frequency of the original signal to avoid aliasing.
33. (B). A three pronged hospital grade outlet should be used. There is no need to connect the EEG machine to the bed. When a patient is connected to more than one electrical device a common ground should be utilized.
34. (C). In neonatal EEGs, multifocal epileptiform discharges (spikes or sharp waves) do not necessarily imply potential epileptogenicity like in adults. In prematures, multifocal sharp transients can be normal when they are rare and random. When multifocal discharges are frequent as in this case, they are often indicative of non-specific encephalopathy.
35. (E). It is not possibly to preferentially "filter in" epileptiform discharges. At best, filters allow to remove some artifacts to allow for easier visual detection of epileptiform discharges.
36. (C). The Sampling Theorem states that if a signal contains component frequencies ranging from 0 to fN, then the minimum sampling frequency that can be used for a digitized data to adequately represent the frequency content of the original signal is 2 fN called the Nyquist frequency (equal to two times of the original frequency sampled). Aliasing refers to the distortion of a signal caused by sampling frequency lower than the Nyquist frequency. In this case, to avoid aliasing, a minimal sampling rate of 120 Hz is needed.
37. (B). West syndrome consists of a triad of infantile spasms, developmental delay, and a grossly abnormal EEG pattern termed hypsarrythmia. It usually affects infants between the ages of 4–8 month. In the majority of cases, West syndrome is associated with serious neurological abnormalities being genetic, structural, metabolic, or infectious.
38. (C). In a bipolar montage, external noise can easily be canceled out as it measures the difference in potential between adjacent electrodes and hence amplifies local potentials.
39. (A). Neonatal seizures often arise from the central region followed by the temporal region. In the exception of myoclonic seizures, all neonatal seizures are unifocal or multifocal at onset, frequently associated with an abnormal EEG background.

Part II
The Abnormal EEG

Ictal and Interictal EEG

5

Mohamad Z. Koubeissi and Nabil J. Azar

Interictal Epileptiform Discharges

Interictal Epileptiform Discharges (IEDs) refer to electrographic patterns seen commonly in individuals with high predisposition for epileptic seizures. Since such waveforms may be present in individuals without seizure disorders [1], the significance of IEDs varies in light of the patient's history and other diagnostic tests. In patients with epilepsy, an initial routine EEG detects epileptiform discharges in about 50% of times. After four routine EEGs, this yield increases to over 90%. Temporal lobe epilepsy tends to be commonly associated with IEDs while frontal lobe epilepsy is least associated with IEDs on scalp EEG.

Focal spikes on scalp EEG are sharply contoured waveforms with durations between 20 and 70 ms. Sharp waves, on the other hand, are similar morphologically except that their duration is longer than 70 ms [2]. There is no clinical significance to this distinction, and it is a mere morphological descriptor. The physiologic basis of a focal epileptiform discharge is the paroxysmal depolarizing shift (PDS).

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The main features of focal spikes/sharp waves are the following:

(1) They are distinct from the background. That means that they are not part of a preceding rhythm, like wicket spikes. Rather, they have an amplitude large enough to stand out from the background, and appear to abruptly arise from a morphologically different background.
(2) They are often followed by a slow wave.
(3) They tend to disrupt the background. The sharply contoured component is often followed by an irregular, slow EEG that is different from the preceding EEG. Thus, even if the sharply contoured component is hidden, the reader may still be able to tell that a disruptive event has just taken place based on the aftergoing EEG.
(4) On scalp EEG, IEDs are often surface negative. Exceptions may occur in individuals who have undergone craniotomy; in whom, spikes may occasionally be positive (Fig. 5.1). Also, infants with intraventricular hemorrhage or periventricular disease may have positive spikes in the central region, the significance of which is encephalopathy rather than propensity for epilepsy [3].
(5) The slopes of The IED are often asymmetrical. The initial, negative component is typically the steepest, followed by a slower positive component with larger amplitude.
(6) IEDs have a field that often extends over a few electrodes. If a relatively high-voltage sharply contoured waveform is seen only on

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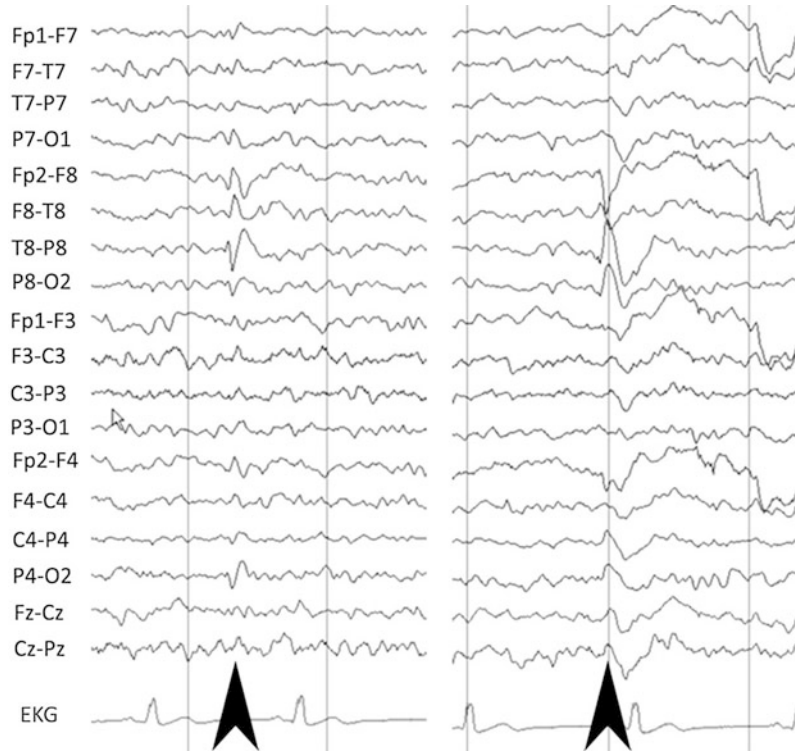

Fig. 5.1 Two spikes (*arrowheads*) from the same patient who had undergone right frontotemporal resection preserving the hippocampus for intractable epilepsy without resolution of seizures. The first spike is positive over the right mid-temporal region, while the other is negative

one contact, but not on neighboring ones, it is often more suggestive of an artifact.

The clinical significance of IEDs of different locations is not the same [4]. For instance, seizures occur in 90% of children with anterior temporal spikes, but in only 40% of those with rolandic spikes or occipital spikes. Occipital spikes can be seen in migraine [5] or in children with congenital blindness [6].

In Benign Epilepsy with Centrotemporal Spikes (BECTS), or Benign Rolandic Epilepsy, spikes are equally negative over the central and temporal derivations with the positive end of the dipole appearing typically in the frontal regions.

Multifocal IEDs referred to spikes or sharp waves are seen independently on both sides. These are often associated with background slowing and the vast majority of patients have seizures, with generalized seizures being very common. In addition, seizure frequency is often very high and medical intractability common. Frequent comorbidities of individuals with multifocal IEDs include cognitive and motor deficits.

Periodic Lateralized Epileptiform Discharges (PLEDs)

As the name implies, PLEDs (also known as Lateralized Periodic Discharges or LPDs) are IEDs that occur on one side on the brain at regular intervals of 0.3–4 s (Fig. 5.2). They are commonly seen in acute brain injury such as herpes encephalitis and stroke, among others. They can also occur for prolonged periods of time after focal status epilepticus. In addition, they can be seen in toxic encephalopathies, including aminophylline or alcohol intoxication. PLEDs can occur in individuals with marked encephalopathy as well as in ones who at their baseline mental status. Half of all patients with PLEDs will have seizures. When PLEDs are associated with low amplitude, high-frequency

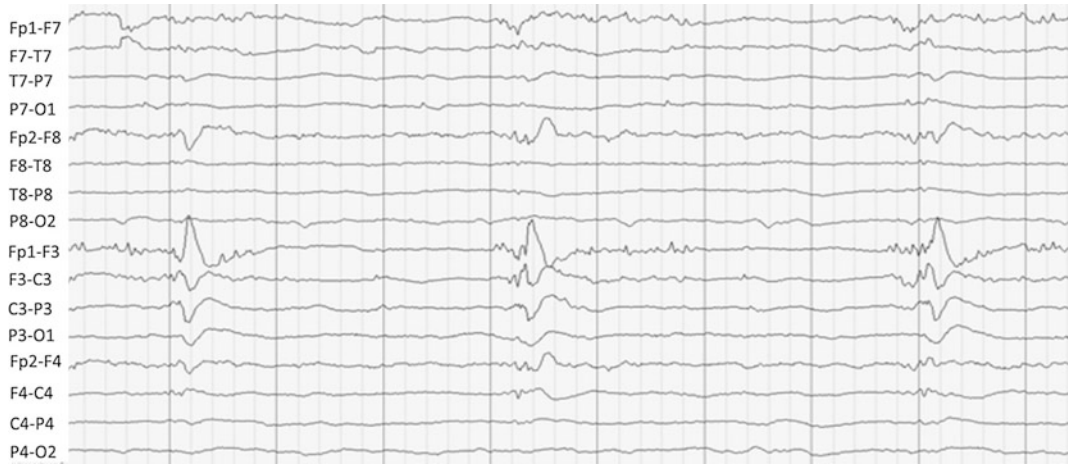

Fig. 5.2 Periodic lateralized epileptiform discharges (*PLEDs*) over the *left* frontal region in an adult patient after resolution of prolonged focal status epilepticus over the same region

rhythmic discharges, often appearing superimposed on or after the sharply contoured waveform, they are termed PLEDs plus and have increased significance for predicting seizures.

BiPLEDs are PLEDs that occur independently on either side of the brain. They occur in individuals with severe brain disease and are associated with a poor prognosis. Multifocal PLEDS refer to 3 or more foci of PLEDs involving both sides of the brain. They are associated with multifocal lesions or severe diffuse brain disease. The majority of patients with multifocal PLEDS have seizures.

Temporal Intermittent Rhythmic Delta Activity (TIRDA)

TIRDA refers to intermittent rhythmic activity of 1–3 Hz frequency occurring over the anterior-to-mid temporal derivations on one side. The duration of the train varies, often lasting for approximately 5 s. The presence of TIRDA is as significant for temporal lobe epilepsy as temporal IEDs are. Indeed, concomitant depth and scalp electrode recordings have shown that TIRDA correlates with intracranially recorded mesial temporal spikes.

Generalized IEDs

The 3-Hz spike-and-wave discharges are the EEG signature of absence epilepsy, often presenting in bursts lasting 1–3 s, and typically activated by hyperventilation. They are often bilaterally synchronous and have a generalized field, typically appearing maximum over the frontal and midline derivations. However, variations of the field of generalized IEDs are not uncommon. Occasionally, some asynchrony or asymmetry may be noted, but often such asymmetries (referred to as fragments of generalized epileptiform discharges) shift in the same record. Phase reversals of the spike components may be seen over F3 and F4 contacts. Although brief runs of 3-Hz spike-and-wave discharges may appear asymptomatic, detail assessments revealed that even brief runs may interfere with continuous motor tasks [7].

In other idiopathic generalized epilepsy syndromes, such as JME, the spike or polyspike-and-slow wave complexes often present in runs of faster frequencies, typically 4–6 Hz, and also occur singly (Fig. 5.3). Atypical generalized spikes may occur as part of other generalized epilepsies. These are medium to high

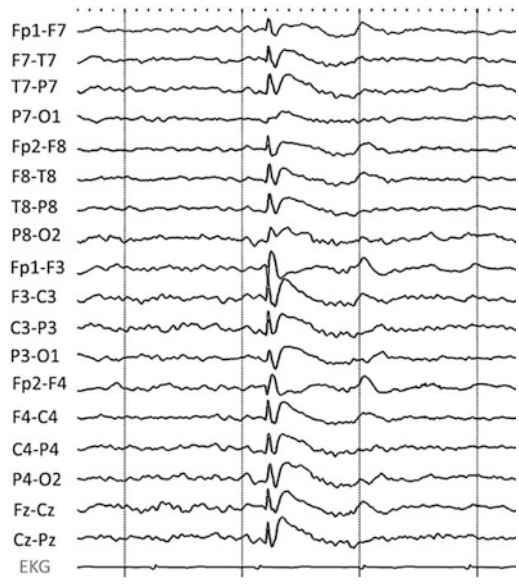

Fig. 5.3 Spike-and-slow wave complex in a patient with JME. Note the phase reversals over F3 and F4

voltage without a prominent after going slow-wave component and may occur singly. They are best seen with a referential ear montage.

Slow spike-and-wave complexes present with a frequency that is slower than the 3-Hz pattern of absence epilepsy. They are a typical electrographic feature of Lennox-Gastaut syndrome. Their typical frequency is around 1.0–2.5 Hz, with wider (less spiky) sharp component than in absence epilepsy. Sleep activates trains of such slow complexes in the extent that they may appear continuous as in electrical status epilepticus during sleep (ESES).

PhotoEpileptiform Discharges (Photoparoxysmal Response)

Photoepileptiform discharges are IEDs that are elicited by photic stimulation. The elicited discharges can be generalized (most common), bilateral posterior, or unilateral predominant (least common). They may occur within the photic stimulation drain or outlast it. When they outlast photic stimulation and are self-sustaining, they may have a higher association with epilepsy, although this is debatable. Up to three out of four patients with photo epileptiform discharges have seizure disorders. Individuals with bioccipital discharges have the least association with epilepsy. These discharges are often part of primary generalized epilepsy and rarely focal epilepsy. Interestingly, occipital spike-and-slow wave discharges may be scotosensitive, i.e., elicited by darkness rather than light and may occur as part of benign epilepsies as well as such mitochondrial disorders as myoclonic epilepsy with ragged red fibers (MERRF) [8].

Ictal EEG

Recording the ictal EEG is an essential part of the surgical evaluation of patients with intractable epilepsy [9]. In such patients, it is important that the recorded seizures are semiologically typical of the patient's habitual episodes before surgical decisions are made. In addition, recording the patient's habitual episodes is essential for characterization of paroxysmal events in individuals with questionable nonepileptic episodes.

Ictal EEG represents a clear deviation from the baseline of a pattern that shows some evolution. By evolution, it is meant that the pattern changes in terms of its frequency, amplitude, field, or morphology as the seizure occurs. This applies most typically to focal seizures, especially temporal lobe seizures, but may start with a semi-rhythmic delta activity over one temporal region and soon evolves into a theta range spike discharge over the same distribution that is typical of mesial temporal generators. However, even in generalized epilepsies, such as absence epilepsy, an evolution pattern can be noted whereby the initial frequency of the spike-and-slow-wave discharge is higher than 3, often 3.5 Hz, whereas toward the end of the burst, the frequency slows down to 2.5 Hz.

Ictal EEG in Focal Epilepsy

Only 22% of all focal seizures that are not associated with alteration of consciousness (formerly named simple partial seizures) have an EEG correlate. In the subset of such seizures where a motor component is present, the electrographic yield increases to 33% versus only 15% of those that have no motor manifestations [10]. On the other hand, seizures that are associated with alteration of awareness (dyscognitive seizures, formerly termed complex partial seizures) are almost always associated with EEG changes. Rare exceptions may apply to seizures originating from the parietal or frontal lobe [11]. When ictal discharges are present in seizures that do not cause alteration of awareness, they are morphologically indistinguishable from focal ictal discharge in dyscognitive seizures, manifesting as focal repetitive spike discharge, low-voltage fast activity, or focal rhythmic slowing, among others. In general, when the ictal discharge consists of fast frequencies, it indicates proximity of the recording electrode to the seizure focus. On the other hand, slow discharges, for example in the delta range, typically represent propagated activity from distant sites.

In temporal lobe epilepsy, simultaneous scalp and depth electrode recordings show that no scalp EEG changes are seen when seizure discharges are limited to the hippocampus (Fig. 5.4). As the seizure propagates outside of the mesial temporal structures into neocortical regions, it is then detected by scalp EEG. A 5–9-Hz temporal ictal discharge is highly associated with seizures of hippocampal onset (Fig. 5.5) [12], while neocortical seizures often are associated with polymorphic, 2–5-Hz On the other hand, seizures originating at the temporal neocortex are often associated with irregular, polymorphic, 2–5-Hz ictal discharge (Figs. 5.6 and 5.7). The main use of sphenoidal electrodes is not only to increase the overall yield of detecting epileptiform EEG abnormalities, but also to further localize interictal and ictal discharges. For example if a discharge is of higher voltage over the sphenoidal electrodes than mid-temporal electrodes (T3 or T4), it signifies more inferior and mesial origin, whereas the opposite scenario suggests a lateral neocortical origin.

In extratemporal lobe seizures, a fast-frequency ictal discharge may be more common than in temporal lobe epilepsy, but, in general, extratemporal seizures are not associated with a clear ictal discharge as often as seizures of temporal origin [11]. For example, only half of frontal lobe seizures have a localizing EEG pattern [13]. Similarly, parietal lobe seizures often have no clearly localizing EEG [14]. Occipital lobe seizures commonly show an ictal discharge over the occipital region. Both occipital and parietal lobe seizures tend to propagate to the temporal lobes, where seizures become semiologically and electrographically indistinguishable from temporal lobe seizures. Occipital lobe seizures can also propagate to frontal and insular regions.

Ictal EEG in Generalized Epilepsy

In generalized seizures, the earliest clinical and EEG changes typically are not lateralizing and indicate diffuse brain involvement [15]. A more recent definition of generalized seizures is "seizures originating at some point within, and rapidly engaging, bilaterally distributed networks. These networks can include cortical and subcortical structures, but do not necessarily involve the entire cortex," and "they can be asymmetric" [16]. In idiopathic generalized epilepsies, the baseline EEG is within normal limits, and the interictal epileptiform and ictal discharges are typically bilateral and maximal over the frontal head regions. In contrast, the EEG background is slow in symptomatic generalized epilepsy.

Idiopathic Generalized Epilepsy

The ictal discharge has an abrupt onset and termination, and, although widespread, it is often maximum over the frontal regions with phase reversals seen over F3 and F4. In absence seizures, rhythmic spike-and-slow-wave runs that

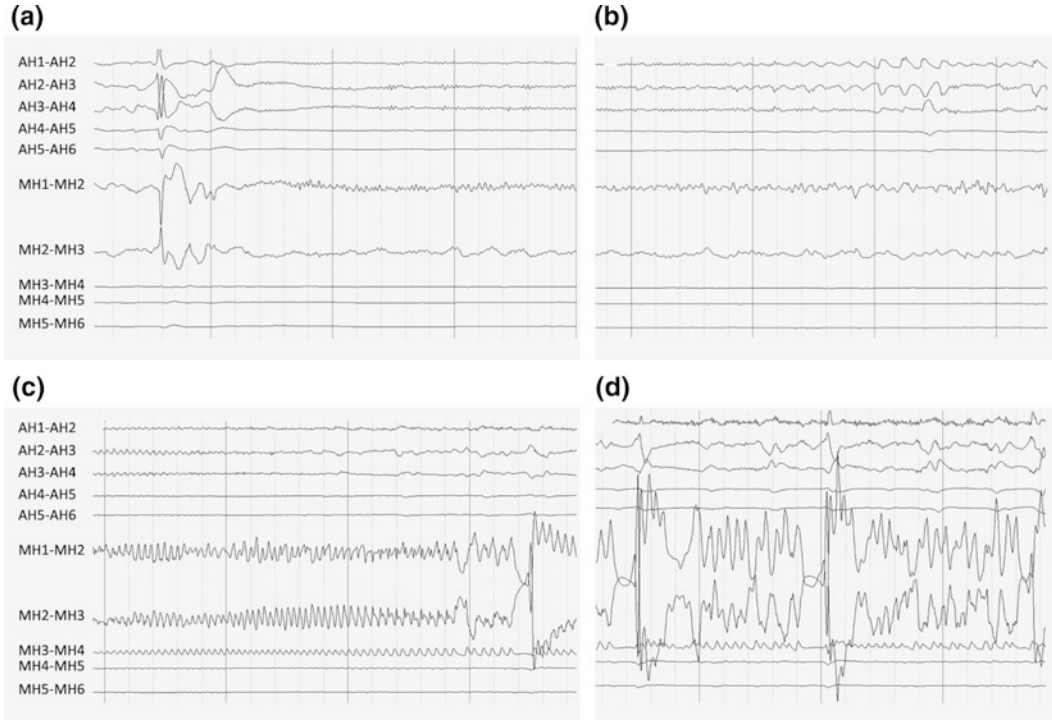

Fig. 5.4 *Right* hippocampal ictal discharge from the same patient in Fig. 5.1 recorded with depth electrodes. **a** Note the initial high-voltage spike that marks the seizure onset, followed by high-frequency low-voltage activity. **b** Evolution of the seizure with slower rhythms now seen in the anterior hippocampus. **c** Further evolution 25 s later, with highly organized ictal discharge in the middle hippocampus. **d** Further evolution 40 s later. Note the amplitude discrepancy between MH2 and MH3, 4, and 5, despite the proximity of these electrodes to one another (5-mm inter-electrode distance), which reflects the closed-field nature of the hippocampus and the importance of recording with depth electrodes in order to detect its activity. *AH* anterior hippocampus; *MH* middle hippocampus

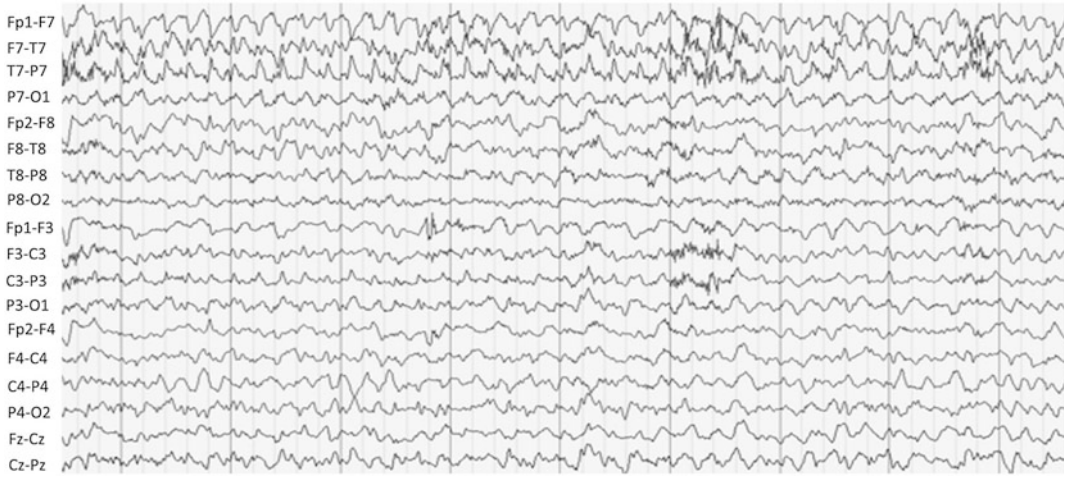

Fig. 5.5 Theta-range *left* temporal ictal discharge

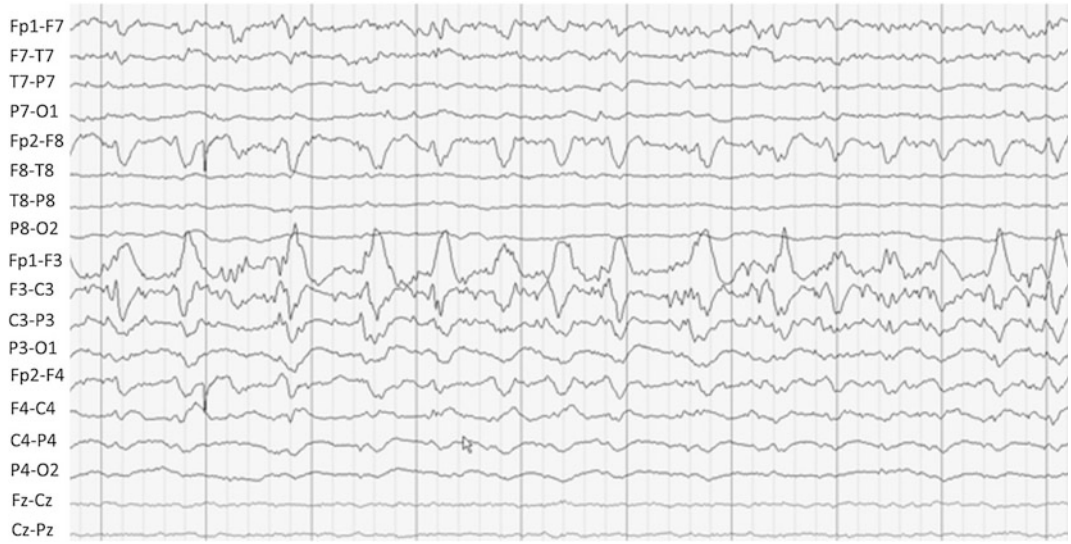

Fig. 5.6 *Left* frontal seizure from the same patient with PLEDs in Fig. 5.2

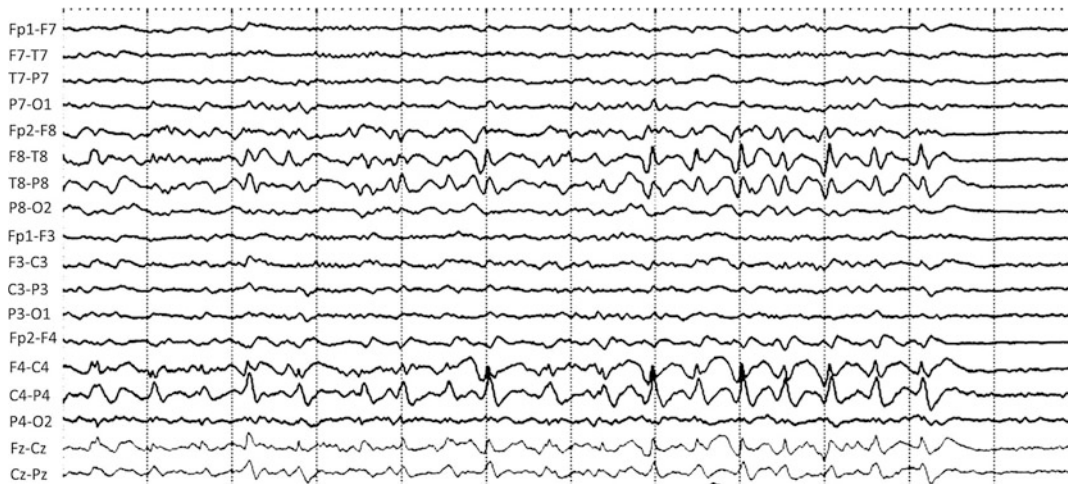

Fig. 5.7 *Right* hemispheric seizure in a patient who presented with acute stroke and altered mental state that prompted an EEG to rule out subclinical seizures

last longer than 3 s often have clinical correlates and may be termed "ictal" as opposed to shorter runs, often termed: "interictal". However, due to the difficulty of assessing subtle, brief alteration of awareness, and the distinction between interictal and ictal is not straightforward. If absence seizures are associated with automatisms, they are called complex absence seizures [17]. The classic ictal pattern of childhood absence epilepsy is that of 3/s spike-and-slow-wave complexes, usually starting at 3.5 Hz and ending at 2.5 Hz. Occasionally polyspikes may be seen.

In juvenile myoclonic epilepsy (JME), bursts of diffuse, bi-frontal maximum polyspike-and-slow-wave discharges are seen interictally or with myoclonic jerks. These are typically faster than in absence epilepsies,

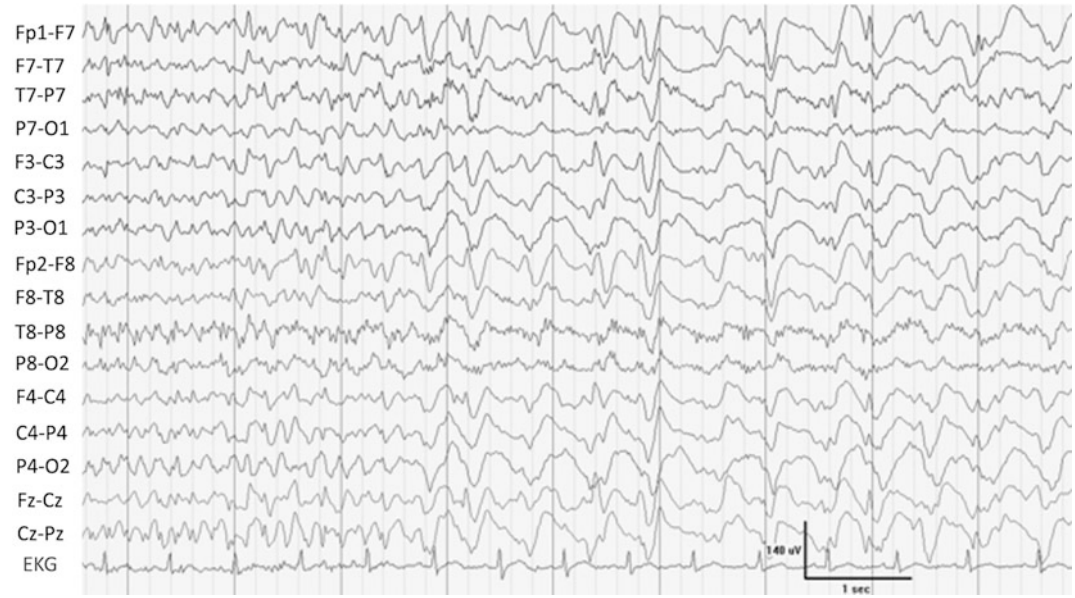

Fig. 5.8 Baseline EEG in LGS syndrome

commonly around 5–6 Hz. One third of individuals with JME show a photoparoxysmal response. An ictal discharge of 10–16 Hz frequency can be seen in association with some myoclonic seizures. When absence seizures occur in individuals with JME, they manifest electrographically as 3-Hz spike-and-slow waves, like in other absence epilepsies.

Tonic seizures are often associated with voltage attenuation with superimposed high-frequency activity of 20–40 Hz. In tonic–clonic seizures, this pattern evolves to patterns with higher amplitude with slower frequencies, followed by yet a slower pattern with intermittent slow waves. Another ictal pattern in tonic–clonic seizures is that of initial fast activity of about 10 Hz that gradually increases in voltage before it starts mixing up with rhythmic slow waves yielding polyspike-and-slow wave complexes [17]. What marks the switch from the tonic to the clonic phase of the seizure is when the slow-rhythm frequency reaches 4 Hz. Clonic jerks correspond to bursts of multiple spikes separated by a slow wave that corresponds to the brief muscle relaxation. Longer postictal phases can be expected after longer seizures and in younger individuals.

Symptomatic Generalized Epilepsies

The ictal discharge in symptomatic tonic–clonic seizures is similar to that of idiopathic generalized seizures. Tonic seizures are typically associated with an electrodecremental pattern or paroxysmal fast activity of 10–25 Hz frequency. This is often followed within 5 s by sharp-and-slow wave complexes. The vast majority of such discharges are bilateral and frontal maximum.

Atypical absence seizures often occur in patients with developmental and cognitive delay and are one seizure type in Lennox-Gastaut syndrome (LGS), which also includes tonic seizures, atonic seizures, and myoclonic seizures. The EEG in LGS is marked generalized, frontal maximum slow spike-and-slow waves (1.5–2.5 Hz) (see Fig. 5.8). Tonic, as well as atonic,

seizures are associated with a low-voltage fast pattern. As mentioned previously, the baseline EEG is slow and disorganized.

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EEG and Semiology in Generalized Epilepsies

6

Nandakumar Bangalore-Vittal

Classification of generalized epilepsies is based on seizure semiology, combined with EEG and appropriate personal and family history. This can help categorize patients into various generalized epileptic syndromes, enhance pathophysiologic understanding, optimize patient care, and provide prognostic implications.

1. For the purpose of discussion in this chapter, the proposed ABPN content outline for seizure classification (based on semiology) will be followed [1].
   Generalized seizures are divided as follows:

   A. Tonic–clonic
   B. Absence

      a. Typical
      b. Atypical
      c. Absence with special features

         i. Myoclonic absences
         ii. With eyelid myoclonia

   C. Myoclonic

      a. Myoclonic
      b. Myoclonic–atonic
      D. Clonic
      E. Tonic
      F. Atonic

Generalized Tonic–Clonic Seizures [1–4]

Primary generalized tonic–clonic seizures are seen in juvenile absence epilepsy, juvenile myoclonic epilepsy, epilepsy with generalized tonic–clonic seizures only, as well as in provoked seizures, including alcohol withdrawal seizures. The semiology discussed below is mainly based on observations in the video-EEG setting.

(i) The entire tonic–clonic event typically lasts 1–2 min and patients have no recollection of the event.

Prodrome: This is a state where some patients might feel a sense of uneasiness, irritability, or difficulty concentration and occur hours to a day before the actual seizure.

Tonic phase:

- Brief flexion spasm of axial and arm muscles is associated with the loss of consciousness. Involvement in respiratory muscles leads to vocalization (the ictal cry), and patients become apneic. During the initial closing of the jaw, tongue biting can happen, more commonly on the side of the tongue or the inner cheek. The normal position of the tongue does not include protrusion for biting to affect the

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tip. Falls can occur if the patient is standing. The eyes move up and the pupils dilate. Autonomic signs consist of increase in heart rate and blood pressure, sweating, and tracheobronchial secretions. Foaming at the mouth can occur due to involvement of the glottic muscles and prolonged seizures can cause cyanosis.

Clonic phase:

- Starts as a tremor, progressing to 4 Hz activity (which denotes the onset of the clonic phase) and slower. This phase involves cycles of inhibition interspersed by brief muscle activity. Each spasm is associated with pupillary contraction and dilation.

Post-ictal state:

- Respiratory activity resumes with slower and deeper phases at times mimicking deep sleep with snoring. The muscles are relaxed, including the sphincters, which can lead to bowel or bladder incontinence. Variable degrees of confusion typically follow the period of stupor or sleep. Headache, generalized body, or muscle aches are also commonly reported. The entire postictal state can last minutes to hours and is proportional to the duration of the seizure and the age of the patient, lasting longer in children. Focal face or limb weakness (Todd's paresis) is less common than in secondary generalized seizures.

Trauma from falls on hard objects, tongue biting, vertebral compression fractures, aspiration pneumonia, and neurogenic pulmonary edema can occur. The last complication in addition to central apnea and cardiac arrest can play a role in sudden unexplained death in epilepsy or SUDEP [5].

(ii) **EEG correlation:** (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8)

- Interictally waking EEG is often normal and the yield of interictal epileptiform discharges is increased by hyperventilation and sleep. Photosensitivity (photic-stimulus-induced generalized epileptiform discharges) can be seen in up to 25 % of cases where there is also a family history of epilepsy.

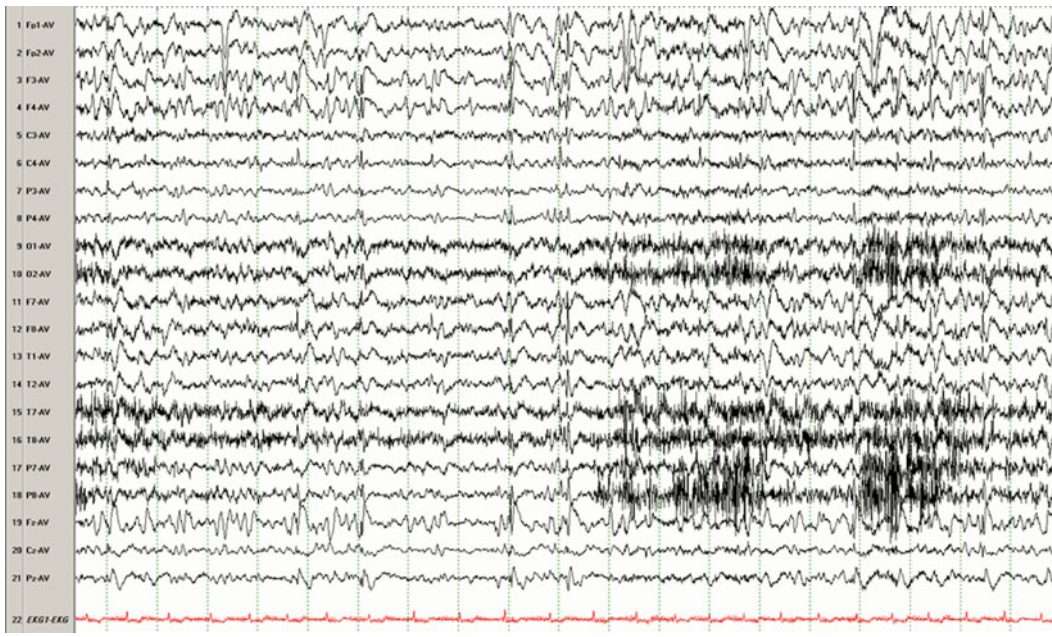

Fig. 6.1 A generalized tonic-clonic seizure each EEG clip represents 20 s

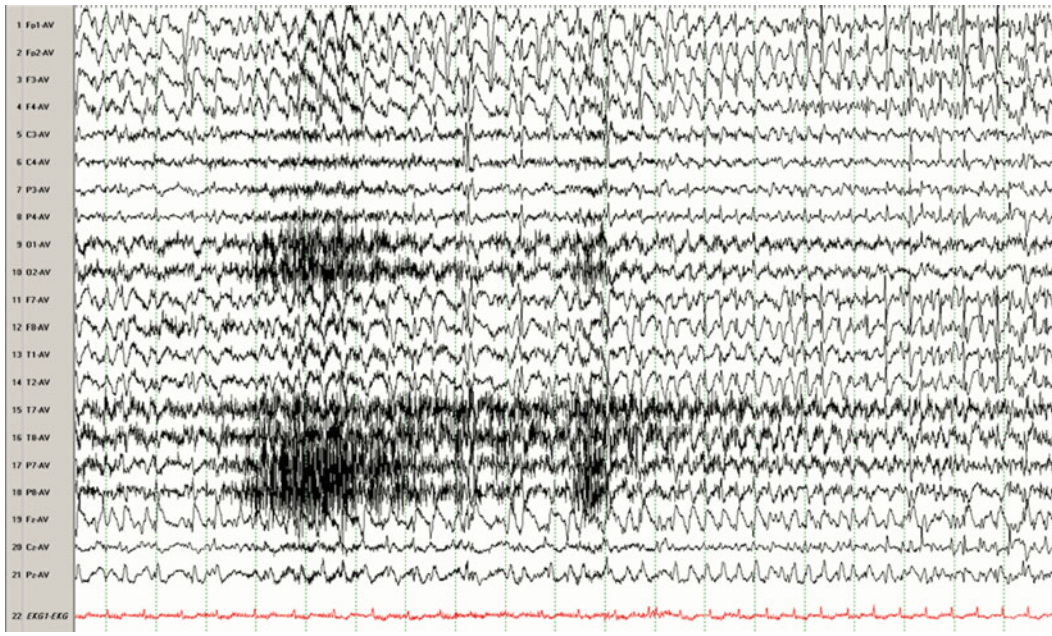

Fig. 6.2 Representation of ictal discharge during generalized tonic–clonic seizure which lasted for 1 min and 45 s. Figure 6.1 shows generalized spike-and-wave discharges that gain rhythmicity as shown in Fig. 6.2

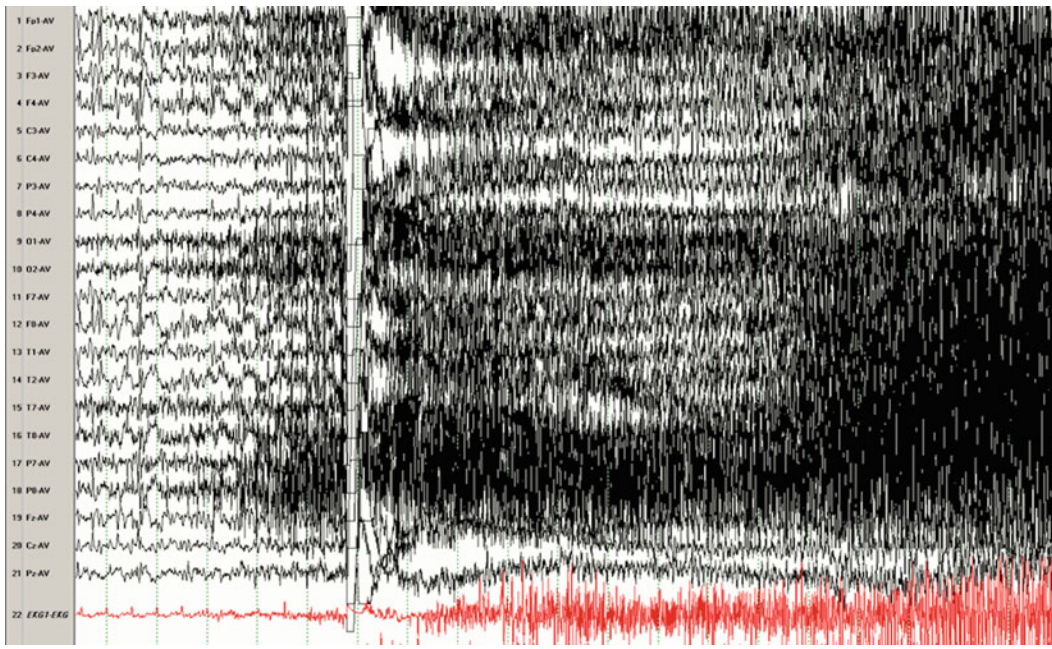

Fig. 6.3 Generalized myogenic artifact obscuring most cerebral activity

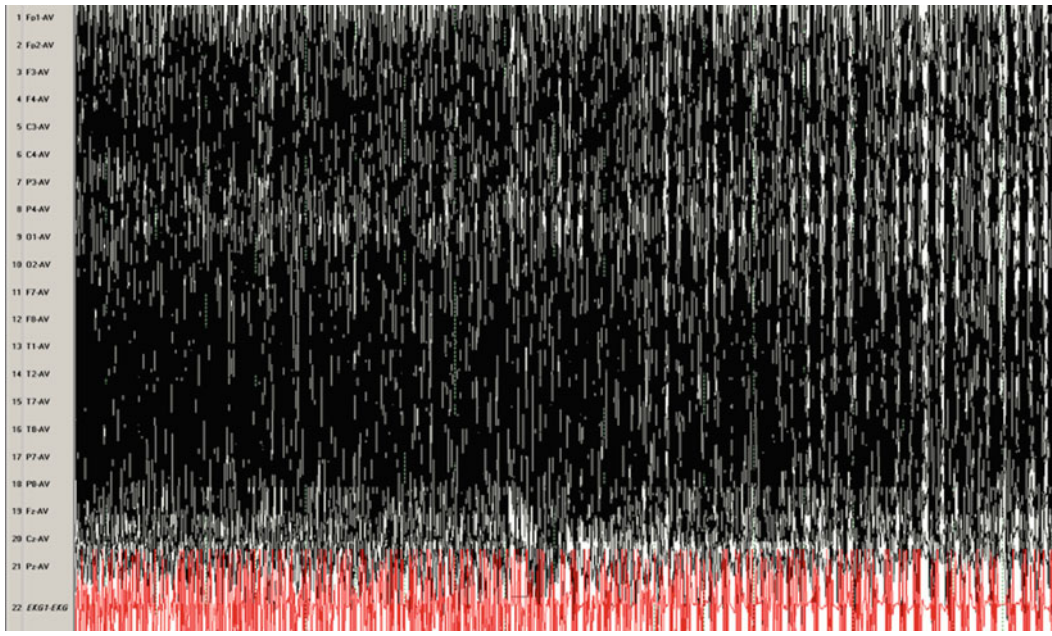

Fig. 6.4 Generalized clonic activity

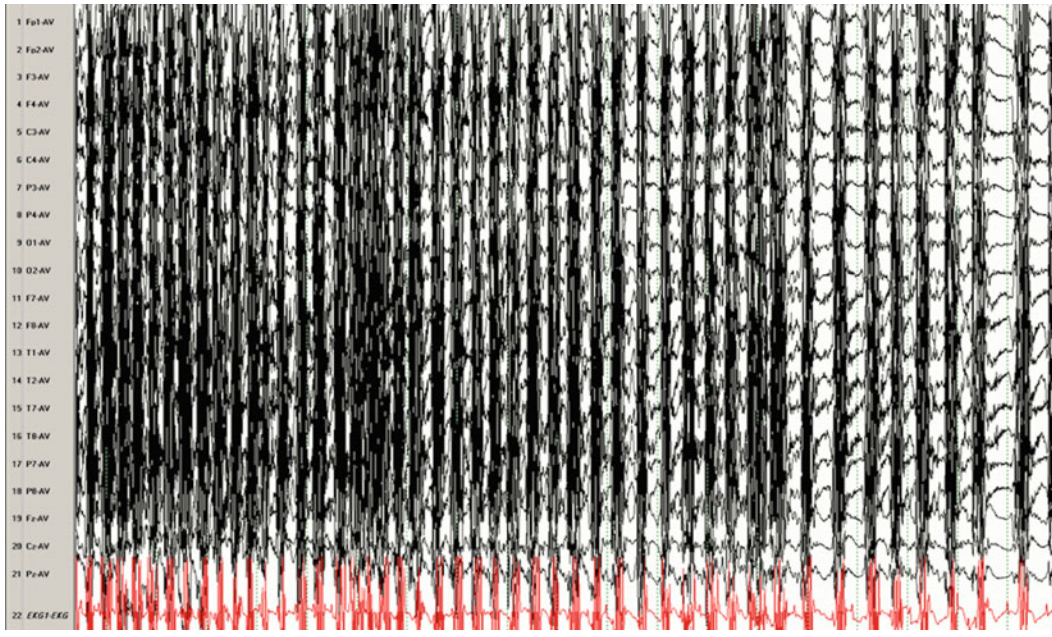

Fig. 6.5 Generalized clonic activity, continued

- Epileptiform discharges, when present, are generalized, high-voltage rhythmic spike-and-wave activity, anteriorly predominant and sometimes can only be seen anteriorly. In children, however, there can be posterior predominance.

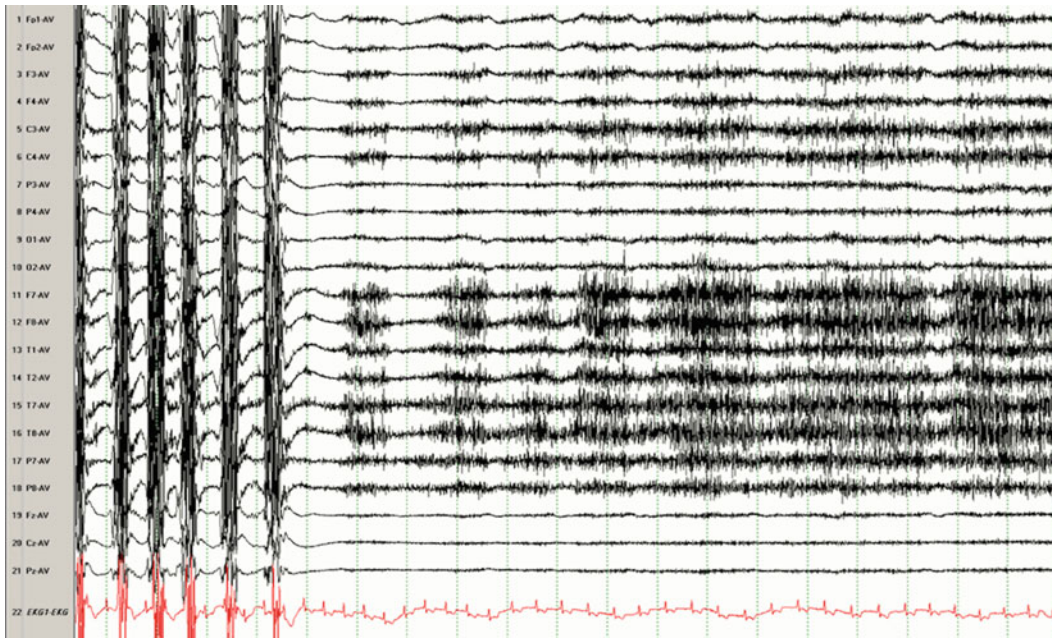

Fig. 6.6 End of clonic activity followed by generalized voltage attenuation

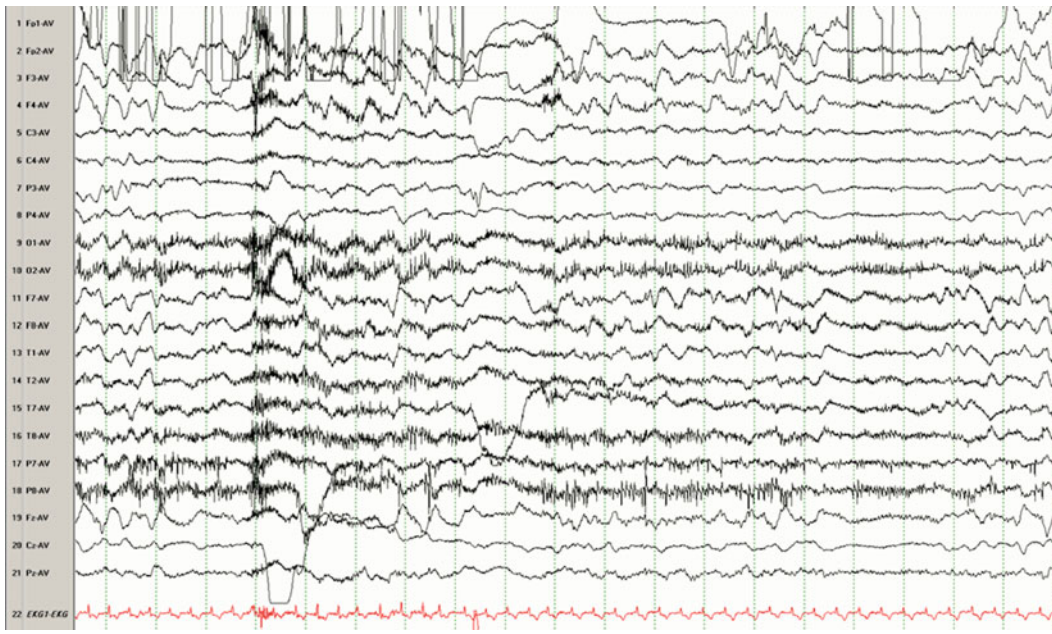

Fig. 6.7 Representation of post-ictal state at 1 min showing generalized voltage attenuation and generalized slow activity

- Subtle asymmetry in the generalized discharges is commonly noted.
- In NREM sleep, briefer, slower, and fragmented discharges can be seen.

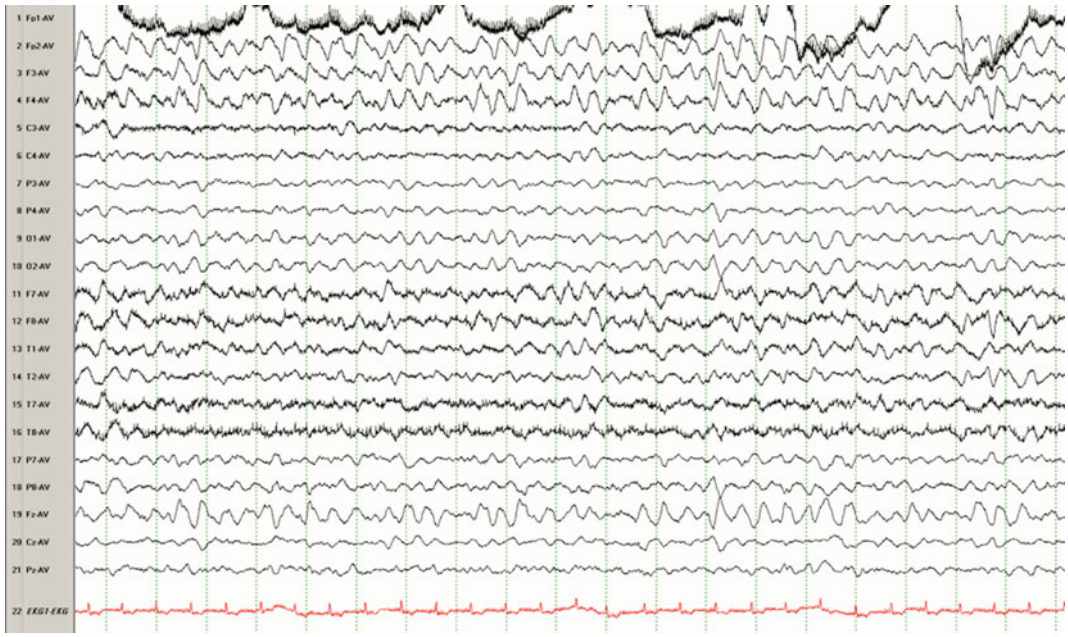

Fig. 6.8 Representation of post-ictal state at 5 min showing continued generalized slow activity

- Nonepileptiform activities such as generalized excessive low-voltage beta-activity or mild-generalized slow activity can be seen secondary to antiseizure medications. Chronic therapy with valproate and benzodiazepines can abolish epileptiform discharges. Frontal intermittent rhythmic delta activity (FIRDA) has also been reported.

Generalized spike-and-wave discharges can be seen in patients with no history of seizures, indicating a familial epilepsy trait. Similar discharges can also be seen in metabolic encephalopathies or drug-withdrawal states where they present as generalized tonic–clonic seizures.

Ictal EEG in Generalized Tonic–Clonic Seizures:

If generalized tonic–clonic seizures are preceded by absence (3 Hz spike-and-slow-wave) or myoclonic jerks (theta-range spikes or polyspikes and slow waves), then corresponding EEG ictal rhythms can be seen.

The tonic phase onset is predominated by muscle artifact obscuring the EEG. If neuromuscular blockers are used, the EEG shows higher amplitude and decreasing frequency discharge in the range of 9–10 Hz called the "epileptic recruiting rhythm." Small side-to-side delay can be noted with computer analysis, but this delay is inconsistent. Slower mixed frequency discharges with increasing amplitude rhythmic spikes are seen bilaterally followed by repetitive complexes of high-amplitude spike-and-slow-wave activity in association with the tremor. Slowing of repetitions occurs with the start of violent jerks of the clonic phase, as cortical inhibition progresses. During the postictal state, an isoelectric EEG followed by diffuse slow activity can be seen, which corresponds to neuronal hyperpolarization. Focal abnormalities during postictal states are not expected and might suggest focal epilepsy with secondary generalization.

Absence Seizures [1, 6]

(i) **Typical Absence**: This is the hallmark of the childhood absence epilepsy (CAE). Girls are affected more often than boys and present between 4 and 8 years of age with very frequent staring episodes (up to hundreds per day). Prognosis is excellent with treatment, and hence, a low threshold should be maintained to obtain EEG for diagnosis.

Semiology:

- Staring episodes associated with cognitive impairment and change in facial expression lasting for approximately 10 s. Rhythmic lid or eye clonic–tonic activity, ocular retropulsive movements that might extend to involve head or trunk, and sometimes oral automatisms can be seen.
- If the events last longer, there can be nonoral gestural motor automatisms.
- Temporal semiological analysis in relation to the EEG discharge can show variability in the same patient.
- Posture is usually maintained and falls are not often reported despite frequent episodes. The patients themselves are not aware of having these episodes. A child who has an event in the middle of a sentence will continue the sentence exactly where it was left off, while observers can appreciate the pause.
- In the physician's office, hyperventilation (in children, performed by blowing on a pinwheel) can elicit a seizure in approximately 90 % of patients with childhood absence epilepsy.

EEG correlation (Fig. 6.9): EEG record is ideally obtained between 8 and 10 am when the event frequency can be maximal.

- "Interictal" and Ictal EEG—The interictal nature of these discharges is debatable. Detailed neuropsychological testing conducted in patients with the absence showed deficits even when discharges were shorter than 3 s. In 30 % of cases, a rhythmic slow posterior activity or occipital intermittent rhythmic delta activity (OIRDA) can be seen.
- Generalized bilaterally synchronous high-voltage 2.5–3.5 Hz rhythmic spike-and-wave discharges with bifrontal predominance are classically seen during absence seizures. The initial negative deflection is of lower voltage compared to the after-wave, which is of very higher amplitude.

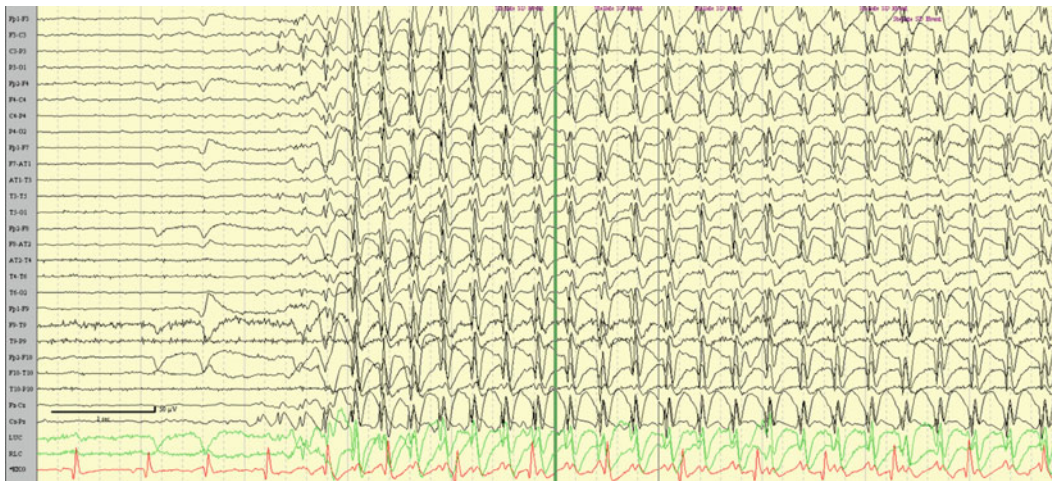

Fig. 6.9 Absence seizure. This 10 s EEG clip shows ictal discharge—typical 3 Hz generalized high-voltage rhythmic spike-and-wave discharge train during which the patient demonstrated delayed responsiveness

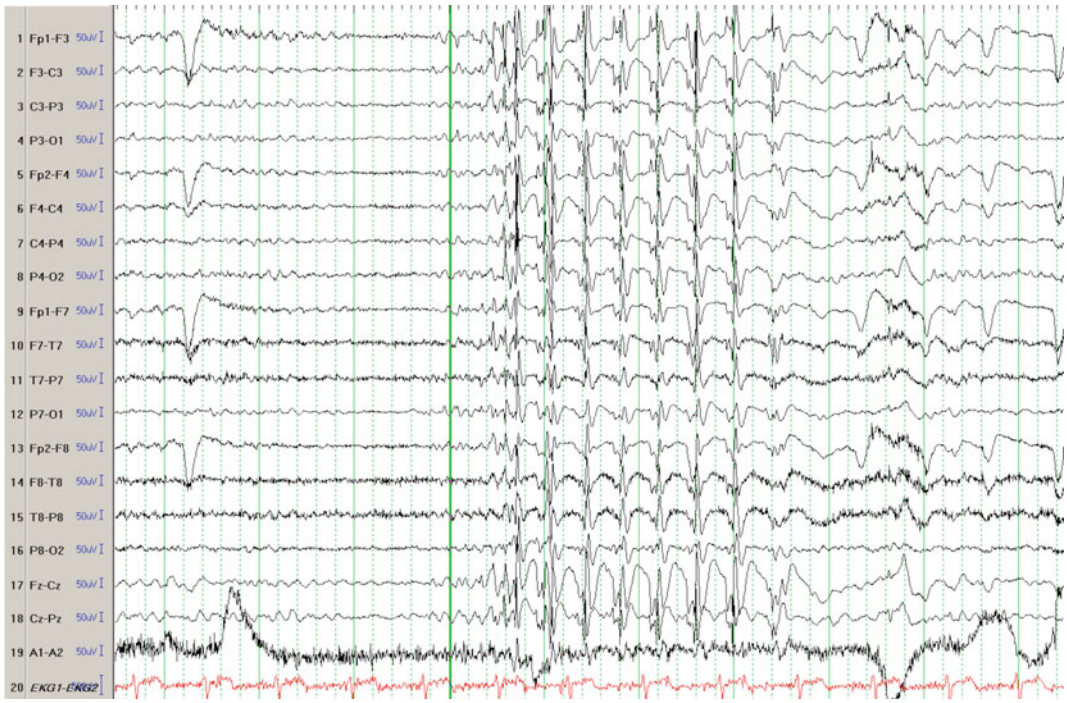

Fig. 6.10 Absence seizure in a patient with juvenile myoclonic epilepsy. Note the polyspike-and-wave discharge at the onset of ictal discharge (center of the EEG clip) that lasts ~3 s

- At the onset the discharge can be of higher frequency ~3.5 Hz and slows down over time. Occasionally, generalized polyspike-and-wave discharges, even bilateral independent focal frontal spikes, can occur in typical absence. These discharge trains often last 5–15 s but can last up to 30 s. Hyperventilation often precipitates longer trains of discharges.
- During non-REM sleep, single or multiple spike-and-wave discharges are frequent.

(ii) **Juvenile Absence Epilepsy** (JAE, Fig. 6.10): JAE has a typical age of onset between 9 and 13 years. Absence seizures typically occur in clusters upon awakening, and ocular retropulsive movements are less often seen. Seizures are less frequent than in CAE. EEG during absences shows generalized high-voltage spike-and-wave discharge, which may be slightly faster (3–4 Hz) than in CAE. About 80 % of patients also have generalized tonic–clonic and myoclonic seizures.

(iii) **Atypical Absence**: This is an important seizure type in patients with Lennox–Gastaut syndrome. Seizures occur lifelong and are more resistant to treatment, and photosensitivity is not a feature.

Semiology:
Onset and end of seizures is more gradual and eyelid myoclonus is not rhythmic. Forward head movement, perioral myoclonus, and drooling are notable. The seizure is usually less than 10 s in duration and the child can continue simple activities during an event.

EEG in atypical absence:
The ictal EEG shows 2–2.5 Hz slow spike-and-wave discharge, which can be irregular. Interictal EEG shows an abnormal

background with diffuse slowing and multifocal interictal spikes.

(iv) **Absence with special features** [6]:

Myoclonic absence: The mean age of onset is seven years with boys more often affected than girls. Cognition and development are abnormal in two-thirds of patients who can have other seizure types such as generalized tonic–clonic seizures. These seizures are very frequent, can occur in sleep, and tend to be resistant to therapy.

Semiology:
Events can be precipitated by hyperventilation or upon awakening. Consciousness is impaired to a variable extent. Eyelid movements are rare, but perioral myoclonia is frequent. The arms tend to stay high due to coexistent tonic contraction, and rhythmic jerks are typically clonic (rather than myoclonic) in nature and involve the arms more commonly than the legs. Rarely, the clonic activity can be unilateral. Events can last for 10–60 s. Falls from seizures are uncommon, and postictal state is not seen. Respiratory arrest and urinary incontinence can occur.

EEG in myoclonic absence (Fig. 6.11): Ictal EEG consists of generalized rhythmic 3 Hz spike-and-wave discharges coinciding with the rhythmic jerking of arms and can last 10–60 s. Occasionally, the classic discharges are intermixed with polyspike-and-wave discharges.

Myoclonic Seizures [7]

(i) Myoclonic seizures are seen in many epilepsy syndromes, including juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), and progressive myoclonic epilepsies, among others.

Semiology: Brief, symmetric, bilaterally synchronous jerks affect mainly the shoulders and arms occurring singly or in clusters. Jerks tend to cluster upon awakening, more often in morning,

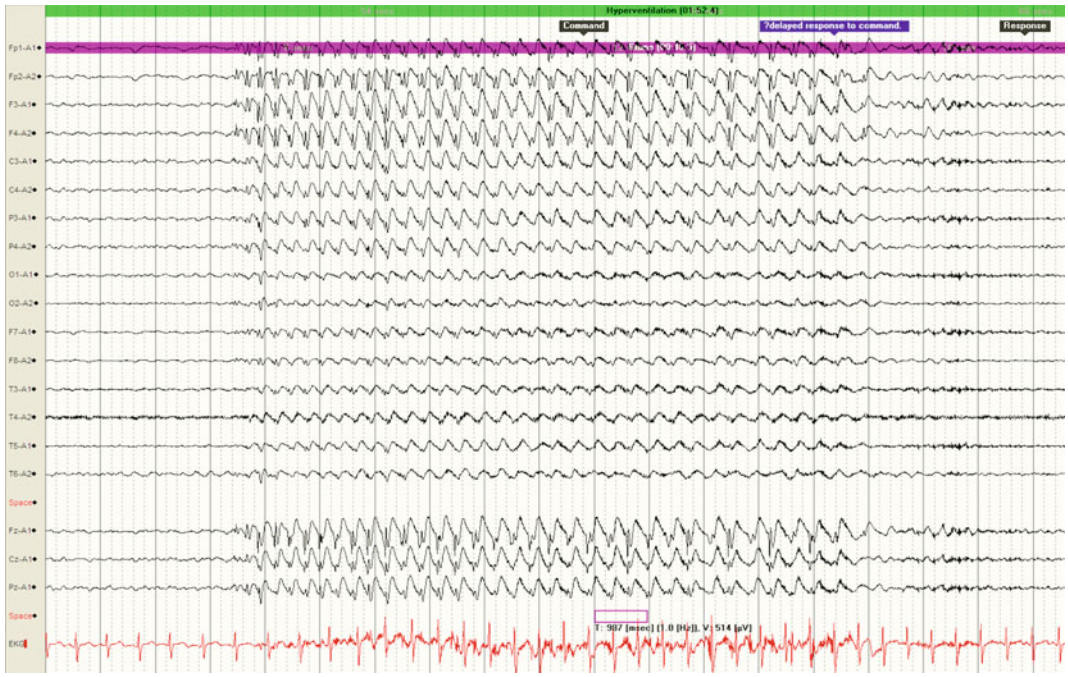

Fig. 6.11 A 20 s EEG clip of a 9-year-old boy with staring and rhythmic symmetric shoulder abduction movements synchronous with generalized 3 Hz spike-and-wave discharges. Also note the delayed responsiveness—command given to touch the nose was followed 7 s later when the discharge had ended

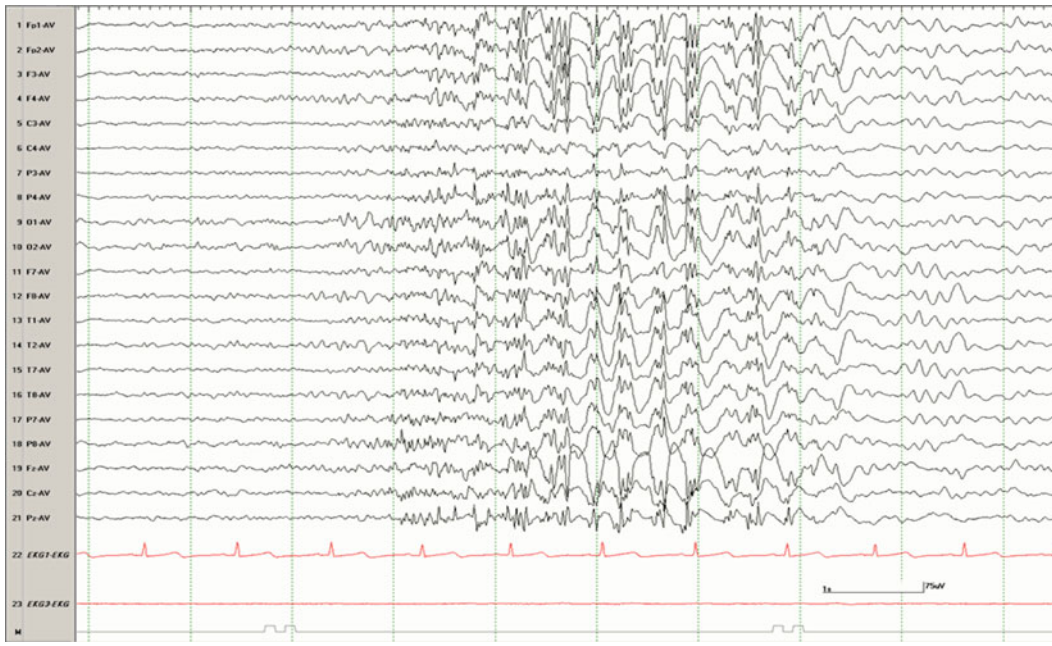

Fig. 6.12 A 10 s EEG clip showing generalized polyspike-and-wave discharge in a patient with juvenile myoclonic epilepsy with myoclonic seizures

and sometimes during nocturnal awakenings or when tired in the evenings. At times, ideation of the jerks can induce myoclonic jerks. Patients remember these jerks and are sometimes only perceived internally as "mild electrical shock." Objects in the hands tend to be thrown off and

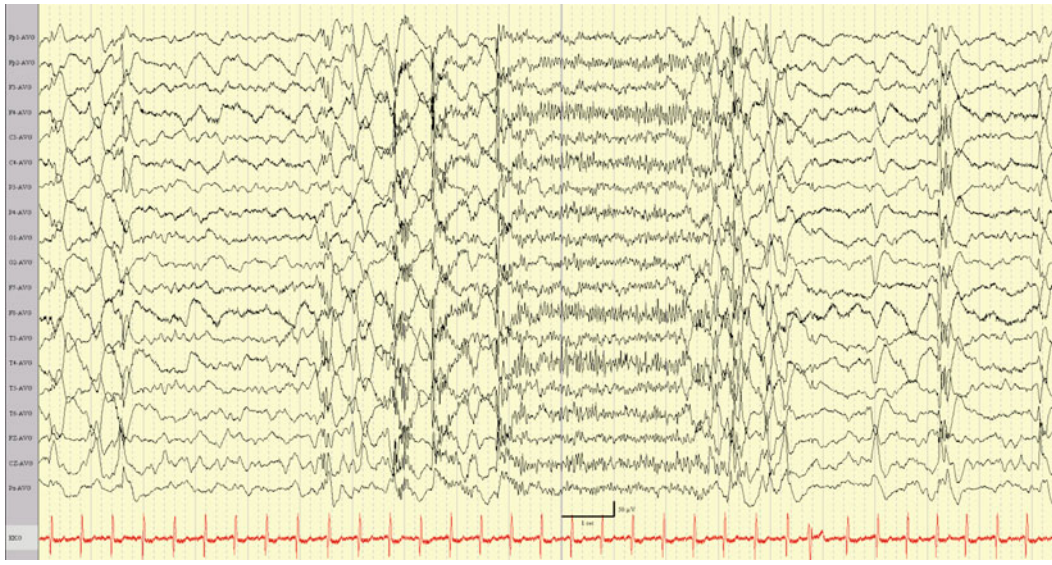

Fig. 6.13 Generalized tonic seizure in a patient with LGS. The EEG clip initially shows background slow activity with intermixed periods of relative voltage attenuation. Tonic arm posturing was accompanied by generalized low-voltage fast activity (middle 1/3 of EEG clip) lasting 4–5 s

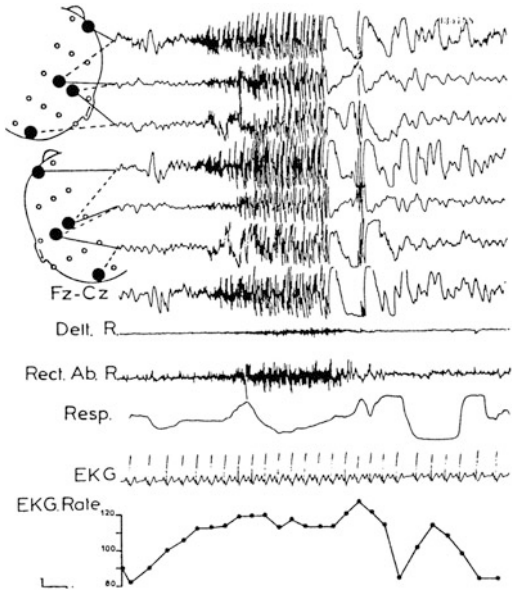

Fig. 6.14 Electrographic ictal discharge of tonic seizure in an 11-year-old boy with Lennox–Gastaut syndrome. Fast activity which is frontally predominant increases in amplitude and becomes slower in frequency with progression of the seizure. Muscle tone is shown by the deltoid and abdominal muscles. EKG and respiratory channels show tachycardia and changes in respiratory rhythm. Generalized tonic seizure: High-amplitude generalized spiking associated with tonic activity seen in rectus abdominis muscle, tachycardia, and pause in respiratory activity (*Picture source* Gastaut and Tassinari [11])

falls can occur with leg muscle involvement while standing.

EEG correlation (Fig. 6.12): The background is typically normal. Interictal epileptiform and ictal discharges consist of generalized high-voltage polyspike-and-wave or spike-and-wave discharges that are bilaterally symmetric with bifrontocentral predominance. They can be induced by photic stimulation. In sleep, fragments of these discharges with shifting right-left predominance can be seen. Limb electrodes can demonstrate the myogenic activity that is time locked with EEG discharges.

(ii) Myoclonic–atonic seizures: These are the main seizure type in myoclonic-astatic epilepsy of early childhood—Doose syndrome.

Semiology: Falls preceded by variable jerky movement of the face/trunk/arms.

EEG: Interictally, generalized slow spike-and-wave discharges are seen. Parietal theta or occipital delta activity can be seen as well. Ictal discharges consist of generalized slow spike-and-wave or polyspike-and-wave discharges of 2–3 Hz. The spike component corresponds to the myoclonic jerk, and slow wave corresponds to atonia.

The EEG can help differentiate from negative myoclonus seen in frontal lobe epilepsy with rapid bilateral synchrony. Negative myoclonus interrupts the tonic activity and is <500 ms in duration without the evidence of antecedent myoclonia causing the drops.

Clonic Seizures [8]

Generalized clonic seizures can be seen in Angelman's syndrome, progressive myoclonic epilepsies, and epilepsy with myoclonic-astatic seizures (also known as Doose syndrome). The generalized clonic or myoclonic activity seen during a syncopal episode (convulsive syncope) may mimic such seizures.

Semiology: Clonic seizures are predominantly seen in infants and children. They can be lateralized at first and then generalize or vice versa. Sometimes, the tonic phase is short and a tonic–clonic seizure appears like generalized clonic seizure. Autonomic changes are seen in prolonged seizures consisting of retention of bronchial secretions leading to respiratory distress.

EEG correlation: The interictal EEG background depends on the underlying etiology of epilepsy. Generalized epileptiform discharges can be seen. The ictal discharge is usually a complex discharge of 10 Hz recruiting rhythm mixed with activity of different frequency over different scalp regions fluctuating over time. Peaking of muscle activity does not coincide with EEG activity. In the postictal state, generalized slow activity can be seen.

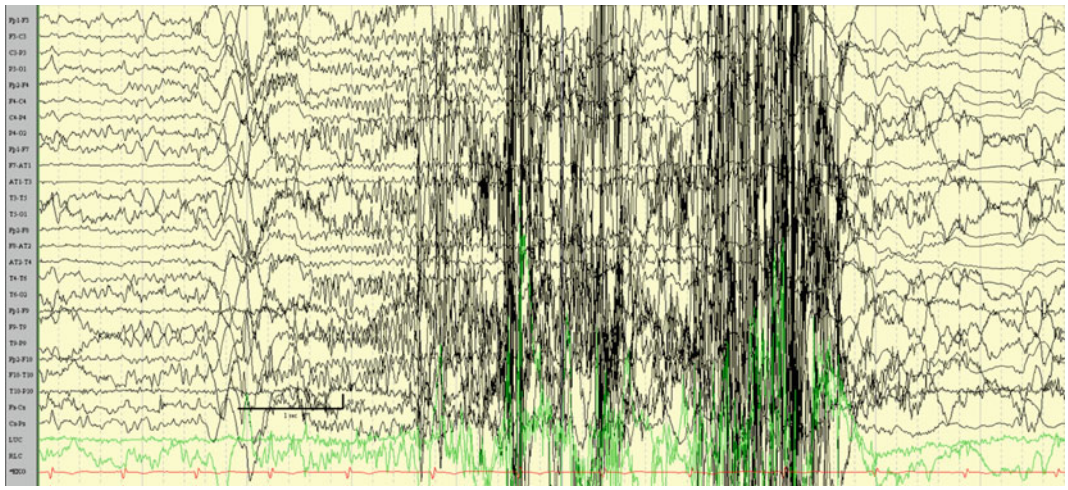

Fig. 6.15 A 10 s EEG clip of atonic seizure in a patient with head drop in sitting posture. Head drop coincides with the high-amplitude slow wave during the third second of the EEG clip below

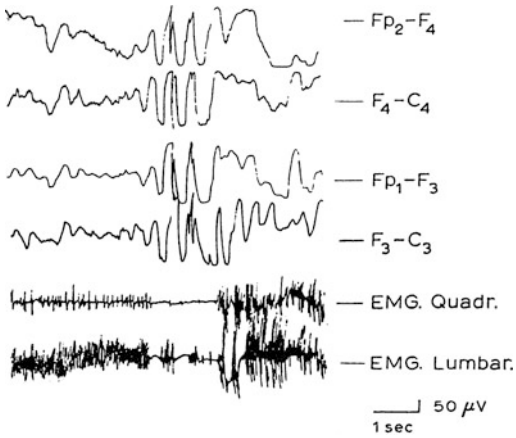

Fig. 6.16 Polygraphic record shows loss of muscle tone recorded in quadriceps and lumbar muscles during atonic seizure. The EEG shows ictal discharge—short burst of multiple spikes and slow waves (*Picture source* Gastaut and Tassinari [12])

Tonic Seizures [9]

Tonic seizures are predominantly seen in epilepsies associated with abnormal neurocognitive examination and abnormal EEG background, classically defined as symptomatic generalized epilepsies. Examples include Lennox–Gastaut syndrome and inverted duplication of chromosome 15.

The semiology of tonic seizures consists of rapid flexor contraction of muscles, starting in body axis associated with loss of awareness, followed by tonic muscle contraction in the arms and legs. In a pure tonic seizure, there is no clonic event following the tonic activity. Tonic seizures usually last 5–20 s but can last up to a minute. They can be occasional or very frequent. Falls usually occur if the patient is standing.

EEG correlation (Figs. 6.13 and 6.14): The interictal EEG and Ictal EEG are variable depending on the epilepsy syndrome. Typically, the ictal EEG consists of the following:

- The most common ictal pattern consists of rhythmic spiking at 10–25 Hz of low-amplitude desynchronized rhythm of 100 μV.
- Another pattern is that of diffuse high-amplitude slow-wave discharges at theta and delta frequency over the vertex region, lasting 0.5–1 s. This is followed by rapid 10–15 Hz rhythm increasing in amplitude over the next 5–10 s.

Table 6.1 Generalized Seizures

Seizure type	Associated seizure types	Epileptic syndrome	Semiology—all are associated with the loss of awareness/consciousness	EEG characteristics—generalized discharges (S&W = spike-and-wave PS&W = Polyspike-and-wave)	
				Interictal	Ictal
GTCSz	Generalized tonic–clonic seizures alone	GMA—grand mal seizures upon awakening	Loss of consciousness at onset of tonic phase followed by clonic and postictal phase Prodrome—not to be mistaken for aura	4–5 Hz high-voltage rhythmic S&W or PS&W particularly upon eye closure	Tonic phase = epileptic recruiting rhythm (9–10 Hz) Clonic phase = inhibitory cycles interspersed with tonic muscle activity Post-ictal phase = electrocerebral silence
	With absence seizures	Juvenile absence epilepsy	Cluster of absences upon awakening can precede GTCSz	3–5 Hz high-voltage S&W discharges	Runs of 3–5 Hz S&W discharges precede the above-described ictal discharge
	With myoclonic seizures or all three together	Juvenile myoclonic epilepsy—higher incidence of photosensitivity	Cluster of myoclonic seizures (upon awakening) precede GTCSz	EEG in wakefulness can show generalized 4–5 Hz S&W or PS&W discharges	Clusters of PS&W discharges prior to the above-described discharge for tonic–clonic seizure
Absence	None	Childhood absence epilepsy—more than 90 % undergo remission with age	Very frequent staring episodes lasting ~10 s, can be associated with ocular myoclonic movements	High-voltage 2.5–3.5 Hz rhythmic S&W discharges	Runs of described Interictal discharges for longer than 3 s more likely cause clinical events
Atypical absence	Tonic seizures Atonic	Lennox–Gastaut syndrome = seizures are lifelong and photosensitivity is not a feature	Gradual onset and end of head movements with perioral myoclonia and drooling last <10 s Can perform simple activities during seizure	Slow background with Interictal spikes	2–2.5 Hz slow irregular S&W discharges
Myoclonic absence	Absence	Absence with special features—myoclonic absence	Frequent arm abduction, with perioral myoclonia lasting 10–60 s without postictal state	High-voltage 3–4 Hz S&W discharges	High-voltage 3–4 Hz S&W discharges time locked with myoclonic jerks and delayed responsiveness when tested

(continued)

Table 6.1 (continued)

Seizure type	Associated seizure types	Epileptic syndrome	Semiology—all are associated with the loss of awareness/consciousness	EEG characteristics—generalized discharges (S&W = spike-and-wave PS&W = Polyspike-and-wave)	
				Interictal	Ictal
Myoclonic seizures	Absence GTCSz	JME, JAE, progressive myoclonic epilepsy	Brief symmetric bilaterally synchronous jerks affecting shoulder and arms—cluster upon awakening or when tired	High-voltage PS&W discharges of 4–5 Hz (can lead to GTCSz)	High-voltage PS&W discharges of 4–5 Hz in trains—can lead to GTCSz
Clonic	Myoclonic, atonic—infants and children Differential diagnosis—syncope—adults more often	Angelman's syndrome, epilepsy with myoclonic-astatic seizures	Clonic activity lateralized or generalized with associated autonomic changes—retention of bronchial secretions	Interictal EEG depends on etiology—generalized epileptiform discharges can be seen (predominance in central regions—Angelman's)	Ictal = 10 Hz epileptic recruiting rhythm with mixed frequency activity varies in different scalp regions Postictally—slow activity
Tonic	Atonic Atypical Absence	Lennox–Gastaut syndrome = frequent seizures, associated falls can lead to trauma	Rigid violent muscular contractions with limbs in stiff state, with lateralized eye deviation	2–2.5 Hz slow S&W activity or multifocal spikes	Rhythmic 10–25 Hz spikes of low amplitude or Vertex central slow activity followed by 10–25 Hz fast activity
Atonic		Lennox–Gastaut syndrome	Brief atonia of head or all postural muscles Can stand up immediately unless prolonged atonia	Slow S&W activity	Burst of PS&W followed by high-voltage slow wave which corresponds to atonia or fast activity or electrodecrement EMG shows ~400 ms of silence

The ictal patterns tend to occur in series and last for minutes with seizures occurring every 20–30 s.

Atonic Seizures [10]

These are also predominantly seen in symptomatic generalized epilepsies. Such patients tend to have severe developmental delay and cognitive impairment as in Lennox–Gastaut syndrome.

Semiology: Brief atonia can be limited to the head or can involve all postural muscles. Loss of consciousness is extremely brief and patients can stand up immediately after a fall. When atonia is prolonged, patients will lay motionless on the floor. Falls occur on the body axis. The arms are not involved by tonic or myoclonic phenomenon. In mild cases, only upper body is involved, and in severe cases, the lower body can be involved.

EEG correlation (Figs. 6.15 and 6.16): The interictal EEG is not specific and can show slow spike-and-wave activity. EMG when recorded shows silence for ~400 ms or polyspike-and-wave activity. The ictal EEG shows generalized polyspike-and-wave activity with atonia coinciding with slow activity (this pattern is most often seen). Other ictal patterns can be seen, including low- or high-voltage fast activity, and flattening or burst of polyspike-and-waves followed by generalized slow wave activity.

Summary: Table 6.1 summarizes the generalized seizure types, other seizures that can occur in the same patient and recognized epileptic syndromes. Emphasis has been placed on clinical seizure semiology along with interictal and ictal EEG findings. All generalized seizures by definition have alteration in consciousness or alteration in awareness.

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EEG and Semiology in Focal Epilepsy

7

Amir M. Arain

The majority of seizures could be divided into generalized or focal (also known as partial) seizures based on ictal EEG onset. Generalized seizures, as the name implies, appear to have a bilateral onset on the EEG since the seizure discharge is believed to rapidly involve bilateral networks. In contrast, focal seizures arise within networks limited to one hemisphere. As electrographic seizure onsets may be discretely localized or widely distributed, the clinical semiology complements the electrographic findings in concluding seizure localization. While historical description of seizures may help in semiology, video-EEG monitoring of habitual seizures is key in analyzing details of seizure semiology. Scalp EEG fails to detect seizure onset in many patients. Scalp EEG fails to lateralize seizures in about 25% of seizures in patients with unilateral mesial temporal lobe epilepsy and as high as 33–50% of seizures in patients with extratemporal epilepsy [1–3]. In these cases, seizure semiology is often very helpful.

Some semiological features are useful for lateralizing seizure onset zone to a hemisphere (Table 7.1), and others can help in further lobar or sublobar localization (Table 7.2). Focal seizures can be divided into (1) seizures without impairment of awareness with or without associated observable motor or autonomic components or involving subjective sensory or psychic phenomenon only. These seizures are also known as simple partial seizures or auras; (2) focal seizures with impairment of awareness, also called dyscognitive, implying a larger cerebral involvement. These seizures are also known as complex partial seizures; and (3) secondary generalized seizures, which are focal seizures that evolve to a bilateral convulsive seizure.

Temporal Lobe Seizures

Temporal lobe seizures may arise from mesial and lateral temporal regions. This distinction is important in the surgical evaluation of refractory epilepsy. Mesial temporal lobe seizures will often be abolished after standard temporal lobectomy or selective amygdalohippocampectomy, while lateral temporal lobe seizures will often require invasive video-EEG monitoring in order to map eloquent cortex and tailor a surgical resection. The clinical features favoring mesial temporal lobe epilepsy include early age of onset, history of complex febrile seizures, congenital brain malformations, CNS infections, tumors, head trauma, perinatal injury, stuttering course of seizure control, and typically with well-controlled seizures in early childhood but re-emergence of refractory epilepsy in adolescence or early adulthood and infrequent or rare secondarily generalized seizures. In contrast, lateral temporal lobe epilepsy is typically characterized by later age of onset of seizures, absence of early risk factors, absence of

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Table 7.1 Semiologic signs that help in lateralization of the epileptogenic focus

Sign	Lateralization of hemisphere
Dystonic limb posturing	Contralateral
Head turning (early)	Ipsilateral
Head turning (late and versive, in transition to generalization)	Contralateral
Figure of 4 sign	Contralateral
Todd's paralysis	Contralateral
Focal clonic activity	Contralateral
Unilateral eye blinking	Ipsilateral
Unilateral limb motor automatisms	Ipsilateral
Postictal nose wiping	Ipsilateral

Table 7.2 Semiologic signs that help in localization of the epileptogenic focus

Sign	Localization
Preservation of ictal speech	Nondominant temporal lobe
Ictal speech arrest	Dominant temporal lobe
Postictal aphasia	Dominant hemisphere
Ictal vomiting	Right temporal lobe
Hypermotor	Frontal lobe, less commonly insular or even temporal
Ictal urinary urge	Right temporal lobe
Limb paresthesia	Contralateral parietal lobe
Simple visual hallucination	Contralateral occipital lobe
Complex visual hallucination	Contralateral temporo–occipital lobe

hippocampal atrophy, and more common negative structural or functional brain imaging.

Mesial temporal lobe seizures often have an aura—with rising epigastric discomfort or inappropriate fear or olfactory feeling and or autonomic signs like; pallor, flushing, mydriasis, irregular respiration or respiratory arrest, abdominal borborygmi, and eructation. These seizures often exhibit contralateral dystonic posturing of the hand (and ipsilateral hand automatisms), preserved ictal language if the focus is in nondominant temporal lobe, ictal speech arrest if the focus is in dominant temporal lobe, postictal nose wiping with ipsilateral hand, ictal vomiting or retching behavior, and head version in transition to secondary generalization.

Mesial temporal lobe seizures are often associated with a rhythmic theta-range ictal discharge on scalp EEG [4]. Typically, an initial focal temporal rhythmic activity of <5 Hz frequency is followed within 30 s by 5–7 Hz sphenoidal maximum theta activity [5]. At times, sudden generalized or lateralized suppression or attenuation is also seen [6]. Interictal EEG abnormalities consist of frequent spikes or sharp waves predominantly in the inferomesial (sphenoidal electrodes) and anterior temporal regions.

Lateral temporal lobe seizures are relatively less common than mesial temporal lobe seizures. However, these seizures may be associated with an aura of vertigo, or with auditory or visual hallucinations. These seizures often evolve early to a unilateral clonic activity and early head turning. On scalp EEG, lateral temporal lobe seizures have a high incidence of repetitive epileptiform discharges at ictal onset [6]. Also if present, a transitional sharp wave at ictal onset favors a neocortical rather than hippocampal seizure onset [7]. Neocortical seizures often start with higher frequency activity (alpha or beta

range) on scalp EEG, but may also be associated with irregular, polymorphic, 2–5 Hz lateralized activity [4]. Interictal EEG abnormalities in neocortical temporal epilepsy may be absent or consist of occasional spikes or sharp waves predominantly in the anterior or mid-temporal regions [8].

While certain semiological features can help lateralize the seizure onset zone and, further, localize it to the temporal lobe, they cannot discriminate between mesial and lateral temporal onsets. These include ictal emeticus, ictal urinary urge, and ictal spitting, which often localize to the right temporal lobe, and piloerection, which localizes to the left temporal lobe.

Extratemporal Lobe Seizures

Extratemporal lobe seizures can mimic temporal lobe seizures semiologically and electrographically (1). These are often referred to as temporal plus epilepsies (TPE) (2). They are often difficult to differentiate simply by using general clinical features. However, early ictal signs and symptoms that suggest involvement of the perisylvian region, the orbitofrontal cortex, or the temporo-parieto-occipital junction should heighten the suspicion of temporal plus epilepsies (2). This is of clinical importance since misdiagnosis as temporal lobe epilepsy and recommending temporal lobectomy will result in surgical failure and persistence of seizures.

Frontal Lobe Seizures

Although they constitute the second most common focal seizures after temporal lobe seizures, frontal lobe seizures can pose a diagnostic challenge. They do not always produce loss of awareness, and when they do, they usually have brief or no postictal confusion. Thus, frontal lobe seizures can be mistaken for psychogenic nonepileptic seizures, movement disorders, or parasomnias. Frontal lobe seizures are typically characterized by stereotypical pattern, frequent nocturnal occurrence, and brief duration [9]. They often occur in clusters and may present as bizarre attacks that appear hysterical with fencing and posturing [9], prominent motor automatisms (hypermotor), usually complex, aggressive sexual automatisms, and vocalizations with variable complexity [10]. Frontal lobe seizures can be grouped into four based on their origin in the frontal lobe.

Supplementary motor seizures may occur without alteration of consciousness, representing simple partial seizures. Typical characteristics include prominent tonic posturing, usually of the contralateral upper extremity, contraversive head and eye deviation, preservation of consciousness in some patients, and postictal Todd's paresis.

Anterior cingulate seizures are characterized by sudden changes in mood and elaborate gestural frequent tonic/dystonic posturing, rare changes of facial expression of fear, vocalization, complex motor automatisms that are often hypermotor, and autonomic features.

Orbitofrontal seizures are characterized by sudden complex gestural automatism, hypermotor activity, olfactory fear and prominant facial expression of fear hallucinations, illusions, and prominent autonomic features.

Dorsolateral frontal seizures are often characterized by unilateral clonic activity involving face and spreading to the arm and leg. These seizures often occur without the alteration of consciousness [11]. They often involve forced head turning to the contralateral side with lateral deviation of the eyes indicating activation of contralateral frontal eye field [12, 13]. In dominant frontal lobe convexity seizures, aphasia is often seen.

In frontal lobe seizures, the ictal EEG often shows excessive generalized muscle artifact at the onset, and the ictal discharge is typically brief and delayed. The ictal EEG can also be falsely localizing. The Interictal EEG is commonly normal, though multifocal epileptiform discharges may be seen in mesial frontal lobe seizures. In dorsolateral frontal epilepsy, the interictal EEG may show focal interictal epileptiform discharges localizing to the epileptogenic focus. Frontal lobe seizures may also be characterized by bilateral synchronous interictal

epileptiform discharges representing secondary bilateral synchrony. Alternatively, focal epileptiform discharges are seen in the ipsilateral or contralateral temporal or frontal lobes.

Parietal and occipital lobe seizures can often present with temporal or frontal symptomatology because of spread of their locus of origin. They are often the cause for pseudotemporal and pseudofrontal seizures.

Parietal Lobe Seizures

The symptomatogenic zone of parietal lobe seizures may be distant from the seizure onset zone, with the seizure semiology representing ictal propagation beyond the parietal association cortex. Propagation pathways can be from the parietal lobe to the sensorimotor cortex, premotor eye field, supplementary motor, or temporolimbic region. These seizures can be characterized by focal motor clonic activity contralateral to the epileptogenic zone, tonic posturing of extremities, oral–gestural automatisms, complex automatisms, painful or thermal or sexual/groin paresthesia, head deviation, Todd's paralysis, or postictal aphasia.

The ictal EEG may be poorly informative and falsely localizing [6]. It may show diffuse voltage suppression followed by sharp waves spreading either anteriorly or posteriorly to the frontal or parietal operculum. Interictal epileptiform discharges, if present, are typically seen in the temporal region.

Occipital Lobe Seizures

Occipital lobe seizures are often characterized by elementary visual hallucinations consisting of flashing or steady spots or simple geometric forms. Other manifestations include repeated eye blinking and tonic eye and head deviation, either ipsilateral or contralateral to the ictal discharge. Occipital seizures are often associated with such vegetative phenomena as vomiting. The ictal EEG in occipital lobe epilepsy may be normal when the seizure focus is in the mesial or basal occipital regions. False localization can also be seen in occipital lobe seizures [6]. Ictal EEG may become more evident as a low-voltage fast activity progressively followed by a rhythmic epileptiform discharge. Ictal EEG in occipital seizures may vary with the pathway of propagation, typically spreading to the temporal or frontal region or bilaterally. At times, the initial occipital onset is missed while the ictal discharge rapidly becomes predominant in the temporal region giving a false localization.

The interictal EEG in occipital lobe epilepsy is typically abnormal. Posterior temporal epileptiform discharges are the most common patterns. Centrotemporal spikes are frequently seen with occipital paroxysms. Other patterns include random unilateral or bilateral occipital spikes, often with fixation-off sensitivity. Fixation-off sensitivity is characterized by posterior or generalized epileptiform discharges that consistently occur after eye closure and last as long as the eyes are closed. It may represent an ictal or interictal phenomenon. Some patients may also have occipital spikes exclusively during sleep, while others may consistently have normal EEG.

Insular Lobe Seizures

The insula is an island of cerebral cortex folded deep within the lateral sulcus. It has extensive connections with temporal, occipital, opercular, and orbitofrontal regions, and with the triangular and opercular parts of the inferior frontal gyrus. Seizures restricted to the insular lobe do not result in impairment of consciousness and may manifest as laryngeal discomfort with thoracoabdominal constriction or dyspnea, vomiting, hypersalivation, laryngeal constriction, followed by unpleasant paresthesias or warmth in the perioral region or involving larger somatic areas, dysarthria or dysphonia, ending with focal motor manifestations.

The distance of the insular cortex from the surface makes scalp recordings imprecise.

Ictal EEG often is marked by muscle artifacts and can show ictal discharges in the temporal regions. Interictal epileptiform discharges on scalp EEG are usually absent.

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Status Epilepticus

8

Pavel Klein

Definition

Status epilepticus (SE) is defined as either (i) ≥ 30 min of continuous seizure activity or (ii) ≥ 2 sequential seizures spanning this period without full recovery between seizures.

Epidemiology

Incidence has been estimated between 18 patients per 100,000 population in a retrospective epidemiological study in Rochester, MN, to 41/100,000 population (with 50 SE episodes/year/100,000) in a prospective epidemiological study in Richmond, VA. Both partial SE and generalized SE occur with a high frequency. Incidence of generalized SE in that study was 6.2/100,000. Generalized SE is more common in children at 7.5/100,000 than in the elderly 22/100,000. There are estimated 126,000–195,000 SE events with 22,200–42,000 deaths per year in the USA [1].

Classification

A simple classification of SE is shown in Table 8.1.

The task force on SE of the ILAE Commission on European Affairs has suggested a more exhaustive classification, as shown in Table 8.2 [2].

Non-convulsive status epilepticus (NCSE) is common and continues to be underdiagnosed. Continuous video-EEG monitoring is essential for its diagnosis. NCSE may present with altered mental status or psychosis, as well as with focal non-convulsive neurological symptoms or deficits. Seizures may not be picked up on a routine EEG, and the diagnosis may be missed unless 24-h-continuous video-EEG (CEEG) monitoring is performed.

In a study of 570 adults with unexplained decrease in level of consciousness who underwent CEEG monitoring, seizures were detected in 19% of the patients. Seizures were exclusively non-convulsive in 92% of these patients. Coma,

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Table 8.1 Classification of status epilepticus (SE)

Generalized	Convulsive
	Non-convulsive
Focal	Convulsive (epilepsia partialis continua)
	Non-convulsive
Non-epileptic ("Pseudo-SE")	

Table 8.2 Classification of SE, European alternative [2]

Classification of SE
1. NCSE occurring in the neonatal and infantile epilepsy syndromes
a. Ohtahara syndrome
b. West syndrome
c. Sever myoclonic encephalopathy of infancy (SMEI; Dravet syndrome)
2. NCSE occurring only in childhood
a. NCSE is early-onset benign childhood occipital epilepsy (Panayiotopoulos syndrome)
b. NCSE in other forms of childhood epileptic encephalopathies, syndromes, and etiologies (e.g., Ring chromosome 20, Angelman syndrome, Rett syndrome, myoclonic-astatic epilepsy, and other childhood myoclonic encephalopathies
c. Electrical status epilepticus in slow wave sleep (ESES)
d. Landau–Kleffner syndrome
3. Convulsive SE occurring only in childhood
a. Febrille SE
4. NCSE occurring both in childhood and adult life with epileptic encephalopathy
a. NCSE in the Lennox–Gastaut syndrome
i. Atypical absence SE
ii. Tonic SE
b. Other forms of NCSE in patients with learning disability or disturbed decerebral development (cryptogenic or symptomatic) without epileptic encephalopathy
c. Typical absence SE in idiopathic generalized epilepsy
d. Complex partial SE:
i. Limbic
ii. Nonlimbic
e. NCSE in the post-ictal phase of tonic–clonic seizures
f. Subtle SE (myoclonic SE occurring in the late stage of convulsive SE)
g. Aura continua [with (i) sensory, (ii) special sensory, (iii) autonomic, and (iv) cognitive symptoms]
5. Convulsive forms of SE occurring in childhood and adult life
a. Tonic–clonic status epilepticus
b. Epilepsia partialis continua 9 EPC; simple partial motor SE
c. Myoclonic SE
6. NCSE occurring in late adult life
a. De novo absence SE of late onset
7. Boundary syndromes[a]
a. Some cases of epileptic encephalopathy
b. Some cases of coma due to acute brain injury with epileptiform EEG changes
c. Some cases of epileptic behavioral disturbances or psychosis
d. Some cases of drug-induced or metabolic confusional state with epileptiform EEG changes

[a]Boundary syndromes are defined as cases in which it is not clear to what extent the continuous epileptiform electrographic abnormalities are contributing to the clinical impairment

age <18 years, history of prior epilepsy and convulsive seizures prior to monitoring were the risk factors for electrographic seizures. Seizures were detected during the first 24 h of CEEG monitoring in 88% of patients, during day 2 of monitoring in another 5%, and after 48 h of monitoring in 7%. 20% of comatose patients required >24 h of monitoring to detect the first electrographic seizure versus 5% of non-comatose patients. Prevalence of NCSE by diagnosis is shown in Table 8.3 [3].

The diagnosis of non-convulsive status epilepticus in patients with altered mental status and ambivalent EEG can be aided with intravenous benzodiazepine bolus injection, e.g., lorazepam 1 mg, which may abolish the

Table 8.3 Prevalence of non-convulsive seizures/SE in adult ICU by diagnosis (n = 570) [3]

	%
Overall	18
Unexplained altered MS	15
Epilepsy	31
CNS infection	26
Tumor	23
Neurosurgery	23
Traumatic brain injury	22
Toxic-metabolic	21
Stroke-SAH	18
Stroke-hemorrhagic	13
Stroke-ischemic	13
Hypoxia	10

Table 8.4 Etiology of SE [4]

Adult	%	Pediatric	%
CVA	25	Fever/infection	35
ASM change	19	ASM change	20
EtOH/recr. drugs	12	Unknown	9
Anoxia	11	Metabolic	8
Metabolic	9	Congenital	7
Unknown	8	Anoxia	5
Fever/infection	5	CNS infection	5
TBI	5		4
Tumor	4	CVA	3
CNS infection	2	EtOH/recr. drugs	2
Congenital	1	Tumor	1

epileptiform discharges, sometimes with associated paradoxical improvement of the patient's level of consciousness.

Etiology of SE for adults and children is shown in Table 8.4 [4].

A variable proportion of patients with status have preceding the history of epilepsy, in some studies estimated up to approximately 45%. In approximately 50% of patients with preceding epilepsy, the epilepsy is acute symptomatic. It is remote symptomatic in 20% cases, idiopathic in 14%, and unclassified in 17%.

Etiology of epilepsia partialis continua is usually due to a fixed or progressive lesion involving the motor strip. These include tumors, vascular lesions (CVA, AVM), infection (abscess—especially TB, encephalitis, HIV, and subacute measles encephalopathy), autoimmune (Rasmussen), systemic lupus erythematosus (SLE), paraneoplastic, cortical dysplasia, Sturge–Weber syndrome, traumatic brain injury (TBI), multiple sclerosis, gliomatosis cerebri, or progressive multifocal leucoencephalopathy.

Medications that may cause SE include theophylline, lithium, isoniazid, cyclosporine, tacrolimus, ifosfamide, amoxapine, flumazenil, and among antiseizure medications (ASMs) tiagabine, vigabatrin and valproate.

Uncommon causes of SE include the following:

- *Paraneoplastic* etiology, with associated autoantibodies (i) Hu, (ii) Ma2, and (iii) CRMP-5—all of them target intracellular antigens. Most common associated neoplasms are small cell lung carcinoma (associated with all of the above antibodies), testicular germ call carcinoma (Ma2), and thymoma (CRMP5). In these conditions, SE may be refractory and respond to tumor removal.
- *Autoimmune* diseases including Hashimoto's thyroiditis, SLE, Rasmussen's encephalitis syndrome, with associated thyroid microsomal antibodies, voltage-gated K channels antibodies, NMDA-receptor antibodies, all of which are extracellular antigens. Rasmussen's encephalitis syndrome is associated with anti-NR2A antibody (NMDA-receptor subunit GluRepsilon2).
- *Infectious, ill-defined* include the recently described new-onset refractory SE (NORSE) in adults and febrile infection-related epilepsy syndrome (FIRES) in previously normal children.
- *Chromosomal*, *genetic*, or congenital *dysplastic and* inborn *errors of metabolism*, all covered elsewhere in this book.

SE Clinical Stages

SE is divided into 4 phases (Table 8.5). Prodromal phase may include confusion, myoclonus, and increasing seizure frequency without intervening loss of consciousness. Stage 1 is divided into incipient (continued seizure of >5 min duration) and early (5–30 min duration).

EEG staging includes (i) discrete seizures with interictal slowing; (ii) waxing/waning of ictal discharges; (iii) continuous ictal discharge evolving into continuous ictal discharges interspersed by flat EEG; and (iv) Post-ictal: PLEDs/PEDs with flat background [5].

Pathophysiology of SE

SE evolves from an isolated seizure when there is a failure of seizure containment leading to the transformation of isolated seizure(s) to SE. Initially (ms/s), there is increased glutamate release and ion channel activation receptor phosphorylation and desensitization. After approximately 30–45 min, there is receptor trafficking with $GABA_A$-R (β2-3, ɤ subunits) internalized from synapse to cytosol where they are endocytosed and destroyed, leading to reduced number of $GABA_A$ receptors at the synaptic membrane, with simultaneous recruitment from cytosol to the membrane of glutamatergic AMPA/NMDA receptors (NR1 subunits). As a result of this trafficking, the number of functional NMDA receptors per synapse increases while the number of functional GABAA receptors decreases [6]. This contributes to the resistance of prolonged SE to GABAergic medication such as benzodiazepines.

Table 8.5 Clinical stages of status epilepticus

Prodromal		
Stage 1 (early)	Incipient	5 min
	Early	5–30 min
Stage 2 (established)		30–60 min
Stage 3 (refractory)		>60 min
Post-ictal		

Pathophysiology of epilepsia partialis continua is poorly understood. It may involve cortical reflex myoclonus which originates from hypersynchronous discharges of neuronal aggregates in the cortex and may involve long-loop reflexes via the ventrolateral posterior nucleus of the thalamus to generate cortical myoclonus [7].

Metabolic Consequences of SE (Table 8.6)

During the initial acute stage of SE, there is an increase in blood pressure, increase in cerebral blood flow and oxygen utilization, increased serum lactate, and, initially, increased glucose levels. There may be associated respiratory and metabolic acidosis. Subsequently, blood pressure normalizes and may fall, respiration becomes depressed, with falling oxygen and rising CO_2 levels, decrease in cerebral blood flow and brain

Table 8.6 Complications of tonic–clonic SE (adapted from Ref. [2])

Cerebral	Hypoxic/metabolic damage
	Excitotoxic damage
	Edema and ↑ ICP
	Venous thrombosis, infarction, hemorrhage
Cardiac	Hypo/hypertension
	Cardiac failure/shock
	Tachy-/brady-arrhythmia, arrest
Respiratory	Apnea, respiratory failure
	Pulmonary edema, hypertension, pneumonia, aspiration, PE
Autonomic	Hyperthermia, sweating
Metabolic/systemic	Hypoglycemia, ↓ Na, ↓ K, Acidosis Acute renal failure Acute hepatic failure DIC Rhabdomyolysis Infections Fractures
Labs (other)	Leukocytosis; CSF pleocytosis

oxygenation, and decrease in glucose level. There may be hyperthermia. These factors result in energy mismatch, with higher brain energy utilization than supply and exacerbation of neuronal injury. During later stages of both convulsive SE and in NCSE, there is an increase in serum levels of neuron-specific enolase, a marker of brain injury. Neuronal injury may occur even in the absence of metabolic derangement, and without hypoxemia, hypotension, hypoglycemia, and hyperthermia.

Management

Outline of the SE management and management timeline is shown in Table 8.7 [8].

Table 8.7 Status epilepticus: management timeline (adapted from Ref. [8])

Time post-onset	Treatment
0–5 min	Diagnose
	ABC: airway, breathing, circulation
	Labs: glucose, chemistry, CBC, toxicity screen ASM levels (if applicable)
	iv Glucose + thiamine 100 mg if applicable
4–5 min	Lorazepam 4 mg (0.1 mg/kg), or Midazolam 10 mg im, or Diazepam 10 mg (0.2 mg/kg) or rectal diazepam
7–8 min	Phenytoin or Fos-phenytoin 20 mg/kg i.v. at $\leq$50 mg/min phenytoin or 150 mg/min Fos-phenytoin ($\leq$0.75 mg/kg/min) Pyridoxine 100–200 mg iv in children under 18 months
10 min	Repeat lorazepam or diazepam if seizures still ongoing
30–60 min	EEG monitoring unless status ended and patient waking up
40 min	Phenobarbital 20 mg/kg at $\leq$5 mg/min (0.75 mg/kg per min)
60+ min	iv Anesthesia: Propofol 3–5 μg/kg load, 5–10 mg/kg/h initial infusion then 10–120 μg/kg/min, as tolerated/needed or Midazolam 0.2 mg/kg load, then 0.05–0.3 mg/kg/h infusion Pentobarbital 3–5 mg/kg load, then 1 mg/kg/h infusion

Evaluations

Labs: Initially, check glucose, chemistry profile —including calcium, magnesium, and phosphate —CBC, and urine toxicity screen ASM levels (if applicable). LP should be done if CNS infection, vasculitis, autoimmune, paraneoplastic, or meningeal neoplastic disease is suspected as a possible cause, after ruling out mass lesions with CT or MRI. Leukocytosis is commonly seen with SE without any infection because of blood–brain barrier breakdown during SE. CSF WBC counts of up to 30×10^6 can be seen.

Continuous EEG monitoring should be started, if available, if SE has continued for >60 min.

Neuroimaging changes associated with SE (Table 8.8; Figs. 8.1 and 8.2). MRI may be focally abnormal during both convulsive and non-convulsive status epilepticus. This may be misdiagnosed as acute lesions, e.g., stroke or encephalitis. Possible MRI abnormalities during SE include increased FLAIR (fluid-attenuated inversion recovery), T2 signal hyperintensity and high-intensity signal DWI (diffusion-weighted imaging), both local at seizure focus and remote, commonly in the ipsilateral posterior thalamus (pulvinar), contralateral cerebellum, and bilateral splenium of the corpus callosum (Table 8.8; Figs. 8.1 and 8.2). These changes may be due to the prolonged ictal activity increasing glucose utilization, which is not adequately matched by the enhanced blood flow. Blood flow–metabolism uncoupling leads to a reduction of high-energy adenosine phosphates and tissue

Table 8.8 Peri-ictal SE MRI imaging abnormalities

Local↑ T2/DWI	Remote −↑ DWI ± flair
Mass effect	Ipsi/bilat thalamic lesions
Hippocampal swelling	Cerebellar diaschisis, contralateral
Focal cortical lesions	Splenium abnormalities
Migratory focal cortical ↑ T2/DWI lesions	Reversible posterior leukoencephalopathy
BBB breakdown	
↑ Blood vessel caliber/flow (MRA)	

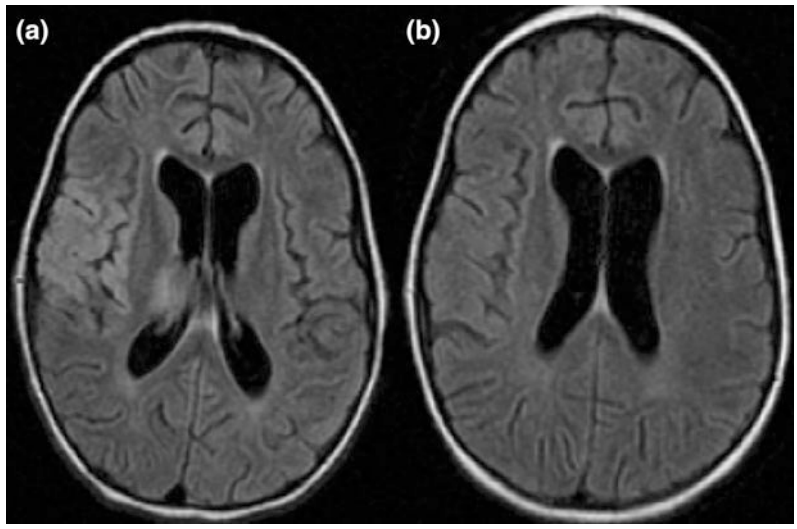

Fig. 8.1 Increased T2 signal (FLAIR protocol) in epilepsia partialis continua arising from the right hemisphere (**a**), with resolution after i.v. anesthesia (**b**)

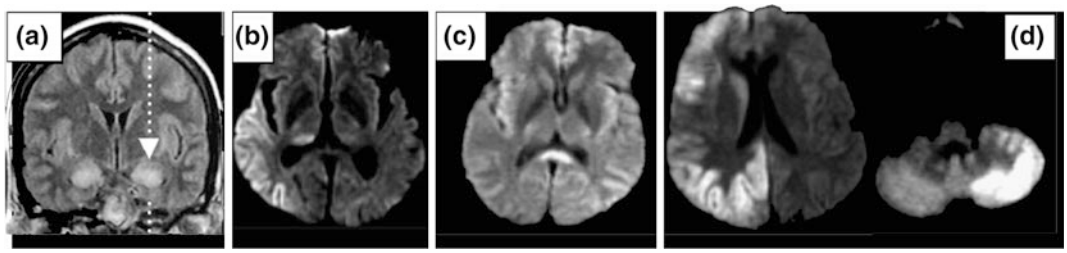

Fig. 8.2 MR images, FLAIR sequences. **a** *Arrow* shows left-sided region of change (shown only on the left side for clarity, but bilateral change is present). **b** Axial DWI showing gyral pattern of restricted diffusion and ipsilateral thalamic (pulvinar) change in a patient with left hemisphere seizures. **c** Axial DWI showing expanded and hyper-intense splenium during bitemporal SE. **d** Axial DWI images showing gyral pattern of restricted diffusion and crossed cerebellar diaschisis in a right hemispheric SE

hypoxia. The regional hyperperfusion serves as a compensatory mechanism, but is insufficient to prevent the stimulation of anaerobic glycolysis due to the prolonged ictal activity.

Treatment

Early, Stage 1 (Table 8.9).

Primary treatment includes benzodiazepines, midazolam, lorazepam, and diazepam. Midazolam i.m. may be the most effective followed by lorazepam followed by diazepam as shown in 2 large phase 3 studies ([9], Table 8.10).

Table 8.9 Treatment of early SE (first-line treatment) (adapted from Ref. [2])

	Route	Adult dose	Pediatric dose
Lorazepam	iv	4 mg	0.1 mg/kg
Midazolam	im	5–10 mg	0.15–0.3 mg/kg
Diazepam	iv ($\leq$2–5 mg/min)	10–20 mg	0.25–0.5 mg/kg
	Rectal	10–20 mg	0.5–0.75 mg/kg

Diazepam has more rapid onset because of greater lipid solubility. Lorazepam has longer anticonvulsant duration (12 h) than diazepam (30 min) and has less potential for respiratory

Table 8.10 Comparative efficacy of diazepam, lorazepam, and midazolam in the treatment of SE before arrival in the hospital. Response = seizure termination prior to arrival in ER without rescue treatment [9, 10]

	Dose/route	Response %
Midazolam	10 mg im	73
Lorazepam	4 mg iv	59–63
Diazepam	10 mg iv	43
Placebo	Im	21

depression and sedation. Seizure recurrence is common after benzodiazepine administration, especially in acute symptomatic SE.

In a study comparing the efficacy of intramuscular midazolam with intravenous lorazepam for children and adults in status epilepticus treated by paramedics outside the hospitals, seizures were stopped prior to arrival in the hospital in 73% subjects treated with midazolam 10 mg i.m. and 63% subjects treated with lorazepam 4 mg i.v. with 4.5 and 6.5 min to the cessation of convulsions, respectively. Seizures recurred in 11% in both groups. Adverse-event rates were similar in the two groups [10].

Secondary treatment includes phenytoin or phenobarbital (Table 8.11). It should be administered at the same time as the benzodiazepine. Phenobarbital may be more effective than phenytoin in suppressing SE, but is less used in practice, possibly because of greater potential for respiratory depression and intubation, particularly in combination with benzodiazepines. Comparison of efficacy of lorazepam, phenobarbital, and phenytoin with or without benzodiazepam is shown in Table 8.12.

Phenytoin has the advantage of lack of sedation or respiratory depression. Maximum CNS concentration is reached in 20 min. Its potential side effects include bradycardia (7%) and hypotension (27%) [11]. Phenytoin is alkaline and with extravasation causes skin irritation and "purple glove syndrome" which occurs in 1–2% of patients [11]. Phenytoin needs to be administered in normal saline as it precipitates in dextrose. Infusion rate is 50 mg/min for adults, 20 mg/min for the elderly, and ≤ 25 mg/min for children. The elderly have a higher risk for cardiovascular complications. Heart rate and blood pressure should be monitored with the reduction of infusion rate if hypotension occurs. Total blood level and free phenytoin level should be checked at the end of the infusion, within 30 min of infusion if seizures persist or 1–2 h after infusion if seizures stop, in order to help with timing of maintenance treatment.

Table 8.11 Treatment parameters of SE treatment with phenytoin and phenobarbital

	Route	Adult dose	Pediatric dose
Phenytoin/f-PHT	iv infusion rate	20 mg/kg, PHT $\leq$ 50 mg/min F-PHT $\leq$ 100 mg/min	Same
Phenobarbital	iv infusion rate	15–20 mg/kg $\leq$ 100 mg/min	Same 20 mg/min in neonates and infants

Table 8.12 Comparison of efficacy of SE treatment parameters phenytoin, phenobarbital, and lorazepam [11]

	Response rate % (Sz end $\leq$ 20 min)	Dose (mg/kg)	Maximal admin rate (mg/min)	Infusion time (min)
Lorazepam	65	0.1	2	4.7
Phenobarbital	58	15	100	16.6
Phenytoin + diazepam	56	18 0.15	50 5	42
Phenytoin	44	18	50	33

Table 8.13 Use of valproate and levetiracetam in Stage 2 status epilepticus (adapted from Ref. [2])

	Route	Adult dose	Pediatric dose
Valproate	iv infus rate	15–30 mg/kg 10–15 min	20–40 mg/kg 10–25 mg/kg neonates
Levetiracetam	iv infus rate	Not established; 2000–4000 used 5–15 min	Not established

Fos-phenytoin, a phosphate ester prodrug of phenytoin, has replaced phenytoin in many institutions. Fos-phenytoin is given as phenytoin equivalent (PE), with the dose of 20 mg/kg. It can be given in dextrose or normal saline. It is water soluble and can be given i.m. as well as i.v. It may cause paraesthesias and pruritus at injection site. Its bioavailability is 100% compared with phenytoin. It is rapidly converted to phenytoin (PHT) by serum and tissue alkaline phosphatases. Its conversion half-life to phenytoin is 7–15 min. Phenytoin levels should be checked 2 h after infusion. It may be difficult to maintain therapeutic levels in infants.

Alternative treatments for Stage 2 SE are shown in Table 8.13. Intravenously formulated ASMs include—in addition to phenobarbital, phenytoin, and benzodiazepine— sodium valproate, levetiracetam, and lacosamide. Valproic acid (VPA) and levetiracetam (LEV) are sometimes used for treatment of Stage 2 SE but their efficacy in SE has not been evaluated in controlled studies [12]. They have the advantage over PHT and PB of lacking cardiovascular side effects (lacosamide can rarely cause atrial fibrillation or tachy- or bradycardia).

Refractory Status Epilepticus (RSE, Stage 3 SE)

It is defined as SE lasting for >1 h which has failed to respond to benzodiazepine + PHT or PB at adequate doses. Approximately 35% of all SE evolve into refractory SE [13]. Convulsive SE may evolve into NCSE in approximately 15% of adults and 25% of children: Convulsions stop but mental status does not improve and CEEG shows NCSE. *Super-refractory status epilepticus* is defined as SE that continues $\geq$24 h after the onset of anesthesia, including SE recurrence after tapering of anesthesia. It occurs in approximately 10–15% of SE [14].

Pathophysiology of refractory SE (RSE): Pharmacoresistance develops after 30–45 min of continuous seizure. This is due to the aforementioned seizure-induced internalization of synaptic GABA-A receptor (subunits $\beta_{2\text{-}3}$, γ_2) and simultaneous externalization of AMPA/NMDA receptors to the synapse. As a result, there is decreased response to GABA and GABA potentiating medications such as benzodiazepine. In animal models, the response to diazepam is reduced 20x in RSE [6].

Evaluation of RSE should include continuous video-EEG monitoring to (a) diagnose the condition and (b) monitor the treatment response. The treatment goal during RSE is electrographic seizure suppression and EEG burst suppression pattern or electrocerebral inactivity. Optimal parameters of burst suppression such as duration of interburst interval have not been determined. Some investigators believe that an interburst interval of $\geq$5 s is desirable.

Treatment of RSE. Mainstay treatment is "therapeutic coma" induced with intravenous anesthetics such as propofol, midazolam (or lorazepam), or pentobarbital, together with intubation and mechanical ventilation. There are no US RSE treatment guidelines, no randomized studies comparing different agents, and little evidence to guide the choice of agent or duration of treatment. Many centers resort to i.v. anesthesia after the failure of benzodiazepine + phenytoin or phenobarbital. Some, however, try a third-standard anticonvulsant such as VPA, LEV, or lacosamide (LCM) before anesthesia. In Europe, this approach is common. Current

Table 8.14 Refractory SE treatment with iv anesthetics propofol, midazolam, and pentobarbital

	Dose, bolus mg/kg	Followed by infusion mg/kg/h	SE control rate (%) [14]
Propofol	1–2	5–10 mg/kg/h	68
Midazolam	0.1–0.3 (at 25 mg/min)	0.05–0.4 mg/kg/h	78
Pentobarbital	5–20	0.1–3	64

European guidance recommends titration of propofol and barbiturate to EEG burst suppression, and midazolam to seizure suppression, maintained for at least 24 h [15].

Therapeutic coma lowers metabolic activity of brain tissue, removes the energy mismatch between brain tissue energy use and supply, and allows neuronal recovery, including recovery of normal neuronal synaptic receptor function.

The three most commonly used i.v. anesthetics are shown in Table 8.14, together with dosing and infusion rate. Following initial bolus injection, the rate of infusion/dose of the chosen agent should be titrated quickly up to electrographic seizure suppression and then EEG burst suppression.

The optimal duration of the treatment has not been determined in controlled studies. Different centers use variably 24–48 h of EEG burst suppression on the i.v. anesthetic before attempting a taper. i.v. anesthetic is restarted if seizures recur. During i.v. anesthesia, non-anesthetic ASMs should be optimized in preparation for withdrawal of the i.v. anesthetic. The duration of i.v. anesthesia is empirical. Side effects are common, include hypotension, pneumonia, gastric paresis, and immunosuppression, and contribute independently to poor outcome and death. Mortality and functional outcome is similar in those with and without EEG suppression.

Propofol is the first-line intravenous anesthetic agent for RSE in many centers because its rapid onset and short duration of action, even after prolonged infusion, allow a greater control of the depth of anesthesia than with pentobarbital or midazolam [14]. Its $t_{1/2}$ is 2 h, but its effect is shorter (minutes) because of its rapid distribution into peripheral tissues. 1–2 mg/kg load is followed by infusion at 5–120 mcg/kg/min, with up-titration in increments of 10 mcg/kg/min every 10–15 min to EEG response/side effects. It has a rapid onset of action: Seizure control occurs in 2–3 min versus 123 min with pentobarbital. It often requires high doses (e.g., $\geq$50–100 mcg/mg/kg/min) to induce burst suppression, often with associated hypotension requiring i.v. pressor support. It has common and potentially lethal side effects, chiefly hypotension, metabolic acidosis, pneumonia, and the "propofol infusion syndrome" (PRIS). PRIS occurs at high doses with prolonged infusion, e.g., >4 mg/kg/h for more than 24 h, more so with co-treatment with catecholamines and steroids. It consists of unexplained lactic acidosis, rhabdomyolysis with elevated creatinine kinase, hypertriglyceridemia, and widespread ECG changes, including cardiac arrest. Prolonged propofol infusion is associated with other serious systemic complications, most commonly pneumonia. In one study of adults with RSE, there was 57% mortality with propofol treatment versus 17% with midazolam.

Midazolam rapidly enters brain tissue. It has a powerful short duration. 0.4 mg/kg/h infusion rate is more effective in RSE than 0.2 mg/kg/h infusion rate, with lower mortality of 40% versus 62%. There is a risk of development of acute tolerance with risk of seizure relapse. Breakthrough seizures may occur in 50% of patients. Side effects include hepatic and renal impairment, respiratory, and cardiac depression, although the latter is less pronounced than with barbiturates.

Pentobarbital has longer half-life, making quick adjustments and evaluation of mental status after discontinuation of the infusion more difficult [16]. It is associated with the greatest incidence of systemic complications, particularly hypotension, splanchnic hypoperfusion (leading to gastric, pancreatic, and hepatic sequelae), immunosuppression, with attendant risks of

infections most commonly pneumonia, but also nosocomial iv sepsis via catheter, or UTI; and reduced GI motility. The side effects may limit treatment dose and duration.

Inhalational agents: Inhalational halogenated anesthetics such as isoflurane and desflurane have been used successfully to control seizures in small numbers of patients who do not respond to intravenous agents [14]. The logistical and safety implications of providing inhalational anesthesia in the ICU are substantial, and such treatment is not a realistic option in most circumstances.

Other agents are used in clinical practice in RSE. They include *valproate*, *topiramate*, *levetiracetam*, *lacosamide*, *ketamine*, and i.v *lorazepam* infusion. Evidence of efficacy of VPA, TPM, LEV, LCM, and ketamine is based on uncontrolled studies, retrospective reviews, and case series reports.

Other ancillary treatments used in continued refractory status epilepticus unresponsive to standard treatments have included hypothermia, ketogenic diet, immunotherapy—including IVIG and plasmapheresis—resective surgery, and vagal nerve stimulation. Their use is based on anecdotal and case series evidence only.

RSE treatment monitoring includes monitoring of electrolytes, calcium, magnesium, blood gases, and pH, and monitoring for and treatment of concurrent infection, fever, rhabdomyolysis, hypotension, and bradycardia, all of which may worsen RSE outcome.

Refractory NCSE: Because the side effects of treatment might outweigh its potential benefits in NCSE, there remains debate about whether NCSE should be treated as aggressively as GCSE. Administration of anesthetic agents is often postponed until a trial of a third-line non-anesthetic anticonvulsant has been completed [15].

SE Treatment Outcome

The two factors that best predict SE treatment response versus resistance are etiology and RSE duration. Poor response is associated with SE caused by acute structural lesions such as CVA, TBI, encephalitis, and other infectious, inflammatory and paraneoplastic causes in previously non-epileptic patients—with RSE duration of >1 h. Good treatment response occurs in idiopathic SE in previously non-epileptic patients; SE is associated with ASM non-compliance in epileptic patients and SE duration of <1 h [13].

SE prognosis: Overall mortality is 3–6% in children, 14% in young adults, 38% in the elderly. It is 3% with SE duration of 30–60 min and 32% with duration of >1 h. It is higher with an acute precipitant, in acute symptomatic epilepsy, after anoxic brain injury, in the elderly, and in SE duration of >24 h. It is low in the context of alcohol withdrawal or ASM non-compliance in an epilepsy patient. Approximately 15% of patients have severe and 15% of patients have mild neurological deficit. 35% of patients recover to baseline [14].

In children with convulsive SE, mortality is 3–5% short term and further 3% long term, with similar risk factors for poor and favorable outcome as with adults. 25–40% of children with SE develop subsequent epilepsy. This is highest with acute symptomatic convulsive SE. 35% children with SE > 30 min go on to have neurodevelopmental decline.

RSE outcome: RSE has mortality of 39–48% in adults and 16–44% in children. 28% adults and 32% children return to baseline.

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EEG in Encephalopathy and Coma

9

Mohamad Z. Koubeissi, Nabil J. Azar and Peter W. Kaplan

The EEG is a very important part of the evaluation of patients with acutely altered mental status. Many of these patients are referred from intensive care settings, and a routine initial step often involves obtaining a 20-min record to screen for seizures, status epilepticus, encephalopathy, or even hypersomnolence. More recently, there has been a move to prolonged monitoring with continuous EEG monitoring (cEEG) also being made available in the intensive care setting with the possibility of remote reviewing of the record. The exact place for extended recordings remains under consideration, but a recent study has revealed that about 20% of comatose ICU patients have non-convulsive seizures [1]. There are some data to suggest that non-convulsive seizures and non-convulsive status epilepticus (NCSE) are associated with worse outcome in patients with subarachnoid hemorrhage, or following head trauma [1–4]. In 88% of ICU patients, seizures may be detected within the first day of monitoring, but in those with coma, the first seizure is typically recorded after the first 24 h. Predictors of seizures on continuous EEG monitoring in the ICU include coma, age <18 years, history of epilepsy, convulsive seizures prior to monitoring [1], CNS infection, brain tumor, recent neurosurgery, and periodic epileptiform discharges [5].

Status epilepticus is discussed in Chap. 8 and will not be discussed in this chapter. Rather, we will explore the principal EEG findings in encephalopathic patients and their clinical relevance. EEGs may be done for diagnosis, monitoring of the effects of treatment, or for prognosis. Regarding the latter, there is an increasing body of work that supports the notion that prognosis depends heavily on the etiology of confusion and coma. For example, a particular coma pattern due to medication toxicity may prove to be reversible, while conversely, it may herald a very poor prognosis if due to hypoxic–ischemic brain injury. Other EEG patterns may predict outcome, independent of etiology. For example, EEG reactivity during which there may be a change in EEG amplitude, frequency, or the appearance of other patterns following noxious stimulation, noise or eye opening may indicate a more favorable prognosis. Spontaneous variability along the course of a recording typically suggests a better prognosis than when the EEG is suppressed, monotonous, and unreactive.

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Intermittent Rhythmic Delta Activity (IRDA)

IRDA refers to diffuse, synchronous 2–3 Hz sinusoidal waves that are often maximal anteriorly. It often occurs on a background of delta- or theta-range slowing and can be occasionally asymmetric. As the term "intermittent" implies, it often has an abrupt onset and offset, and is typically a reactive pattern that is blocked by eye opening. In children, it may be maximum in the posterior head regions and termed occipital intermittent rhythmic delta activity, or OIRDA.

IRDA was long believed to be a pattern indicative of deep-midline dysfunction originally seen in children with midline tumors and raised intracranial pressure [6], and latter with structural lesions involving both the cortical gray matter and deep nuclei [7]. With time, it came increasingly to be seen in the elderly, typically with a frontal predominance (FIRDA), associated with background slowing. It signifies cerebral dysfunction, commonly diffuse encephalopathy, although it can be seen with focal lesions. It is seen early in coma, soon after loss of the posterior basic rhythm, but is non-specific in terms of pathology. As for all encephalopathic patterns, the prognosis of IRDA depends largely on the underlying pathology.

Building on the work of others, Accolla and colleagues in a prospective study noted that FIRDA occurred with toxic-metabolic disturbances and with structural lesions, but did not correlate with epilepsy [8]. More recently, a large retrospective study found significant statistical correlations with strokes and noted its favorable prognostic significance [9]. While IRDA is not associated with epilepsy, OIRDA in children can have either an encephalopathic or epileptiform significance, as it has been described in association with focal epilepsy and generalized epilepsy, especially absence seizures [10].

Triphasic Waves

As the name implies, triphasic waves consist of three phases of increasing duration and decreasing slopes. The initial phase is negative, brief, and steep, and is followed by a second positive trough of longer duration and slightly slower slope. The magnitude of this second positive phase is the largest, generally higher than 70 μV. It is followed by a third phase that is negative and largest in duration. The duration of the triphasic wave is 150–500 ms. The distribution is generally anterior-dominant, although they may be posterior-dominant in some cases. On the longitudinal bipolar montage, the positive trough may show an anterior-to-posterior lag (Fig. 9.1). When they are maximal in the occipital region, a posterior to anterior lag may be seen (Fig. 9.2). Triphasic waves often occur with a frequency of

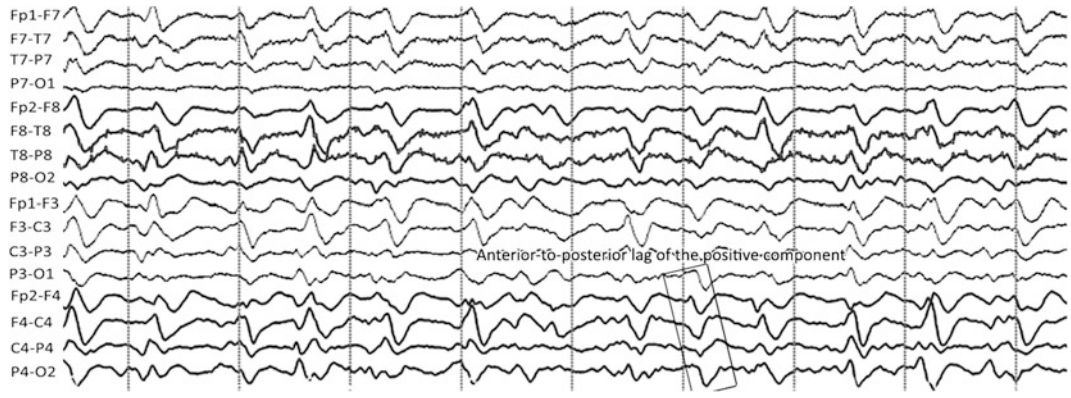

Fig. 9.1 Triphasic waves in an encephalopathic patient. Notice the anterior-to-posterior lag in the second (positive) component of the triphasic wave (*boxed*)

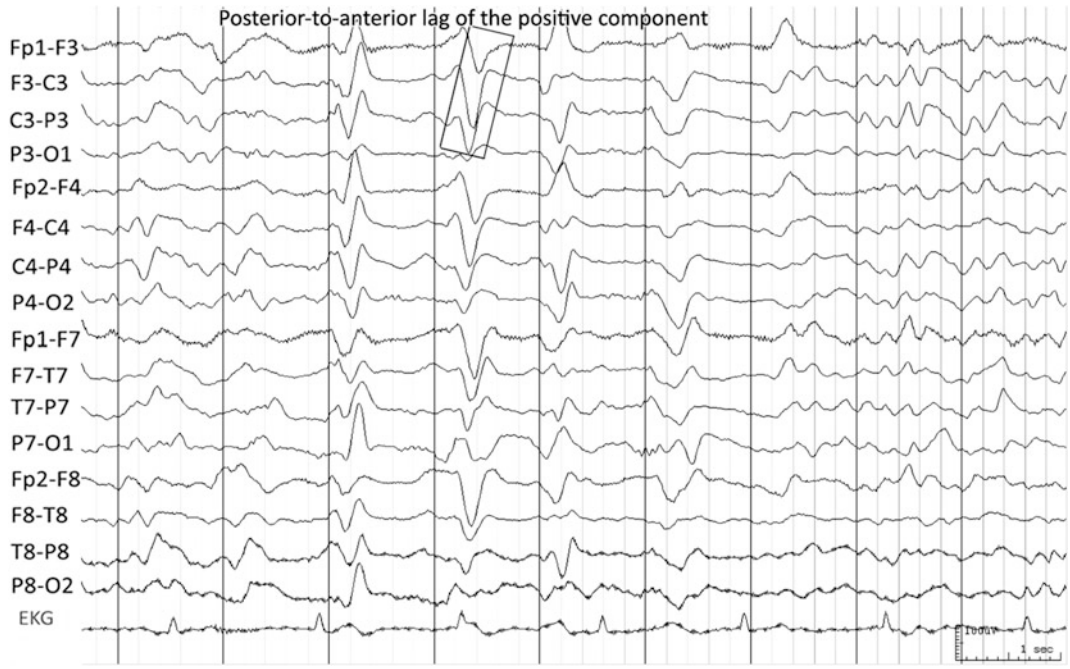

Fig. 9.2 Notice the posterior-to-anterior lag in the second (positive) component of the triphasic wave (*boxed*)

once or twice per second on a slow background. They can be bilaterally synchronous or appear independently on either side.

The cause of triphasic waves has classically been attributed to metabolic encephalopathy such as liver or kidney failure. However, they have also been described in the other toxic and metabolic conditions, including lithium toxicity and hyponatremia, or even with subcortical white matter disease [11]. Interestingly, they may decrease upon administration of benzodiazepines without an improvement in sensorium, making the distinction from epileptiform discharges difficult.

Continuous High-Voltage Polymorphic Delta (PDA)

PDA is 1–2 Hz, high-amplitude, arrhythmic slow-wave activity that is generally seen in the later stages of coma than IRDA and triphasic waves, but may still attenuate with stimulation. As the coma deepens, the predominant frequency in PDA becomes slower and loses its reactivity to stimulation.

PDA is believed to be generated in pyramidal neurons in cortical layers II, III, and V. Schaul and colleagues found that this pattern was largely seen in dysfunctions of the subcortical white matter or with lesions which partially deafferented white matter [12, 13]. Further studies revealed that it could be seen with metabolic, toxic, or infectious encephalopathies [14], and less commonly with infratentorial lesions involving the thalamus and rostral brainstem [15, 16]. Occasionally, PDA or more frequently continuous RDA occurs with deep-seated epileptic foci that are remote from the scalp surface, with limbic encephalitis and with limbic status epilepticus.

Figure 9.3 shows bilateral waxing and waning medium-to-high voltage 1–3 Hz delta activity with some interspersed lower voltage theta frequencies. There is little alpha or beta activity. The patient had severe head trauma and remains alive but with little functional recovery.

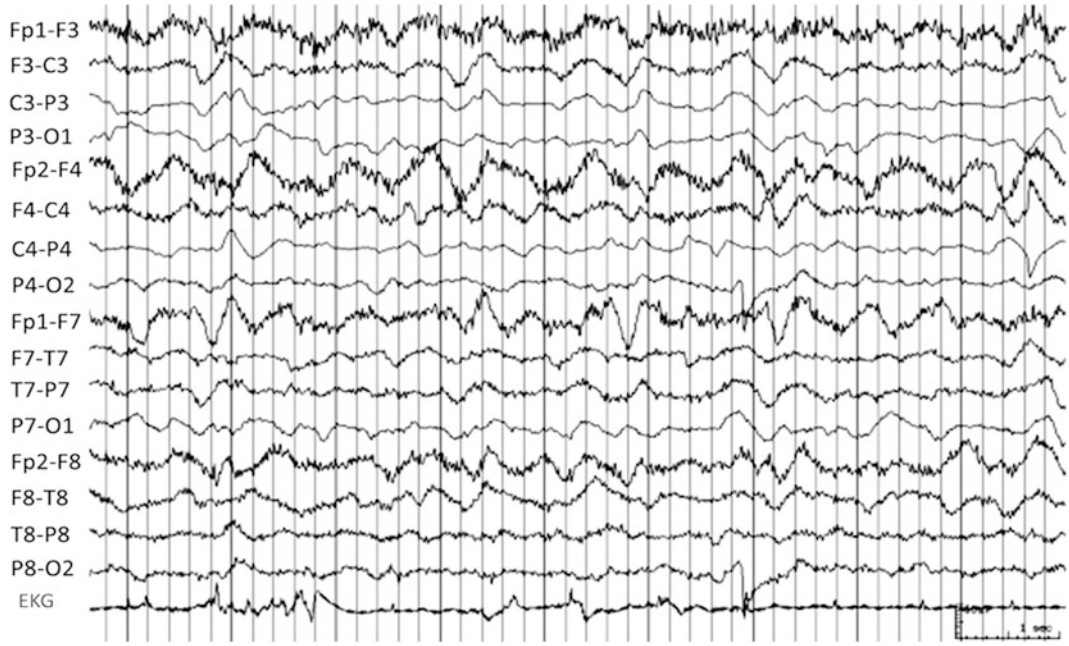

Fig. 9.3 Medium-to-high-voltage 1–3 Hz polymorphic delta activity in a patient with severe head trauma who had little functional recovery

Generalized Periodic Epileptiform Discharges

GPEDs are generalized, usually high-voltage sharp or spike morphologies, occasionally polymorphic, occurring synchronously and bilaterally. The discharge frequency typically is 0.5 Hz or slower and occurs in an unreactive coma, sometimes with low-amplitude face or limb myoclonus. There is often little background activity between discharges, but theta and delta may occur. As the coma deepens, amplitude of the inter-GPED activity decreases.

There is a high association of clinical seizures or electrographic seizures before or after the recording of periodic discharges, more so with GPEDs. The most frequent cause is cerebral anoxia after cardiorespiratory arrest. A poor outcome (mortality or vegetative state) is >97%. Severe metabolic disease and overdoses of lithium and baclofen may also cause GPEDs. The EEG should raise the suspicion of CJD. Patients with later stages of subacute sclerosing encephalitis (SSPE) can have GPEDs with longer inter-GPED interval.

Figure 9.4 shows GPEDs at 1.2 Hz in a patient after cardiac arrest. The record showed little background and no reactivity to stimuli. There were no brainstem reflexes and the patient died.

Burst Suppression Pattern

Burst suppression pattern refers to synchronous bursts of high-voltage, mixed frequency activity, separated by periods of EEG suppression to less than 10 μV (Fig. 9.5). The bursts contain spikes and discharges of almost any other frequency. The duration of the suppression increases with deepening coma or anesthetic agent dose. Etiologies that are commonly associated with burst suppression pattern include anoxic encephalopathy, drug

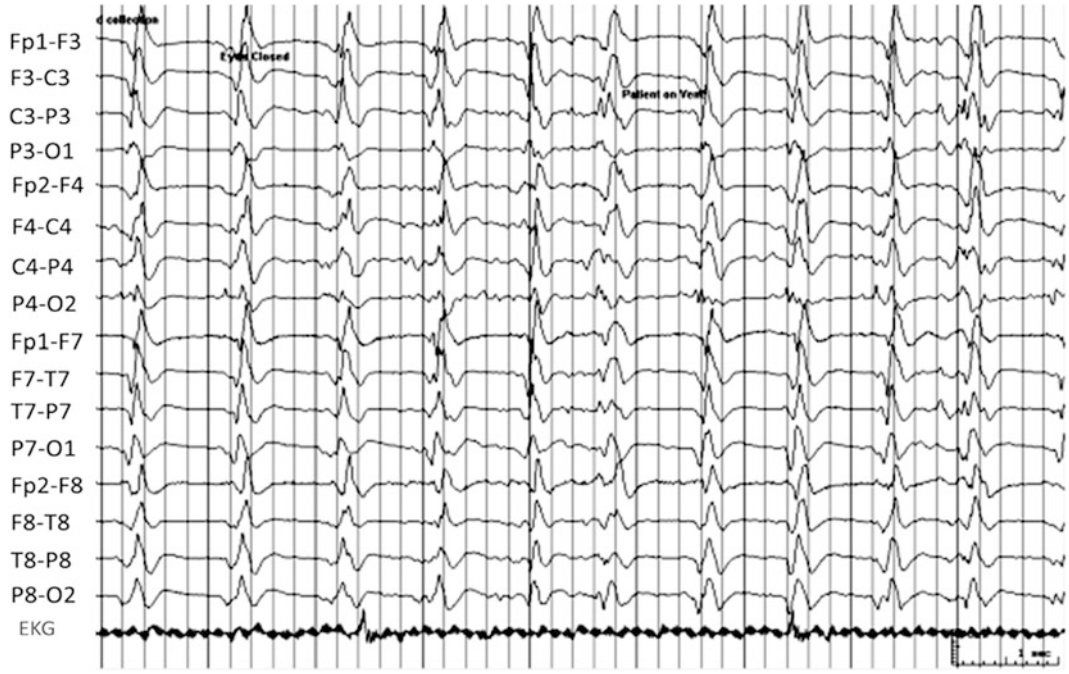

Fig. 9.4 GPEDs at 1.2 Hz in a patient after cardiac arrest

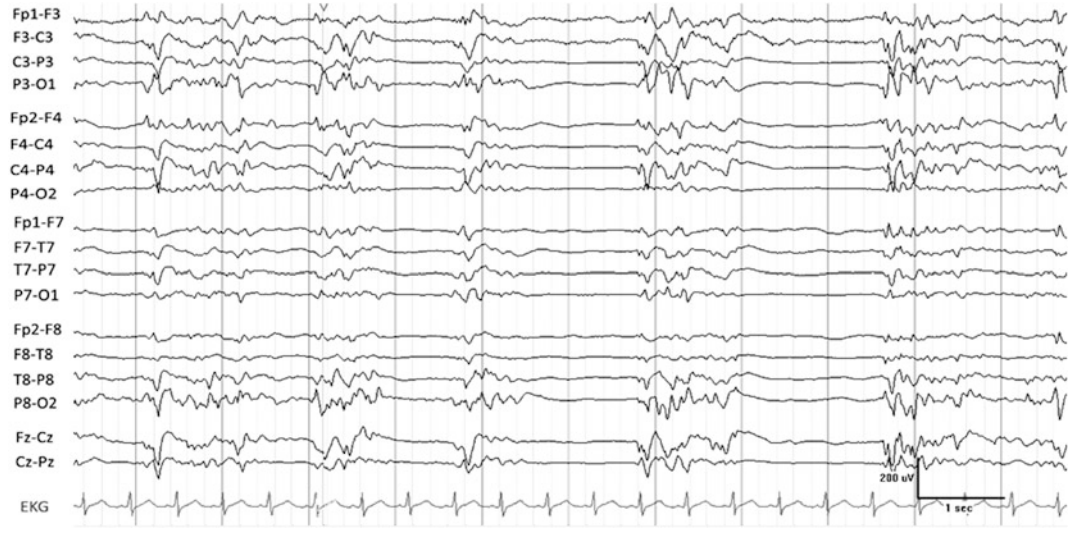

Fig. 9.5 Burst suppression pattern

intoxication, anesthetics, and hypothermia. This pattern is generally reversible if induced by hypothermia or anesthetics, including barbiturates or benzodiazepines. However, if it occurs in the setting of anoxic encephalopathy, it is associated with poor prognosis. Indeed, this pattern occurs shortly before progression to electrocerebral inactivity.

Low-Voltage Slow Non-reactive EEG

Low-voltage records (<20 μV) without variability or reactivity occur with anoxia or less frequently with severe metabolic and ischemic disturbances. Following cardiac arrest, it carries a zero percent prognosis for return to consciousness, but care must be taken to exclude significant hypothermia and sedative or anesthetic agents. Low-voltage fast patterns conversely may be seen in ~5% of the normal population and with alcoholism and sometimes with benzodiazepine use, but will also possess normal variability and reactivity.

Electrocerebral Inactivity

Electrocerebral inactivity (ECI) (Fig. 9.6) represents an EEG pattern where no activity of cortical origin can be seen. The EEG often shows many types of artifacts, such as EKG, respiration, and intravenous drips. The record must be run so as to conform to the Guidelines of the American Clinical Neurophysiology Society (ACNS) (http://www.acns.org/pdf/guidelines/Guideline-3.pdf):

- *Minimum of 8 scalp electrodes and earlobe references*
- *Electrode Impedance must be between 100 and 10,000 Ω*
- *Interelectrode distance should exceed 10 cm*
- *EEG must be read with sensitivity of 2 μV/mm and a*
- *τ = 0.3–0.4 s*
- *Integrity of the whole system should be tested*
- *Monitoring techniques (EKG, Ventilator,* etc.*) should be kept in mind as sources of artifact*
- *Reactivity to pain and loud sound must be checked*
- *Assessment of adequate core body temperature is required*

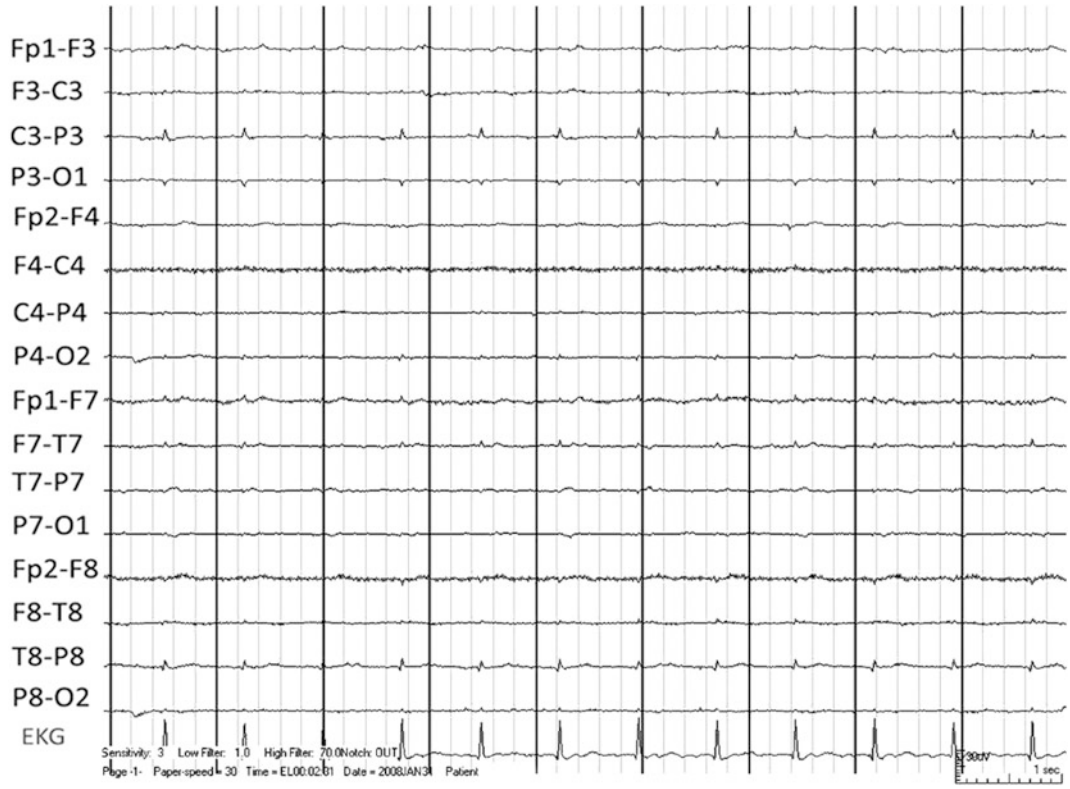

Fig. 9.6 Electrocerebral inactivity (ECI)

- *Recording should last for at least 30 min, and done by qualified technologists*
- *Electroencephalographers should read the EEG at the bed side, and are advised to repeat the following day if they suspect electrocerebral silence.*

Once these criteria are satisfied, and if the presence of anesthetic or suppressant drugs is excluded, the finding of ECI in concert with an appropriate clinical examination (demonstrating the lack of brainstem reflexes) indicates "brain death." These recordings are usually obtained after cardiorespiratory arrest, severe head trauma, and intractable malignant raised intracranial pressure.

Spindle Coma

Spindle coma is a pattern of sleep architecture in which bilateral bursts of fronto-central 9–14 Hz "spindles" are recorded (Fig. 9.7). If the coma deepens, the spindle frequency slows. Often the spindles occur in concert with generalized slow negative waves constituting K-complexes. The spindles may be prolonged and exceed 2 s Typically, the EEG tracing of sleep architecture is unreactive to external stimuli or at least returns to this pattern without a clinical return to consciousness.

First described by Jasper and Van Buren [17] in a patient with a midbrain tumor near the 3rd ventricle, it has since been reported in >250 patients with an aggregate prognosis for death of ~25%. Spindle coma pattern is seen with head injury, anoxic encephalopathy, viral encephalitis, drug intoxication, metabolic encephalopathy, and post-ictal states. It also may be due to lesions in the pontomesencephalic junction. Prognosis is often favorable, but generally depends on associated features, particularly reactivity. Studies have also shown the prognosis to depend on the etiology of coma, and to be about 73% with structural abnormalities of the brainstem, a third after hypoxia, about 15% after head trauma, and negligible when with following seizures or with drugs [18].

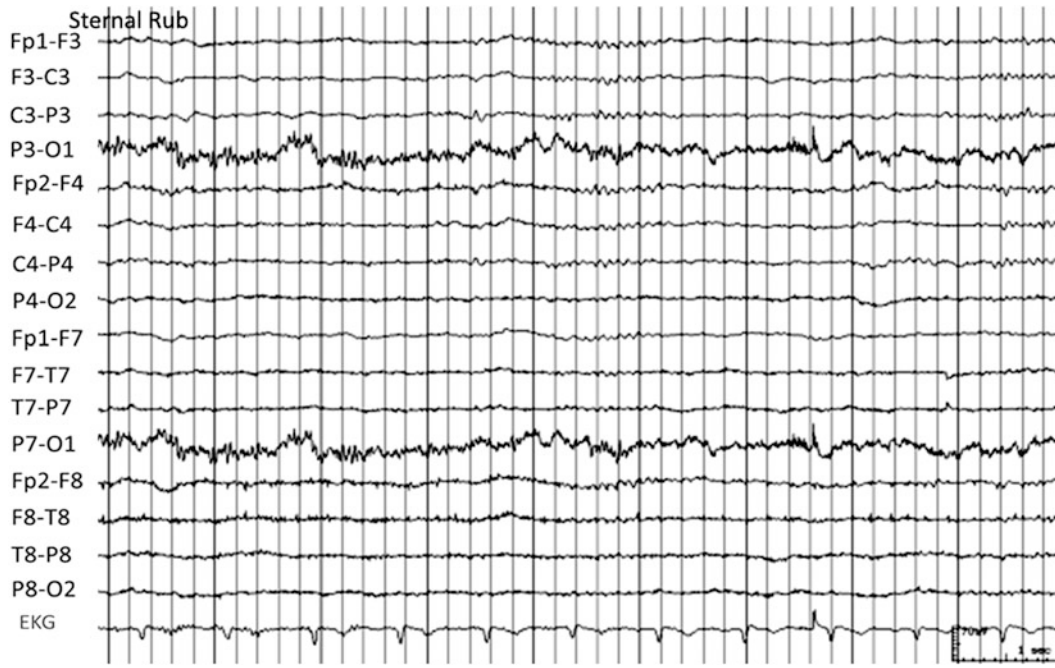

Fig. 9.7 Sleep-like bursts of spindles that are non-reactive to external stimuli. The patient recovered

Alpha-Theta Coma

Alpha frequency patterns in coma, and "alpha coma" was first described by Loeb and Poggio in 1953 in a patient with brainstem hemorrhage [19]. Unlike a waking alpha rhythm, it is usually diffusely distributed and often anteriorly dominant, and typically invariable and unreactive to external stimuli (Fig. 9.8). The coma pattern is named after the predominant rhythm, which can be in the alpha or theta range. The rhythm is generally diffuse, commonly anterior-maximum, and monomorphic. Alpha coma is seen in individuals with anoxic brain injury, in which case it is non-reactive to stimuli and signifies poor prognosis. When alpha coma is due to toxic encephalopathy, it is also anterior-maximum, but with possible superimposed beta activity. It may result from overdoses of benzodiazepines, barbiturates, anesthetic agents, imipramine, and meprobamate. When alpha coma occurs as a consequence of drug overdose, some degree of reactivity is usually maintained, and it typically evolves into a more favorable pattern. The overall mortality for the aggregate 335 cases with alpha coma was 76%, with mortality varying according to etiology [20, 21]. Brainstem infarction and anoxia after cardiorespiratory arrest was ~90%, while other causes, including drug intoxication, were much less (<10%) [18].

The alpha rhythm may be maximum posteriorly (similar to the posterior-dominant rhythm) in comatose individuals after brainstem lesions at the pontomesencephalic level. Like the posterior basic rhythm, the posterior dominant pattern may be reactive to sensory stimulation and photic driving. However, the prognosis is poor.

Beta Coma

Despite the ubiquity and abuse of benzodiazepines, and previously of barbiturates, this pattern remains infrequent, in contrast to the

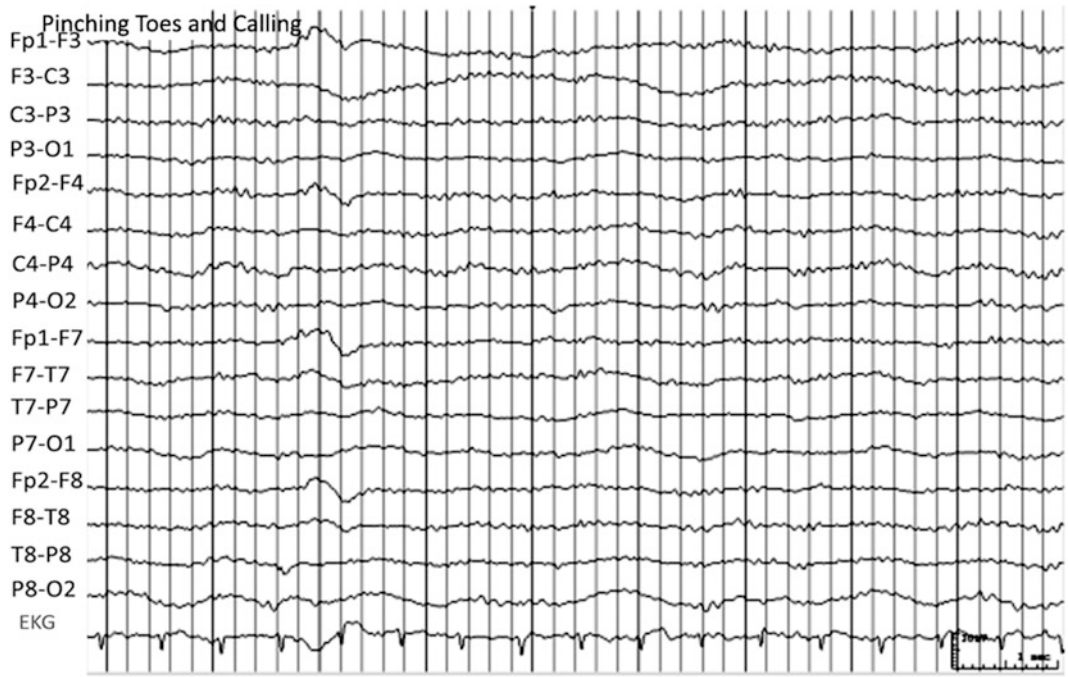

Fig. 9.8 Low-voltage recording of a patient after cardiorespiratory arrest with alpha frequencies seen diffusely bilaterally and prevalent in the frontal head regions. Following noxious stimulation, there is no evidence of EEG reactivity. The patient died

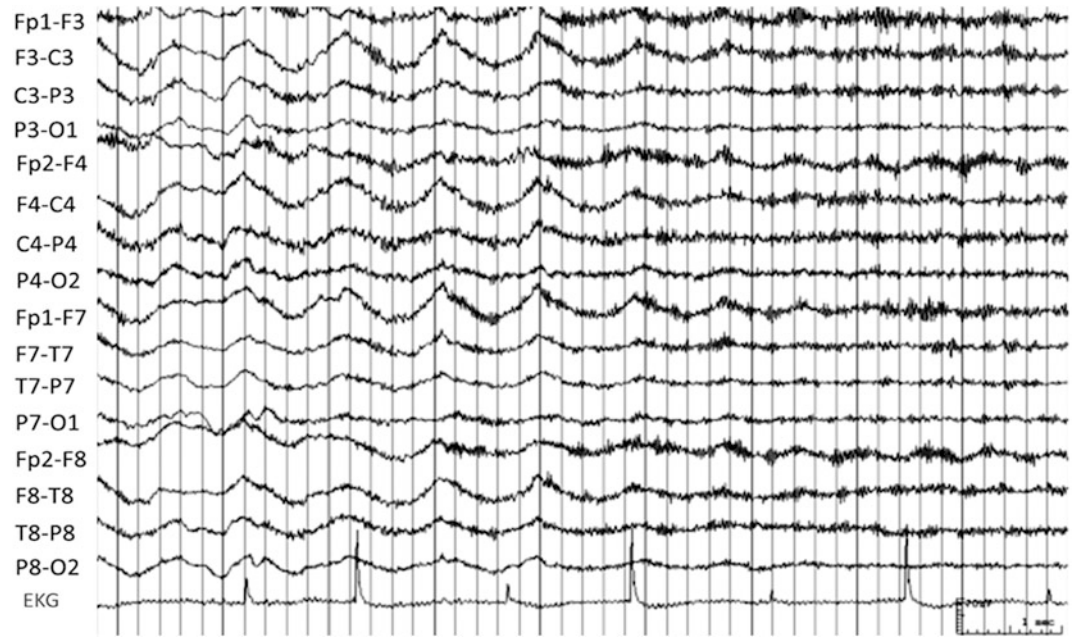

Fig. 9.9 Beta coma pattern

frequently encountered excessive fast activity in the EEG non-comatose patients receiving benzodiazepines or barbiturates. Beta coma or encephalopathy (Fig. 9.9) produces an EEG with high-frequency spindle-like bursts at ~20–25 Hz, often diffusely, but typically involving the fronto-central regions. Waking background is often seen, as is theta activity, and the patient is rarely deeply unresponsive. The beta activity is usually little reactive to external stimuli. Causes include benzodiazepines and barbiturates. Excess EEG beta activity can be seen in awake or confused patients with alcohol or other withdrawal states.

Creutzfeldt–Jakob Disease (CJD)

CJD is a transmissible prion disease that can be familial, sporadic, or iatrogenic. CJD is the most common of all prion diseases, and 5–15% of the cases are clustered in families. Progressive dementia is the hallmark of the first stage of the disease. In the second stage, rigidity and the myoclonus appear. In the third stage, there is stupor, coma, worsening rigidity, and progression to death. The EEG shows slowing and disorganization of the background rhythms in the first stage (Fig. 9.10). In the second stage, there are periodic bilaterally synchronous discharges of diphasic or triphasic morphology with voltages reaching 300 μV. With more disease progression, multiphasic discharges or polyspikes may appear. Classically, the frequency of these periodic discharges is 1 per second, and they may be associated with myoclonic jerks. These periodic discharges persist into the third stage with gradual increase in the interdischarge interval, gradually evolving into further attenuation of the background activity.

Subacute Sclerosing Panencephalitis (SSPE)

SSPE is a result of a delayed immunological reaction to measles infection, and the EEG has a characteristic pattern of extremely high-voltage periodic discharges with very low interdischarge frequency, occurring every 4–14 s. Unlike the

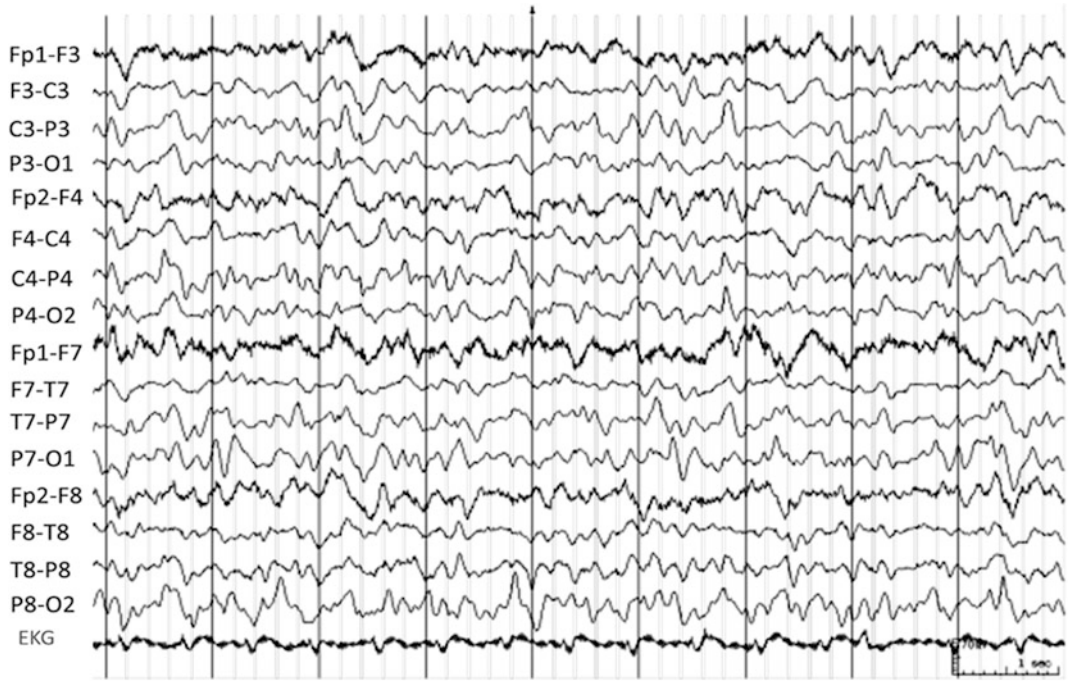

Fig. 9.10 EEG in the early stages of Creutzfeld–Jakob disease

diphasic or triphasic discharges of CJD, the periodic complexes of SSPE are often slow waves with or without sharply contoured waveform components. They are generalized often with frontal predominance. Interestingly, these periodic discharges may initially appear while the background is still within normal limits. This is in contrast to CJD when the background disorganizes invariably prior to the appearance of the periodic discharges.

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Multiple Choice Questions for Part II

1. A 9-month-old-male infant has a seizure that lasted for 20 min and started with left-sided clonic jerking. He had a similar episode 6 h later. About 1 h before the first seizure, he had a fever of 102.7 °F, and he was diagnosed in the Emergency Department with an otitis media. There is a family history of febrile seizures but not epilepsy. Which of the following factors makes it most likely he will develop epilepsy?

   A. This was a complex febrile seizure
   B. Temperature prior to seizure
   C. Presence of otitis media
   D. Family history
   E. Age

2. Auras associated with neocortical temporal lobe seizures are characterized by all except:

   A. Visual hallucinations
   B. Clonic activity
   C. Auditory hallucinations
   D. Vertigo
   E. Inappropriate fear

3. What duration of continuous EEG monitoring in the ICU is needed to detect most of the seizures in a comatose patient?

   A. 20 min
   B. 1 h
   C. 12 h
   D. 48 h
   E. Data are not available

4. A 6-year-old boy presented with his first seizure, characterized by facial twitching on the left-side and left-arm jerking, both of which lasting 45 s. The seizure occurred 1 h after he went to sleep at night. Which of the following is true about the most likely diagnosis?

   A. It typically persists until mid-adulthood.
   B. Most patients have 10–20 seizures over their lifetime.
   C. Most patients with this syndrome have medically intractable epilepsy.
   D. Patients can have associated language-related developmental abnormalities.
   E. The EEG in this syndrome typically is normal.

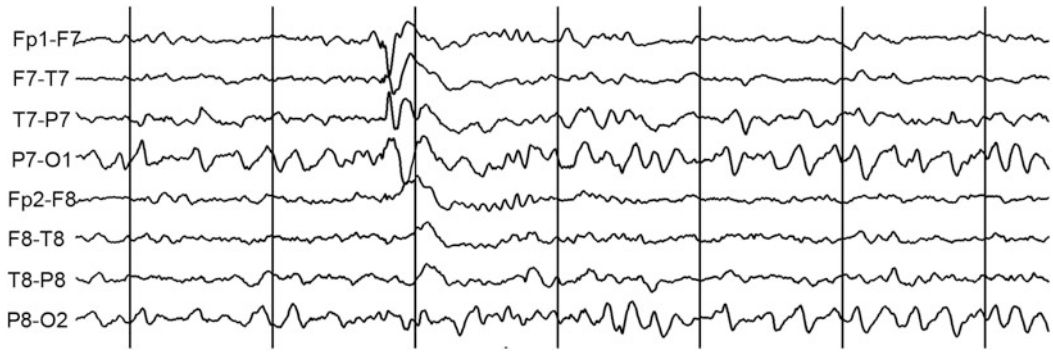
5. Among ICU patients with altered mental status, continuous EEG monitoring shows non-convulsive status epilepticus to be present in approximately:

   A. 55%
   B. 20%
   C. 5%

D. 75%
E. None of the above

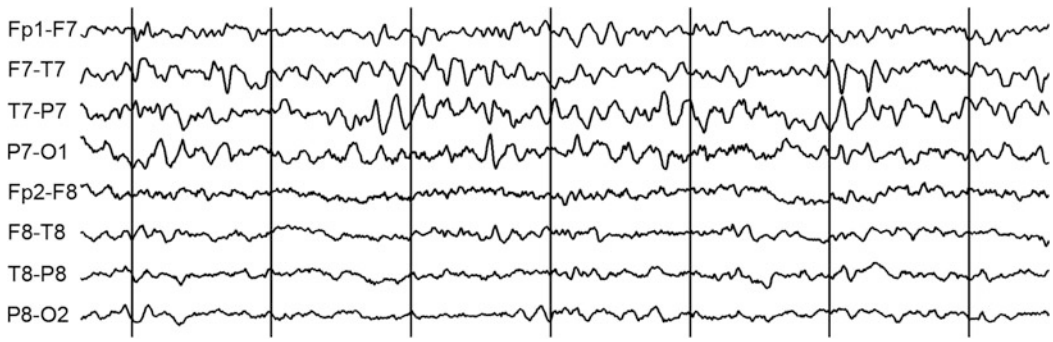
6. The following EEG illustrates which of the following findings?

A. Sleep spindles
B. Left temporal sharp and slow wave
C. Occipital lobe seizure
D. Triphasic waves
E. A & B



7. Which of the following is true about the following EEG?

A. It suggests a seizure focus in the left inferior parietal region
B. It is consistent with the previous brain surgery



C. It is indicative of encephalopathy
D. It shows triphasic waves
E. C & D

8. Which of the following are among the 3 most common causes of SE in children?

A. Change in antiepileptic drug treatment, administration, or compliance
B. Congenital abnormalities
C. Tumor
D. CNS infection
E. None of the above

9. Clinical features of mesial temporal lobe epilepsy include all except:

A. Early age of onset
B. History of complex febrile seizures
C. Stuttering course of seizure control
D. Clonic movements
E. Hippocampal atrophy

10. All of the following are true about initial investigation into patient with seizure in ER except:

A. CK levels obtained between 6 and 12-h post-event show elevated levels in convulsive seizures and not in PNES
B. Prolactin level should be drawn within 20 min of event to differentiate organic event with the loss of consciousness with PNES
C. Lactic acid levels drawn soon after an episode will show elevated levels after convulsive seizure
D. Repeat EEG should be performed in patients with alcohol withdrawal seizures and EEG showing generalized spike-and-waves
E. All of the above are true

11. Which of the following is true about recurrence of febrile seizures?

A. Phenytoin is effective in preventing recurrences.
B. The risk of recurrence is increased if the temperature was high at the time of the seizure.
C. The older the age, the more likely the febrile seizure is to recur.
D. Complex febrile seizures are more likely to recur than simple febrile seizures.
E. Frequency of febrile illness is directly correlated with recurrence risk.

12. During carotid endarterectomy, intraoperative EEG monitoring can help avoid:

A. Seizures
B. Carotid clamping
C. Hypotension
D. Shunting
E. EEG is useless

13. In treatment of refractory status epilepticus all of the following statements are true except:

A. Continuous propofol infusion of >50 mcg/kg/min is associated with a risk of hypotension
B. Hypothermia may be used as adjunctive treatment
C. Levetiracetam dose used should not be less than 2000 mg/day
D. Mortality rate is higher with i.v. midazolam than with i.v. propofol
E. Lacosamide may be effective adjunctive treatment

14. Seizures with generalized onset are seen in which of the following genetic epilepsies?

A. Benign childhood epilepsy with centrotemporal spikes
B. Autosomal dominant nocturnal frontal lobe epilepsy
C. Temporal lobe epilepsy with auditory features
D. Dravet syndrome
E. None of the above

15. Among the following factors, the one that is associated with the most favorable outcome in SE is:

A. Early treatment initiation
B. Non-compliance with anticonvulsant medications in patients with established epilepsy
C. Epilepsy onset in the elderly
D. Early arrival in the hospital
E. None of the above

16. Which of the following is false about idiopathic generalized epilepsy (IGE)?

A. Family history of epilepsy is often present
B. Motor seizures have a tendency to occur upon awakening
C. Photosensitivity seen in ~5% of patients
D. EEG background is often abnormal
E. Family history of febrile seizures can be positive

17. Which of the following statements is true about slow spike-and-wave complexes?

A. They have a frequency that is faster than that of absence epilepsy
B. Seen in Lennox–Gastaut syndrome
C. Are deactivated by sleep
D. Are associated with normal posterior basic rhythm
E. None of the above

18. A 5-year-old girl is seen in the first seizure clinic after a nocturnal episode of vomiting, pallor, behavioral irritability, and then eye deviation to the right and unresponsiveness, followed by a generalized tonic clonic seizure. The total duration of the episode was 5 min. Her development has been normal, and there is no family history of seizures. Which of the following is true?

A. This epilepsy syndrome has a poor prognosis for seizure control.
B. Treatment typically includes corticosteroids and vigabatrin.
C. Most patients with this disorder have major structural brain malformations.
D. Trauma is a frequent antecedent of this epilepsy syndrome.
E. The EEG likely will show paroxysms of occipital spikes.

19. Which of the following is not true about atonic seizures:

A. Slow waves correspond to atonia
B. Loss of muscle tone lasts <100 ms
C. Ictal EEG can consist of generalized polyspike-and-wave activity
D. Ictal EEG may consist of low-voltage fast activity
E. All of the above are true

20. Which of the following statements is not true about ictal EEG?

A. It is marked by monomorphic features
B. It is often not seen in association with seizures that do not cause alteration of awareness
C. When seen on the EEG before clinical seizure onset, it tends to be of more localizing value to the epileptogenic zone
D. When onset is characterized by high-frequency activity, it indicates proximity of the recording electrodes to the epileptogenic zone
E. None of the above

21. Which of the following statements is true about EEG in generalized epilepsies?

A. In absence epilepsy, the ictal discharge has an abrupt onset and termination
B. In juvenile myoclonic epilepsy (JME), polyspike-and-slow-wave discharges are seen at a frequency of around 5–6 Hz
C. Tonic seizures are often associated with voltage attenuation
D. Tonic–clonic seizures may start with 10 Hz activity that gradually increases in voltage
E. All of the above are true

22. A 6-month-old female is referred by a gastroenterology colleague for episodes of trunk flexion that occur in clusters four times per day. This has been occurring for the last 3 days. There have been some concerns about her vision, and her head control is poor. Which of the following is true?

A. She has gastroesophageal reflux and should be referred back to her gastroenterologist
B. She has an exaggerated startle reflex and should be referred back to her pediatrician for routine care and developmental follow-up
C. She has one of the benign epilepsy syndromes of infancy and, after an EEG, should be followed routinely in 3 months in your clinic
D. She has a malignant epilepsy syndrome of infancy and should have an EEG, MRI, and further genetic and/or metabolic workup, depending on the initial findings
E. She likely has seizures originating from the left temporal region and, after an EEG, should be started on levetiracetam

23. Which of the following statements is not true about epileptiform discharges?

A. Anterior temporal spikes have higher association with seizures than occipital spikes
B. Spikes can be seen in non-epileptic conditions, such as congenital blindness
C. Multifocal spikes are commonly associated with a slow EEG background
D. Multifocal spikes tend to be associated with cognitive but not motor deficits
E. In BECTS (Benign Epilepsy with Centrotemporal Spikes), the positive end of the dipole is in the frontal regions

24. Recognized pathophysiological mechanisms of pharmacoresistance in refractory status epilepticus include:

A. Failure of presynaptic synthesis of GABA
B. Failure of release of GABA from pre-synaptic vesicles
C. Failure of synaptic glutamate transport mechanism
D. Internalization and destruction of synaptic GABA-A receptors
E. None of the above

25. On day of life 3, you are consulted by the neonatal intensive care unit about an infant who has recurrent tonic spasms in clusters. The EEG shows a suppression-burst pattern. Which of the following is true about this epilepsy syndrome?

A. The prognosis for normal psychomotor development is poor
B. Seizures stop after the first few days of life
C. Seizures are treated easily, regardless of which medicine is used
D. Further workup frequently is not indicated
E. Mortality in this condition is low

26. Postictal aphasia localizes the seizure focus to the:

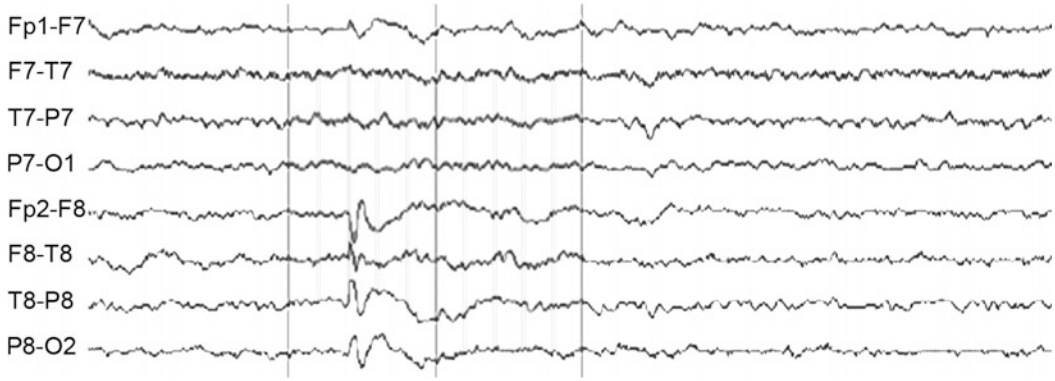
A. Right temporal region
B. Left temporal region
C. Right parietal region
D. Left parietal region
E. Right frontal region

27. Advantages of Fos-phenytoin in comparison with phenytoin include:

A. Lesser risk of allergic reaction
B. Water solubility
C. Subcutaneous administration
D. Lesser protein binding
E. None of the above

28. Which of the following is not true about the following EEG?

A. Suggestive of multifocal epilepsy
B. Suggestive of right temporal dysfunction



C. Suggestive of unilateral temporal lobe epilepsy
D. Seizures are unlikely to be associated with postictal aphasia
E. Comorbidities, including cognitive and psychiatric, are common in patients with such EEG

29. Seizures from the dorsolateral frontal convexity are characterized by all except:

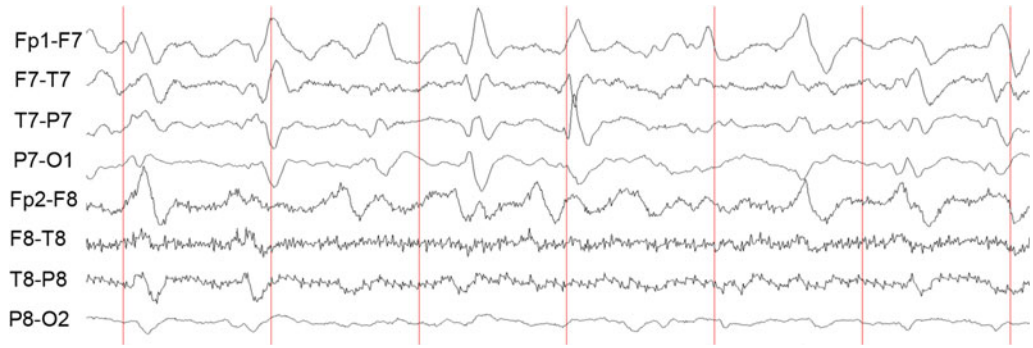
A. Forced head turning
B. Unilateral clonic activity
C. Preservation of consciousness
D. Olfactory hallucinations
E. Forced eyes turning

30. Which of the following is true about the ictal EEG of seizures that do not cause alteration of awareness?

A. When of neocortical origin, they are always associated with a beta range ictal discharge
B. When of mesial temporal origin, they are always associated with a delta range ictal discharge
C. Two-thirds of all such seizures will have a lateralizing ictal discharge
D. They are more likely to have an ictal discharge if they include motor phenomena
E. Their clinical semiology does not assist in their localization

31. Established effective treatment of status epilepticus treatment by EMS personnel on the way to the hospital includes:

A. Diazepam 20 mg i.v. bolus
B. Midazolam i.m. 10 mg bolus
C. Midazolam i.v. 10 mg bolus
D. Lorazepam 1 mg i.v. bolus
E. Clonazepam 2 mg intranasally



32. Which of the following is true about the EEG shown above:

    A. Pathognomonic of liver failure
    B. Left hemispheric seizure focus
    C. Normal sleep EEG
    D. Caused by medication toxicity
    E. Requires prophylaxis with antiseizure medications

33. Parietal lobe seizures are characterized by all except:

    A. Focal motor clonic activity
    B. Tonic posturing of extremities
    C. Painful or thermal paresthesia
    D. Sexual paresthesia
    E. Prominent autonomic features

34. According to the guidelines of the American Clinical Neurophysiology Society (ACNS), which of the following is needed for the recording of electrocerebral inactivity?

    A. Minimum of 12 scalp electrodes and earlobe references
    B. Interelectrode distance should be less than 10 cm
    C. Reactivity to pain and loud sound must be checked
    D. Electrode Impedance must be between 10 and 1000 Ω
    E. Time constant must be 0.3–0.4 ms

35. The incidence of SE in the USA has been estimated to approximately

    A. 0.9% of population
    B. 0.01% of population
    C. Between 18 and 40 per 100,000 population
    D. 6–7 per 100,000 population
    E. None of the above

36. Which of the following is true about generalized periodic epileptiform discharges (GPEDs)?

    A. Associated with clinical seizures
    B. The most common cause is drug overdose
    C. The outcome is very poor in <30%
    D. Distinct from the typical EEG of CJD
    E. Distinct from the typical EEG of SSPE

37. Metabolic consequences of convulsive status epilepticus may include all of the following except:

    A. Hypoglycemia
    B. DIC
    C. Renal alkalosis
    D. Hypotension
    E. Hyponatremia

38. A progressive change (increase or decrease) in which of the following will help identify ictal discharges on the EEG?

    A. Frequency
    B. Amplitude
    C. Field
    D. Morphology
    E. All of the above

39. Celiac disease has been associated with:

    A. Thalamic bleeds
    B. Occipital calcifications
    C. Chiari malformation
    D. Optic Glioma
    E. Any of the above

40. Which of the following is true about seizures in patients undergoing dialysis?

    A. Previous history of epilepsy does not increase risk of seizures in peritoneal dialysis
    B. Hypocalcemia in these patients is a significant cause of seizures
    C. Seizures can occur in patients who develop dialysis-associated dementia/chronic dialysis encephalopathy

D. Change in BUN pre- and post-dialysis is directly related to occurrence of seizures
E. In peritoneal dialysis, monitoring of glucose content can prevent seizures in nonketotic hyperosmolar coma
F. All of the above

41. Which of the following is not true about triphasic waves?

A. May occur in lithium toxicity
B. May occur in renal failure
C. Do not correlate with epilepsy
D. Worsen with administration of benzodiazepines
E. May occur in white matter disease

42. MRI scan of the brain during or after status epilepticus may show an increase in T2 signal in

A. The cerebellum contralateral to the side of ictus
B. The ipsilateral hippocampus
C. The ipsilateral posterior thalamus
D. The splenium
E. All of the above

43. The EEG target pattern during continuous EEG monitoring in refractory status epilepticus (RSE) includes:

A. Burst-suppression pattern with inter-burst intervals of at least 10 s
B. Any burst-suppression pattern
C. Burst-suppression pattern with suppression intervals of at least 3 s
D. Burst suppression with burst duration of no longer than 2 s
E. None of the above

44. Occipital seizures are characterized by all except:

A. Complex visual hallucinations
B. Repeated eye blinking
C. Vomiting
D. Tonic eye and head deviation
E. Simple visual hallucinations

45. Which of the following is not true about frontal intermittent rhythmic delta activity (FIRDA)?

A. Occurs with toxic disturbances
B. Occurs in liver failure
C. Correlates with epilepsy
D. Occurs in stroke
E. Associated with good prognosis

46. Insular lobe seizures are characterized by all except:

A. Dysarthria
B. Perioral warmth feeling
C. Hypersalivation
D. Laryngeal constriction
E. Complex gestural automatisms

47. The following is not true regarding generalized epilepsies.

A. Vagal nerve stimulator and disconnection of the two hemispheres are options in certain refractory cases
B. Many patients with JME have seizure relapse if antiepileptics are stopped even after years of seizure freedom
C. Almost half of the cases of childhood absence epilepsy outgrow the seizures by adulthood
D. Prognosis of JAE is similar to CAE

48. In burst-suppression pattern:

A. Suppression phases have voltage of less than 10 μV
B. Bursts contain mixed frequency activity
C. Bursts contain spikes
D. Pattern is reversible in hypothermia
E. All of the above

49. The incidence of photosensitivity is highest in which of the following:

    A. Juvenile myoclonic epilepsy
    B. Juvenile absence epilepsy
    C. Childhood absence epilepsy
    D. Epilepsy with myoclonic absence
    E. Epilepsy with grand mal seizures upon awakening

50. Auras associated with mesial temporal lobe seizures are characterized by all except:

    A. Déjà vu
    B. Rising epigastric discomfort
    C. Pallor
    D. Vertigo
    E. Borborygmi

51. Ictal EEG with focal right temporal rhythmic activity that evolves to 5–7 Hz rhythm within 30 is consistent with an ictal focus in the:

    A. Right neocortical temporal region
    B. Right mesial temporal region
    C. Right parietal region
    D. Right occipital region
    E. Right frontal region

52. The overall mortality in alpha coma is:

    A. 10%
    B. 20%
    C. 50%
    D. 75%
    E. 100%

53. Hypermotor seizures with prominent expression of fear localize the seizure focus to the:

    A. Supplementary motor region
    B. Orbitofrontal region
    C. Cingulate region
    D. Dorsolateral frontal convexity
    E. Parietal region

54. Myoclonic absences differ from absence seizures in childhood absence epilepsy by all of the following except:

    A. Faster frequency of ictal discharges
    B. Not precipitated by hyperventilation
    C. Occur in older patients
    D. Response to treatment is incomplete as in CAE
    E. Patients more often have abnormal cognition

55. Ictal emeticus lateralizes the seizure focus to:

    A. Right temporal region
    B. Left temporal region
    C. Right parietal region
    D. Right occipital region
    E. Right frontal region

56. Frontal lobe seizures are characterized by all except:

    A. Stereotypical pattern
    B. Nocturnal occurence
    C. Nocturnal enuresis
    D. Bizarre attacks
    E. Aggressive sexual automatisms

Answers

1. (A). Risk factors for developing epilepsy after of febrile seizures include complex febrile seizures (i.e., lasting >15 min, focal-onset seizures, and more than one seizure in 24 h), family history of epilepsy, abnormal development, and the presence of a post-ictal Todd's weakness.
2. (E). Inappropriate fear is commonly seen with mesial temporal lobe seizures because of the involvement of amygdala. The leading role of the amygdala, as well as that of the hippocampus and the parahippocampal gyrus, in the mechanisms of inducing a

fearful perception is well established by studies of electrical stimulation performed intraoperatively or during presurgical evaluation using intracranial depth electrodes.

3. (D). Explanation: Continuous EEG monitoring in the ICU is essential since approximately 20% of comatose patients in the ICU prove to have non-convulsive seizures detected on EEG. Studies have shown that most EEG seizures can be detected after 48 h of monitoring (88% of seizures in the first day and another 5% in the second day).
4. (D). This patient has benign epilepsy with centrotemporal spikes, also known as benign rolandic epilepsy. Most patients outgrow the diagnosis by mid-adolescence and have less than 5 seizures in their lifetime (thus, not medically intractable). The EEG shows bilateral spikes maximal over the central and temporal regions, with an increase in the frequency of epileptiform activity during drowsiness and sleep. On careful examination, many patients have developmental language disorders. Thus, consideration should be given to ordering neuropsychological testing in these patients.
5. (B). In a study of 570 adults with altered mental status in the ICU who underwent continuous EEG monitoring, seizures were detected in 19% of patients. Seizures were exclusively non-convulsive in 92% of these patients. Seizures were detected during the first 24 h of CEEG monitoring in 88% patients, during day 2 of monitoring in another 5%, and after 48 h of monitoring in 7%. 20% of comatose patients required >24 h of monitoring to detect the first electrographic seizure versus 5% of non-comatose patients.
6. (E). There are no triphasic waves in this page. The EEG shows a sharp and slow wave in the left temporal region with phase-reversal over F7 in this bipolar (double-banana) montage in the third second. The bilateral occipital waveforms are positive occipital sharp transients of sleep occurring in runs, rather than a seizure discharge. A sleep spindle is seen in the fourth second of this page.
7. (B). The asymmetry in the EEG amplitude between the two sides is consistent with a skull defect (breech artifact) on the left. The patient indeed has a history of left temporo-parietal craniotomy. The EEG is acquired during sleep and is not indicative of encephalopathy.
8. (A). Please refer to Table 8.4 for explanation.
9. (D). Clonic activity is not seen mesial temporal lobe complex partial seizures. Lateral temporal lobe complex partial seizures often evolve early to unilateral clonic activity.
10. (E). Generalized spike-and-wave discharges can be seen in the context of alcohol withdrawal seizures and generalized seizures in the context of metabolic encephalopathies such as hyponatremia and hence do not necessarily support a diagnosis of Epilepsy. Hence, repeat EEG is recommended once seizures have been controlled.
11. (E). Medication typically is not used to prevent febrile seizure recurrences because the benefits do not outweigh the risks. Even if medicines were used, phenytoin would not be effective. Recurrence risk of febrile seizures is higher if the temperature was low at the time of the seizure, in younger children, and with increased illness frequency. Complex febrile seizures increase the risk of epilepsy but not recurrence.
12. (D). During carotid endarterectomy, carotid shunting can be prevented if EEG monitoring remains symmetrical after carotid clamping. Carotid shunting is associated with six fold increase in risk of embolic infarcts.
13. (C). Please refer to Chap. 8.

14. (D). The common seizure types in Dravet syndrome that is associated with a mutation of the alpha 1 subunit of the voltage-gated sodium channel gene (SCA1) are generalized tonic–clonic and myoclonic seizures. The remaining genetic epilepsy syndromes are characterized with focal-onset seizures. Rolandic epilepsy presents with facial motor seizures and has complex inheritance patterns. As the name implies, seizures in autosomal dominant nocturnal frontal lobe epilepsy (associated with mutations in the nicotinic acetylcholine receptor) are nocturnal frontal lobe seizures. Seizures in temporal lobe epilepsy with auditory features or autosomal dominant lateral temporal lobe epilepsy (associated with the leucine-rich, glioma inactivated-1 or LGI1 gene) are marked by auditory hallucinations.
15. (B). In SE, good response to treatment is seen in idiopathic SE in previously non-epileptic patients—SE associated with medication non-compliance in epileptic patients and SE duration of less than an hour.
16. (D). The background in IGE is typically normal. Myoclonic seizures tend to occur upon awakening. In generalized epilepsy with febrile seizures plus (GEFS+) patients experience febrile seizures early in childhood and other types of seizures later in life.
17. (B). Slow spike-and-wave complexes present with a typical frequency of 1.0–2.5 Hz, with wider (less spiky) sharp component than in the absence epilepsy frequency. They are a typical of Lennox–Gastaut syndrome. Sleep activates trains of such slow complexes in the extent that they may appear continuous as in electrical status epilepticus during sleep (ESES). They are associated with slow EEG background.
18. (E). The patient has benign occipital epilepsy or idiopathic childhood occipital epilepsy (most likely Panayiotopoulos syndrome). The symptoms and signs described in the question are classic for this diagnosis. The EEG classically shows occipital spikes that are best brought out by darkness but other types of epileptiform activity have been noted, as well. Because the frequency of seizures is low, many patients do not need to be treated with antiseizure medicines.
19. (B). In atonic seizures, the slow wave corresponds to atonia. The loss of muscle tone usually lasts for $\sim$400 ms. The ictal EEG can have multiple patterns, including generalized polyspike-and-wave activity, bursts of polyspike-and-wave followed by generalized slow activity, and low- or high-voltage fast activity (this pattern can be seen with tonic seizures).
20. (A). Ictal EEG is characterized by evolution, rather than being monomorphic. By evolution, it is meant that the pattern changes in terms of its frequency, amplitude, field, or morphology as the seizure occurs.
21. (E). Please refer to Chap. 5.
22. (D). This patient has infantile spasms, one of the most malignant (and frequently under-recognized) forms of epilepsy in infancy. Approximately 75% of patients have an underlying cause of the syndrome, including structural, genetic, metabolic, post-ischemic, or post-infectious problems. Developmental outcomes for patients with these underlying abnormalities are very poor.
23. (D). The clinical significance of spikes of different locations is not the same. Seizures occur in 90% of children with anterior temporal spikes, but in only 40% of those with rolandic spikes or occipital spikes. Occipital spikes can be in children with congenital blindness. In BECTS, spikes are equally negative over the central and temporal derivations with the positive end of the dipole appearing typically in the frontal regions. Multifocal spikes are often associated with background slowing and comorbidities including cognitive and motor deficits.
24. (D). Pharmacoresistance in SE is due to seizure-induced internalization of synaptic

GABA-A receptor (subunits β2-3, ɤ2) and simultaneous externalization of AMPA/NMDA receptors to the synapse. As a result, there is decreased response to GABA and GABA potentiating medications such as benzodiazepine.

25. (A). This patient has early infantile epileptic encephalopathy (EIEE), also known as Ohtahara syndrome. Age of onset typically is within the first few months and patients can have tonic spasms, partial seizures, and myoclonus. The EEG shows a suppression-burst pattern. A wide variety of structural, metabolic, and genetic etiologies are associated with EIEE. Although seizures may resolve in up to 50% of survivors, the prognosis for normal psychomotor development is very poor. Many patients progress to developing infantile spasms and Lennox–Gastaut syndrome.
26. (B). Postictal aphasia in complex partial seizures is seen if the ictal focus is in the dominant temporal lobe while preserved ictal language in complex partial seizures is seen if the focus is in nondominant temporal lobe.
27. (B). Fos-phenytoin, a phosphate ester prodrug of phenytoin, has replaced phenytoin in many institutions. Fos-phenytoin is given as phenytoin equivalent (PE), with the dose of 20 mg/kg. It can be given in dextrose or normal saline. It is water soluble and can be given i.m. as well as i.v. Its bioavailability is 100% compared with phenytoin. It is rapidly converted to PHT by serum and tissue alkaline phosphatases. Its conversion half-life to phenytoin is 7–15 min. Phenytoin levels should be checked 2 h after infusion.
28. (A). The EEG shows a right temporal spike and slow wave and evidence of right temporal slowing before and after the spike, compared with the left temporal tracings. The slowing is indicative of regional dysfunction. There are no other spike populations to suggest multifocal epilepsy. Postictal aphasia localizes to the dominant, commonly left, hemispheric seizures. Cognitive and psychiatric comorbidities are common in temporal lobe epilepsy.
29. (D). Olfactory hallucinations/auras are not seen with dorsolateral frontal convexity seizures. Mesial temporal structures especially the amygdala play an important role in the genesis of olfactory auras. Selective amygdalectomy has a dramatic effect on the olfactory aura in some patients.
30. (D). Seizures that do not cause alteration of awareness will have EEG changes in only 21% of the cases. This increases to 33% if the seizures include motor phenomena and drops to 15% if they don't.
31. (C). In a study comparing the efficacy of intramuscular midazolam with intravenous lorazepam for children and adults in status epilepticus treated by paramedics outside hospitals, seizures were stopped prior to arrival in the hospital in 73% subjects treated with midazolam 10 mg i.m. and 63% subjects treated with lorazepam 4 mg i.v. with 4.5 and 6.5 min to cessation of convulsions, respectively. Seizures recurred in 11% in both groups. Adverse-event rates were similar in the two groups.
32. (D). The EEG shows triphasic waves, which can occur in a variety of clinical settings including lithium toxicity, white matter disease, hyponatremia, and metabolic encephalopathy, among others. There is no correlation with increased seizure risk.
33. (E). Prominent autonomic features are commonly seen with insular cortex stimulation and seen with insular seizures. Autonomic features are not a feature of parietal lobe seizures.
34. (C). The ACNS guidelines include:
    - Minimum of 8 scalp electrodes and earlobe references
    - Electrode Impedance must be between 100 and 10,000 Ω
    - Interelectrode distance should exceed 10 cm
    - EEG must be read with sensitivity of 2 μV/mm and a
    - τ = 0.3–0.4 s

- Integrity of the whole system should be tested
- Monitoring techniques (EKG, Ventilator, etc.) should be kept in mind as sources of artifact
- Reactivity to pain and loud sound must be checked
- Assessment of adequate core body temperature is required
- Recording should last for at least 30 min and done by qualified technologists
- Electroencephalographers should read the EEG at the bedside and are advised to repeat the following day if they suspect electrocerebral silence.

35. (C). The incidence of SE in the USA is between 18 patients per 100,000 population, according to a retrospective epidemiological study in Rochester, MN, and 41/100,000 population (with 50 SE episodes/year/100,000) in a prospective epidemiological study in Richmond, VA.
36. (A). There is a high association clinical seizures or electrographic seizures before or after the recording of GPEDs. The most frequent cause is cerebral anoxia after cardiorespiratory arrest. A poor outcome (mortality or vegetative state) is >97%. Severe metabolic disease and overdoses of lithium and baclofen may also cause GPEDs. The EEG should raise the suspicion of CJD. Patients with later stages of subacute sclerosing encephalitis (SSPE) can have GPEDs with longer inter-GPED interval.
37. (C). Complications of SE include hyponatremia, hypoglycemia, acidosis, acute renal failure, acute hepatic failure, and DIC, among others.
38. (E). Seizures are marked by evolution in any of the mentioned criteria.
39. (B). Celiac disease has been associated with bilateral occipital calcifications. This can potentially result in visual symptoms and occipital seizures.
40. (F). Unlike hemodialysis, peritoneal dialysis does not increase the risk of seizure occurrence.
41. (D). Triphasic waves have been classically associated with metabolic encephalopathy such as liver or kidney failure. However, they are also seen in the other toxic and metabolic conditions, including lithium toxicity and hyponatremia, or even with subcortical white matter disease. Interestingly, they may decrease upon the administration of benzodiazepines without an improvement in sensorium, making the distinction from epileptiform discharges difficult.
42. (E). In SE, MRI may be focally abnormal showing increased FLAIR, T2 signal hyperintensity and high-intensity signal DWI (diffusion-weighted imaging), both local at seizure focus and remote, commonly in the ipsilateral posterior thalamus (pulvinar), contralateral cerebellum, and bilateral splenium of the corpus callosum.
43. (B). The treatment goal during RSE is electrographic seizure suppression and EEG burst-suppression pattern or electrocerebral inactivity. Optimal parameters of burst suppression such as duration of interburst interval have not been determined. Some investigators believe that an interburst interval of ≥ 5 s is desirable.
44. (A). Occipital lobe seizures are associated with simple visual hallucinations. Complex visual hallucinations are commonly originated in visual association cortex at temporo–occipital junction.
45. (C). A prospective study noted that FIRDA occurred with toxic-metabolic disturbances and with structural lesions, but did not correlate with epilepsy. More recently, a large retrospective study found significant statistical correlations with strokes, and noted its favorable prognostic significance.
46. (E). Complex gestural automatisms are not seen in insular seizures rather they are manifested in complex partial seizures from

frontal lobe seizures (cingulated, orbitofrontal) or temporal pole.

47. (D). The prognosis of CAE is better than JAE as patients with JAE have other seizure types and might not outgrow their seizures. Treatment response is incomplete compared to CAE where most patients respond to ethosuximide or valproic acid.
48. (E). Burst-suppression pattern consists of bursts of high-voltage, mixed frequency and spike activity, separated by the periods of EEG suppression to less than 10 μV. Etiologies include anoxic encephalopathy, drug intoxication, anesthetics, and hypothermia. This pattern is generally reversible if induced by hypothermia or anesthetics, but is indicative of poor prognosis in the setting of anoxic encephalopathy.
49. (A). Incidence of photosensitivity is highest in patients with juvenile myoclonic epilepsy.
50. (D). Auras of vertigo and dizziness are more frequent in patients with extratemporal complex partial seizures than in patients with mesial temporal epilepsy.
51. (B). Risinger et al. tested the reliability and accuracy of scalp ictal EEG with sphenoidal electrodes, as a predictor of seizure localization in 110 patients with suspected temporal lobe epilepsy who subsequently underwent intracerebral EEG monitoring. Unilateral 5-Hz or greater temporal or sphenoidal rhythm was the first discernible ictal activity or was evident within 30 s after seizure onset indicated mesial temporal onset. In this case, it would mean right mesial temporal region.
52. (D). The overall mortality for the aggregate 335 cases with alpha coma was 76%, with mortality varying according to etiology. Brainstem infarction and anoxia after cardiorespiratory arrest was ~90%, while other causes, including drug intoxication, were much less (<10%).
53. (C). Hypermotor seizures with prominent facial expression of fear are primarily associated with a ventral-prefrontal epileptic zone (cingulate region), whereas those presenting with lower agitation and tonic/dystonic posturing are associated with a mesial premotor epileptic zone.
54. (B). In myoclonic absences, the frequency of the ictal discharge is 3–5 Hz and discharges are time-locked to myoclonic jerks. Similar to seizures in CAE, myoclonic absences are precipitated by hyperventilation. They occur in older patients—mean age of 7—and two-thirds of the times have abnormal cognition, and treatment response is incomplete.
55. (A). Ictal vomiting results from the activation of nondominant mesial temporal structures. Intense nausea and vomiting can occur with insular stimulation in animals. Fiol et al. suggested that insular areas trigger ictal vomiting but require the mesial temporal cortex for completion.
56. (C). Nocturnal enuresis is not typically seen with frontal lobe seizures.

Part III
Specific Epilepsy Syndromes

Electro-Clinical Syndromes by Age of Onset—Childhood, Adolescence, and Adult

10

Tesfaye Zelleke

Childhood Absence Epilepsy (CAE)

Childhood absence epilepsy occurs in children 4–8 years of age with peaks around 6 years. It is more frequent in girls. CAE is characterized by very frequent absence seizures (pyknolepsy). Hyperventilation induces the absence seizures. Based on clinical and electrographic features, absence seizures are classified as typical and atypical absence seizures.

Typical absence seizures are associated with transient impaired consciousness (behavioral arrest, staring) with or without eye fluttering and automatisms. Onset and cessation are abrupt. Ictal EEG shows >2.5 Hz generalized spike and wave lasting >3 s (average <10 s).

Atypical absence seizures tend to have less abrupt onset and cessation, greater change in tone, longer duration, and variable impairment of consciousness. Interictally, the EEG shows generalized irregular and asymmetric slow spike and waves (1.5–2.5 Hz). The ictal EEG is similar to the interictal discharges but may be associated with diffuse fast activity.

Pathophysiology:

According to the cortical focus theory, spikes are generated at a cortical focus and propagate rapidly via cortico-cortical networks to both hemispheres resulting in rapid synchronization. Paroxysmal oscillation in the cortico-thalamic loops amplifies and sustains the spike-wave discharges.

Genetics:

Genetic mutations currently account for a small proportion of patients with absence epilepsy. Mutations in GABA receptor (GABRG2, GABRA1), calcium channels, and non-ion channel proteins have been identified in CAE. Glut-1 transporter deficiency is described in about 10% of children with early-onset (under the age of 4 years) absence epilepsy.

Animal models (generalized epilepsy/absence epilepsy):

Several animal models are available for generalized epilepsy and absence epilepsy, which include acute pharmacologic models [pentylenetetrazole (PTZ), penicillin, THIP, GBL], chronic models [genetic absence epilepsy rats from Strasbourg (GAERS), Wistar Albino Glaxo/Rijswijk (WAG/Rij)] and other models [AY-9944, MAM-AY].

Treatment options:

These include ethosuximide, lamotrigine, and valproate [1]. A double-blinded, randomized, comparative clinical trial compared the three medications in CAE and found that ethosuximide provided the best combination of seizure control and fewest attentional side effects, making it the optimal initial monotherapy in CAE.

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Ethosuximide provided better seizure control compared to lamotrigine and fewer attentional effects compared to valproic acid. Although CAE is often perceived as "benign", many children with CAE have cognitive deficits and long-term psychosocial problems.

Epilepsy with Myoclonic Absences

The majority (70%) of children with epilepsy with myoclonic absences are boys. The average age of onset is 7 years. In about one-third of patients a specific cause is identified. Family history of epilepsy is reported in 20%. Neuroimaging abnormalities, mainly some degree of diffuse atrophy, are seen in 17% of patients.

Patients have variable impairment of consciousness. Myoclonic jerks involving shoulders, arms, and legs are seen. Tonic contractions, particularly elevation of the arms, are often noted. At times, the tonic activity may be asymmetric. Arrest of respiration and urinary incontinence may occur. Seizures last 10–60 s and frequent seizures may occur on awakening. Other seizure types such as GTC, absence, and drop seizures may also occur. Some children may evolve to Lennox-Gastaut syndrome (LGS), and cognitive impairment may occur.

The ictal EEG shows 3 Hz rhythmic, bilateral, synchronous, and symmetric spike-wave discharges. Intermixed polyspikes may be seen. Bilateral myoclonias occur at same frequency as spike waves, i.e., 3/second. Treatment options include valproate and ethosuximide [2].

Epilepsy with Myoclonic-Atonic Seizures

[Also known as Doose syndrome, or Epilepsy with myoclonic astatic epilepsy]

Age of onset is 1–5 years, and the child is normal at onset. There is strong family history of idiopathic epilepsy in 15–32%. Myoclonic and atonic seizures with falls suggest the diagnosis. A mix of generalized seizures occurs including myoclonic, atonic, absence, GTC, and tonic (less common). Non-convulsive status epilepticus may occur on awakening from sleep or nap. GTC is usually the first seizure and is seen in 75–95% of patients. Prognosis for seizure and cognitive outcome is variable.

EEG shows bursts of 2–3 Hz generalized spike wave and polyspike waves, which increase with sleep. 4–7 Hz rhythmic theta activity over the central regions and vertex is a specific finding. Myoclonic-atonic seizures are electrographically associated with a single generalized spike/polyspike wave (unlike LGS which shows secondary bilateral synchrony) or 3–4 Hz activity lasting 2–6 s.

Neuroimaging is normal. Glut-1 deficiency syndrome is identified in about 5 % of children with Doose syndrome. SCN1A mutation is reported as a cause. Treatment options include valproate, lamotrigine, ethosuximide, topiramate, levetiracetam, and the ketogenic diet.

Lennox-Gestaut Syndrome (LGS)

LGS is characterized by the triad of 1. multiple seizure types: tonic (nocturnal tonic seizures are characteristic), atonic, atypical absence, GTC, and partial seizures; 2. EEG features of slow background with generalized slow spike-wave discharges at 1.5–2 Hz, multifocal discharges, and generalized fast activity at 10–25 Hz in sleep; and 3. cognitive dysfunction and intellectual disability.

The peak age of onset is 3–5 years. Infantile spasms precede LGS in 10–25%. LGS results from structural/metabolic causes in 70–78%, including meningo-encephalitis, cortical dysplasia, hypoxia, and traumatic brain injury, among others. In 22–30% of children the cause is unknown. Family history of epilepsy is reported in 3–30%.

Several medications are used in the treatment of LGS, but seizure control is usually inadequate [3].

Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (CSWS)

Electrical status epilepticus in sleep (ESES) is defined commonly as epileptiform activity occupying >85% of NREM sleep. Two syndromes, Landau–Kleffner Syndrome (LKS) and continuous spike and wave during sleep (CSWS), are associated with ESES.

1. Landau–Kleffner Syndrome (LKS):
   LKS usually occurs in children 3–10 years of age and manifests as language regression with verbal auditory agnosia (word deafness with normal hearing test). Seizures occur in two-thirds. ADHD features are common.
   Brain MRI is normal; however, cases with structural causes have been reported. Functional studies, such as SPECT and PET, have demonstrated temporal lobe abnormalities.
2. Continuous spike and wave during sleep (CSWS)
   CSWS manifests as global regression in cognition and behavior. The majority of patients have seizures. CSWS is sometimes associated with identifiable pathology; e.g., neuronal migrational disorders, polymicrogyria, shunted hydrocephalus, porencephaly, and thalamic lesions. Family history of seizure is reported in 10–15%.
   Treatment: Various medications, including valproate, ethosuximide, and benzodiazepines; immune modulatory therapy (steroids, IVIG); and surgery have been used in the treatment of ESES.

Juvenile Absence Epilepsy (JAE)

JAE, unlike CAE, is associated with less frequent absence seizures (one to a few per day) and is more frequently associated with GTC seizure (in 80%). The impairment of consciousness is less severe in JAE. The age of onset ranges from 10–17 years.

Juvenile Myoclonic Epilepsy (JME)

The age of onset for JME is 12-18 years (mean age 14.6). Seizures occur mostly upon awakening in the morning but can occur after waking from a nap. Sleep deprivation, stress, fatigue, and alcohol are major seizure provoking factors.

Seizure types in JME include myoclonic seizures (may be repetitive), GTC seizures (occur in 80–95% of patients; typically preceded by clusters of myoclonic jerks; clonic–tonic–clonic seizures; frequency—one or two/year), and absence seizures (in 18–38% of patients).

Interictal EEG demonstrates high amplitude generalized symmetric and synchronous 4–6 Hz polyspike-wave discharges. Photosensitivity is noted in about 30% of patients.

Family history of epilepsy is reported in 40–50%. Inheritance is unclear, likely polygenic, but both autosomal dominant and recessive inheritance have been reported. Gene mutations identified in some families include GABRA1 (GABA-A receptor gene on chromosome 5q34), CLCN2 (chloride channel 2 gene on chromosome 3q26), and myoclonin1/EFHC1 (EH-hand motif protein on chromosome 6p12; found in 9% of JME).

Treatment: Valproate, lamotrigine (may worsen myoclonus), topiramate, and levetiracetam are used in the treatment of JME.

Epilepsy with GTC Seizures Only

Seizures may predominate in the morning (the earlier classification of epilepsy with grand mal on awakening included). Sleep deprivation is a trigger. Family history of generalized epilepsy and photosensitivity may be present.

Progressive Myoclonic Epilepsy (PME)

PME is a group of disorders presenting with severe myoclonic seizures (and tonic–clonic seizures) with progressive neurologic

deterioration (ataxia, dementia). EEG shows progressive slowing, generalized and multifocal discharges, and photosensitivity typically at lower flash frequency.

PME includes Lafora disease, Myoclonus Epilepsy with Ragged Red Fibers (MERRF).

Neuronal Ceroid Lipofuscinoses, Sialidosis, and Unverricht-Lundborg Disease. Dentatorubral-pallidoluysian atrophy (DRPLA) may also cause PME [4].

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)

ADNFLE is caused by mutation of genes coding for neuronal nicotinic acetylcholine receptor subunits (CHRNA4, CHRNB2, CHRNA2). Seizure onset is in childhood with mean age of 11.7 years, and seizures persist into adulthood. The typical seizure manifests with sudden arousal from NREM sleep (stage II) with hyperkinetic or tonic movements. Seizures may cluster. Awareness is usually retained. Auras, which may be specific with sensory and psychic symptoms or non-specific, are frequently reported. Neuroimaging is normal. Interictal EEG is usually normal. Ictal EEG may show bifrontal discharges.

Familial Temporal Lobe Epilepsy (Autosomal Dominant with Incomplete Penetrance)

1. Familial mesial temporal lobe epilepsy (FMTLE): FMTLE may occur with or without hippocampal sclerosis.

    A. Benign FMTLE without hippocampal sclerosis or febrile seizures has its onset in adolescence or adulthood with aura of mesial temporal origin (psychic and autonomic features). Prognosis is excellent.
    B. FMTLE associated with hippocampal sclerosis presents with complex partial seizure with automatisms. The mean age of onset is 10 years. Asymptomatic family members may have hippocampal sclerosis. The course is benign in the majority.
    C. FMTLE associated with febrile seizures starts in the first to second decade of life and has a benign course.

2. Familial lateral temporal lobe epilepsy (Autosomal Dominant Partial Epilepsy with Auditory Features (ADPEAF)):
ADPEAF is associated with focal seizures. Elemental or complex auditory aura is prominent in 64% of patients. The epilepsy has a benign course. Leucine-rich glioma-inactivated 1 (LGI1) gene mutation is identified in 50% of families.

Familial Focal Epilepsy with Variable Foci

Different focal epilepsies are seen in different family members. Seizures and EEG abnormalities are consistent in each affected family member. Frontal lobe seizures predominate. Features that help to differentiate from ADNFLE include less frequent seizures, daytime seizures, more frequent secondary generalization, and rare clusters and auras. Seizure foci may also be temporal or occipital. Inheritance pattern is autosomal dominant with 70% penetrance; mapped to chromosome 22q12 [5].

Reflex Epilepsies

In reflex epilepsies, a specific stimulus or event repeatedly elicits seizure. Trigger stimuli include visual stimuli (light, patterns), startle, reading, tactile, music, drawing/praxis, bathing, thinking, arithmetics, decision making, and gaming.

Gelastic Seizures—Hypothalamic Hamartoma (HH)

Gelastic seizures are true diencephalic seizures, and the secondary epileptogenesis may be related to the connectivity of hypothalamus with frontal lobes, limbic circuity, and thalamus. Seizures are almost always drug resistant and associated with encephalopathy, but symptoms resolve with surgical ablation of hypothalamic hamartoma.

HH is a developmental, non-neoplastic malformation in the area located between infundibular stalk and mamillary bodies. It may be intrahypothalamic (wide-based attachment to hypothalamus) or parahypothalamic (attached with the floor of 3rd ventricle by a peduncle). HH is usually sporadic but is rarely associated with autosomal dominant Pallister-Hall syndrome (GLI3 gene mutation). The hamartoma has neurons and interspersed glial nuclei. GABA expressing spontaneously firing neurons may drive the synchrony of large output neurons resulting in epileptogenicity. The clinical features of HH include epilepsy, developmental retardation, behavioral disorders (PDD, ADHD), and central precocious puberty.

In HH the characteristic seizure type is gelastic, a brief stereotyped mechanical laughter without mirth and with no loss of consciousness; autonomic signs may be present. Other seizure types include crying ("dacrystic") seizure, tonic, and atonic seizures. Interictal EEG shows slow background, and focal/multifocal and generalized epileptiform activity. Ictal patterns are variable, sometimes no epileptiform activity is seen. Treatment includes laser surgery, gamma knife, surgical resection [6].

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Seizures and Epilepsy in Early Life

11

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Neonatal Period

Benign Familial Neonatal Seizures (BFNS) [1]

Also known as "3rd day fits," this disorder has mapped to chromosomes 20 and 8 (*KCNQ2 and 3*, K+ channels). Seizures consist of tonic posturing, apnea/cyanosis, autonomic signs, face and limb clonus, and last 1–3 min. If treatment required, medications can be continued until 3–6 mos of age. Patients may develop other types of seizures later in life.

Early Infantile Epileptic Encephalopathy: EIEE (Ohtahara Syndrome) [2]

The primary semiology consists of frequent tonic spasms in isolation or clusters (other seizure types can occur, as well). The onset is in first 3 months of life. Neonates can have hundreds of seizures per day. Structural brain lesions are the most common etiology but the following genes also have been associated with EIEE: *STXBP1*, *CDKL5*, *ARX*, *KCNQ2*. There is a high mortality rate in infancy. Prognosis is characterized by profound neurodevelopmental deficits in survivors. Seizures are typically resistant to treatment but controlled by school age in half of children. Many neonates later progress to West syndrome (see below).

Early Myoclonic Encephalopathy: EME [2]

The onset of EME is very early, typically in first month of life (some cases are familial). The seizure semiology typically is myoclonus in the limbs and face. Focal seizures and tonic spasms are common. In terms of etiology, concurrent metabolic disorders are common (the classic one is glycine encephalopathy but others have been noted, as well—a B6 trial is reasonable but it typically is unsuccessful). The EEG (while awake) shows multifocal spikes on slow background ± periodic activity. Unlike EIEE, suppression-burst is observed primarily during sleep. Conventional treatments are typically used with very limited success. Corticosteroids have only a minimal effect on seizures. Myoclonus usually resolves by weeks to months but focal seizures persist. Mortality is high in the early ages. The prognosis is poor for resolution of seizures and neurodevelopment.

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Infancy

Migrating Partial Seizures of Infancy [3]

In this syndrome, development is initially normal, and then seizure starts between 1 week and 7 mos (mean = 3 mos). Initially, there are sporadic focal motor seizures but eventually they become prolonged or occur in clusters and may secondarily generalize. The interictal EEG initially shows multifocal slowing, which progresses and later includes a disruption of sleep architecture. The ictal EEG shows multifocal origins of seizures with migration to different regions (morphologically, including rhythmical delta or sharp waves/spikes). There are associated extrapyramidal signs and tone worsens over time. There is early intractability but seizure control may improve with age in survivors. Early deaths may be associated with respiratory difficulties.

Neurodevelopmental prognosis in survivors generally is poor. The list of genetic mutations associated with this syndrome is expanding rapidly.

Infantile Spasms [2]

Clinically, this epilepsy syndrome is characterized by flexor or extensor spasms in clusters. The peak onset is 5 mos (typically 4–8 mos). The eponym West syndrome is defined by the triad of spasms, the EEG appearance of hypsarrhythmia, and developmental delay. The etiologies may be symptomatic (i.e., with an identifiable underlying cause, representing 75–85% of patients) or asymptomatic. Underlying conditions may be genetic (*ARX*, *STXBP1*), metabolic, congenital infection, neonatal infection, among many others. Intellectual disability is seen in 75–90% of patients. The differential diagnosis includes benign myoclonus, benign myoclonic epilepsy, and gastroesophageal reflux (EEG easily distinguishes these from one another). Treatment includes steroids (ACTH, prednisolone), vigabatrin, the ketogenic diet, zonisamide, and vitamin B6, noted in different published case series. Animal models are generated by inducing early injury and genetic manipulations.

Myoclonic Epilepsy in Infancy (MEI) [2]

With an onset of 4 mos–3 yo, this syndrome is eventually outgrown in most patients. Clinically, there are axial or upper extremity myoclonic jerks with head drops; trunk flexion or extension has been noted, and the lower extremities are only involved rarely. The EEG shows generalized spike/polyspikes lasting 1–3 s. This syndrome is associated rarely with antecedent febrile seizures. Reflex myoclonic seizures are a subgroup (induced by auditory, tactile stimuli); some patients are photosensitive. The differential diagnosis includes infantile spasms and benign myoclonus. The EEG and normal development differentiate MEI from infantile spasms (hypsarrhythmia) and benign myoclonus (normal EEG). Neurodevelopment generally is normal but patients may develop other seizures later in life. Treatment typically is with VPA, LEV, or CZP.

Benign Infantile Seizures [4]

The terminology used for this family of disorders is in development as of this writing but both familial and non-familial forms have been noted. The onset is between 3 and 20 mos in a developmentally normal infant. The non-familial form onset can be in the 2nd year of life, with equal sex predominance. In the familial form, onset typically is 4–7 mos, with a female predominance. Seizures are characterized by focal onset (head, face, limbs) clonic seizures, may secondarily generalize, and can occur in clusters with varying lateralization. Medicines usually are prescribed but seizures generally are easy to treat. Structural and metabolic workup is negative. The EEG shows a focal ictal onset (posterior or temporal); interictal EEG typically is normal. In the familial form, mutations in *PRRT2* (same gene as paroxysmal kinesigenic dyskinesia), *ASC-1* (amino acid transporter), and *SCN2A* have

been noted (there likely are others). The prognosis is good for both seizures and development.

Myoclonic Encephalopathy in Nonprogressive Disorders

Three forms of this epilepsy syndrome have been described [5]:

1. Absence + myoclonic seizures. The EEG shows theta–delta or delta with spikes. Typically, this is diagnosed in the 1st year of like. There usually is a genetic etiology (Angelman, Prader–Willi, Rett, others). Treatment in combination with ESM-VPA may work in some patients.
2. Alternating bilateral positive and negative myoclonus. The EEG shows diffuse rhythmic slow spike-waves or multifocal spike-waves or theta–delta. There may be dyskinetic movements. The onset usually is $\leq$6 yo. Seizures are medically intractable seizures, and infants show poor neurodevelopment. Structural brain malformations have been noted in some patients.
3. Mild onset with focal facial (then limbs) seizures. Onset in this form typically is 7 mos–5 yo. The EEG shows generalized spike-waves or bilateral continuous slow activity and then EEG and clinical deterioration (with both pyramidal and extrapyramidal signs, as well as myoclonus). This form may be associated with neonatal anoxia. Seizures are medically intractable.

Because the prognosis is somewhat different, this syndrome should be distinguished from the progressive myoclonus epilepsies.

Childhood

Febrile Seizures (FS): The Basics [6]

By definition, febrile seizures have an onset between 1 mo and 5 years. Any seizure semiology can be seen but generalized tonic–clonic seizures are the most commonly noted one. By definition, there is no evidence of intracranial infection or defined cause for the seizure. The incidence is 3–5% of the US population. The median age of presentation is 18 mos and half of patients present between 12 and 30 mos. In terms of genetics, 10–20% of siblings also have these seizures.

Recurrence of febrile seizure is:

$\sim$33% will have a second FS (range in studies is 23–42%);
$\sim$½ of those will have a 3rd FS (range in studies is 7–30%);
$\sim$50% recur in 1st 6 months; 75–90% recur in 1st year.

Recurrence risk is influenced by: age (<1 year doubles the risk), FS in 1st degree relative (up to double the risk), low-grade fever at seizure onset, and illness frequency. Risk factors for developing epilepsy after a FS include a positive family history of epilepsy, abnormal neurodevelopment, occurrence of a complex febrile seizure, a postictal Todd's paralysis, number of febrile seizures (more seizure = greater risk), and duration of febrile seizure (longer seizure = greater risk).

Genetic Epilepsy and Febrile Seizures Plus (GEFS+) [7]

FS+ is defined as a FS after 6 yo or occurrence of other seizure types. Almost any type of seizure has been documented for FS+. FS+ is associated with mutations in *SCN1A*, *SCN1B*, or *GABRG2* but importantly, mutations only are seen in 10–20% of those with GEFS+ (so genetic testing generally is not advised).

Dravet Syndrome (also called Severe Myoclonic Epilepsy of Infancy or SMEI)[7]

Characterized by a prolonged FS in 1st year of life, there is a seizure-free period followed by the appearance of myoclonic seizures at 1–4 years

(8% of patients have an onset <3 yo). Development is normal early and then deteriorates clinically (including pyramidal signs and ataxia). The EEG shows spike and wave or polyspike and waves. Approximately 70–80% of patients have mutations in *SCN1A*, so genetic testing generally is indicated for prognosis and to obviate the need for further diagnostic workup. The so-called SMEI "borderland" (SMEB) lacks certain core features of SMEI but has been documented in various pedigrees but is no longer believed to be a separate entity. Treatment with Na-channel medications (e.g., carbamazepine, lamotrigine) may worsen seizures in these patients. Some patients have clear seizure exacerbations when exposed to extrinsic (or even generating intrinsic) heat—thus, these environmental stimuli should be avoided when possible and practical.

Benign Epilepsy with Centrotemporal Spikes BECTS ("Rolandic Epilepsy") [8]

This is the most common focal epilepsy in childhood, with an onset between 2 and 14 years (peak 7–10 years). Sensory symptoms may be seen in the tongue, lips, gums, or cheek; drooling also may be noted. Motor symptoms typically are in the tongue, larynx, or pharynx. Seizures usually occur during sleep (1st part of the night) but 10–20% of patients have seizures only while awake. The interictal EEG shows spikes that are diphasic with a phase reversal over temporal, central, or parietal regions (longitudinal bipolar montage). They typically are bilateral but one side may have more spikes than the other. Salvos of central and temporal spikes are seen, with an increase in persistence during drowsiness and sleep. Slowing after spikes suggests seizures will be more challenging to control. When seen by those unfamiliar with this syndrome, spikes may be mistaken for multifocal epilepsy. The differential diagnosis includes malformations of cortical development, vascular anomalies, and other lesions. These conditions should be considered if there are unilateral spikes, very frequent seizures, or lack of improvement. EEG findings suggesting other diagnoses include decreased frequency of spikes in sleep, fast spikes or polyspikes, or a suggestion of burst suppression following spikes. In terms of prognosis, BECTS typically is outgrown by age 16. Nearly 80% of patients have <6 seizures so treatment is not recommended for most patients. There are concerns about language development, which should be specifically screened even if school performance is average (high-functioning students may not need this). Occasionally, BECTS resolves only to have other types of seizures develop after 18 years of age. Treatment, if needed, has included CBZ, OXC, LEV, VPA, GPN, and sulthiame.

Panayiotopoulos Syndrome (Early Childhood Onset "Occipital" Epilepsy) [8]

With a peak onset between 3 and 6 years, seizures start with behavioral agitation and then headache, autonomic symptoms, and motor (hemiclonic or generalized tonic clonic) seizures. Seizures tend to be prolonged. Autonomic symptoms (including status epilepticus) include vomiting, pallor, cyanosis, among other symptoms. The interictal EEG classically shows occipital spikes in salvos (increased in sleep) but spikes can be seen over any region. This condition is treated only rarely because 85% of patients have ≤ 5 seizures over their lifetime. Approximately 2/3 of patients have seizures out of sleep.

Gastaut Syndrome (Late Childhood Onset "Occipital" Epilepsy) [8]

With a peak onset of 8–11 years, seizures start with elementary visual auras and may progress to partial vision loss or classical focal-onset seizures (only rarely will they generalize). In contrast to Panayiotopoulos syndrome, autonomic symptoms are not prominent but headache is seen commonly. Seizures are fairly frequent but of short duration. Also in contrast to Panayiotopoulos syndrome, a daytime occurrence of seizures is common. The interictal EEG classically shows occipital spikes in salvos but spikes can be

seen anywhere. There is an increased frequency of epileptiform activity during sleep and with eye closure. Because seizures are fairly frequent, this epilepsy syndrome usually requires treatment but seizures tend to remit 2–7 years after onset.

Rasmussen Syndrome

With an onset typically between 3 and 14 years, patients are almost always neurodevelopmentally normal prior to the onset of seizures. On occasion, there will be an antecedent nonspecific febrile illness days to weeks before the first seizure. Rarely, this syndrome will develop in patients with other autoimmune diseases. There likely is an immune-mediated etiology but a specific organism or trigger has not been identified to date, despite exhaustive research (the association with mGluR3 antibodies has since been disproven because it is neither sensitive nor specific, although depending on his/her perspective, examiners may ask this question on a test).

Diagnostic criteria include the following [9]:

Need either all three criteria in Part A or two of three in Part B (start with Part A).

Part A:

1. Clinical: Focal seizures (±epilepsia partialis continua) and unilateral cortical deficit(s).
2. EEG: Unihemispheric slowing ± epileptiform activity and unilateral seizure onset.
3. MRI: Unihemispheric focal cortical atrophy and at least one of the following:
   - Gray or white matter T2/FLAIR hyperintense signal
   - Hyperintense signal/atrophy of ipsilateral caudate head

Part B:

4. Clinical: Epilepsia partialis continua or progressive unilateral cortical deficit(s).
5. MRI: Progressive unihemispheric focal cortical atrophy.
6. Histopathology: T-cell-dominated encephalitis w/activated microglial cells (typically, but not necessarily forming nodules) and reactive astrogliosis.

Treatment initially is with antiseizure medicines, although seizures become refractory to treatment. Immunomodulators such as corticosteroids, intravenous immunoglobulin, and certain chemotherapeutic agents (e.g., cyclophosphamide) have been used to mitigate the impact of the progressive nature of this disease, with only limited success. Unfortunately, most patients eventually need a hemispherectomy for seizure control (the unihemispheric nature of the disease, which remains unexplained, makes this surgery an option). Prognosis is largely determined by preoperative level of function. Postoperative rehabilitation is necessary to optimize outcomes.

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Imitators of Epilepsy

12

Dewi Frances T. Depositario-Cabacar and Nabil J. Azar

List of the common nonepileptic paroxysmal disorders by age:

A. Infants and neonates:
- Sandifer syndrome,
- Self-gratification syndrome,
- Benign myoclonus of early infancy,
- Shuddering attacks,
- Startle disease or hyperekplexia,
- Benign neonatal myoclonus,
- Jitteriness, head banging and body rocking,
- Spasmodic torticollis, and
- Apnea.

B. Older children:
- Breath-holding spells,
- Movement disorders (tics, paroxysmal kinesigenic choreoathetosis, etc.),
- Parasomnias and sleep disorders,
- Migraine headaches,
- Psychogenic nonepileptic seizures,
- Behavioral disorders (rage attacks, inattentiveness), and
- Syncope.

C. Adolescences and adults:
- Nonepileptic psychogenic seizures (also known as pseudoseizures),
- Syncope,
- Panic attacks and hyperventilation,
- Migraines, and
- Parasomnias and sleep disorders (such as narcolepsy and cataplexy).

Sandifer syndrome: This syndrome consists of intermittent abnormal posturing such as stiffening and opisthotonic posturing usually primarily due to gastroesophageal reflux. It is usually associated with feedings. It can be mistaken as paroxysmal dystonia, epileptic spasms, or tonic seizures. This usually improves with antireflux medications.

Self-gratification syndrome: This is also referred to as infantile masturbation. This occurs in infants and young children. It involves rubbing of the thighs against each other, thrusting of the pelvis associated with sweating, grunting, or flushing of the face with variable degree of responsiveness. After the event, the child is back to baseline. Treatment involves reassuring the family of its self-limiting and benign nature.

Benign myoclonus of infancy: This usually occurs in the first year of life, mostly seen between the age of 3–8 months. It consists of brief tonic or myoclonic contractions involving the axial muscles. These spasms usually occur in cluster and are different from benign neonatal

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sleep myoclonus. Neurological examination, EEG, and development are all normal. Treatment involves reassurance since myoclonus usually resolves by 2 years of age.

Shuddering attacks: These usually occur between the ages of 4–6 months. The events consist of tremor in the head, arms, and trunk with adduction and flexion of the elbows. Communication and responsiveness are usually impaired. They can be triggered by emotions such as fear, anger, or frustration. They tend to gradually subside with age and completely resolve by 10 years of age. Reassurance of the family is usually enough.

Hyperekplexia: This is also referred as stiff baby syndrome or startle disease. It appears more like an exaggerated startle response and may result in falling. It usually occurs at the age of 6 months to 6 years and peaks at the age of 2–3 years old. It consists of a triad of generalized stiffness, nocturnal myoclonus, and tonic spasms with auditory or tactile stimuli. In affected neonates, tapping the tip of the nose or glabella may elicit a typical response. It is secondary to gene mutations affecting inhibitory glycine receptor (GLRA1 and GLRB). Commonly used treatments are clonazepam, followed by valproic acid or levetiracetam.

Breath-holding spells: Breath-holding spells commonly occur between the ages of 6 and 18 months. Spells are divided as cyanotic or pallid.

Cyanotic breath-holding spells are usually precipitated by an emotional cause such as frustration. The child cries and then holds the breath in expiration resulting in cyanosis and may be followed by loss of consciousness and loss of tone. The precipitating event can be from the child being upset. If the apnea is prolonged, clonic jerks may be observed. Treatment is usually reassurance and behavioral modification of parental response. If recurrent, then screening for iron deficiency anemia can be done.

Pallid breath-holding spells usually occur in response to a minor trauma or fright. The child stops breathing, becomes pale, may have a brief cry followed by loss of consciousness. Clonic jerks and incontinence may also occur. Bradycardia or asystole may occur. Main treatment is also parental reassurance, with some studies suggesting a role for atropine.

Migraines: Migraines are common causes of recurrent headaches. The dilemma occurs if the neurological event occurs without significant headaches and the event can be mistaken for seizures, such as in the case of confusional migraine or migraine with aura.

For example, confusional migraines are episodes of confusion, agitation/hyperactivity, partial or total amnesia, disorientation, lethargy, or vomiting that may last for several minutes or hours. Headache and visual complaints may occur but are not prominent symptoms. These may be mistaken for temporal lobe seizures but other etiologies such as encephalitis, substance abuse, metabolic causes, and vasculitis should be considered.

On the other hand, migraines with aura can appear as focal seizures if the visual disturbances are more prominent than the headache, such as "Alice in wonderland" syndrome where visual micropsia, macropsia, and distortions can all occur. This can be easily mistaken for temporal or occipital lobe seizures.

Parasomnias and sleep disorders: Some sleep disorders can be mistaken for complex partial seizures, commonly of frontal lobe origin due to their hypermotor features and nocturnal occurrence. These mostly include night terrors (occurring in non-REM sleep) and REM behavior disorder (occurring in REM sleep).

In the case of night terrors, the child wakes up from sleep, appears terrified and agitated, is inconsolable, and has no recollection of the event. They occur around the age of 4 years and typically resolve by 8 years.

While in REM behavior, excessive and violent motor activity with no recollection of events is frequent. Polysomnography (with EEG normal recording) is the gold standard diagnostic tool.

On the other hand, narcolepsy is characterized by a tetrad of cataplexy, sleep paralysis, hypnagogic hallucinations, and excessive daytime sleepiness. Cataplexy is a sudden loss of muscle tone precipitated by touch, emotional excitement, or laughter. It may occur several times during the

day and may often be mistaken for atonic seizures. Two tests that are commonly used in diagnosing narcolepsy are the polysomnogram and multiple sleep latency test (MSLT).

Syncope: Syncope is very common and up to 10% of the population will experience it at least one time during their life. It is caused by a transient interruption of cerebral blood flow to the brain resulting in loss of consciousness.

Neurocardiogenic syncope (or vasovagal syncope) is the most common type of syncope. The event is often preceded by prodromal symptoms of feeling of warmth, nausea, blurring or tunnel vision, diaphoresis, and lightheadedness. Events are usually provoked by emotions (pain, anxiety, blood drawing) particular situations (crowded environment, hot weather, prolonged standing, fatigue). It may be caused by decreased blood volume or venous return, or parasympathetic cardioinhibitory response causing vasodepression. Common reflex causes of syncope are coughing, micturition, and swallowing. Tilt table tests are occasionally done in recurrent syncopal cases. Diagnosis is made by history, orthostatic measurements, or tilt table testing. Treatment includes reassurance, avoiding precipitating factors, increasing fluid and salt intake. If needed, beta-blockers, alpha-adrenergic agonists, anticholinergics, and mineralocorticoids (such as fludrocortisone) can be used.

In contrast, cardiogenic syncope is less common but may be more life threatening. In such case, syncopal episodes occur without warning or prodromal symptoms and may occur during physical exertion. Common causes include structural cardiac diseases (such as hypertrophic cardiomyopathy, aortic stenosis), or dysrhythmias. An initial cardiology workup including cardiac echocardiography and Holter monitoring is warranted.

Convulsive syncope refers to syncope that is followed by brief tonic or rarely clonic activity, which may occur in prolonged cerebral hypoperfusional states.

During syncopal episodes, the EEG typically show transient high-voltage delta activity or complete voltage attenuation.

Psychogenic nonepileptic seizures (PNES): PNES are by far the most common imitators of epilepsy. It has been reported that 25–40% of all admissions to inpatient video-EEG studies end up with the diagnosis of PNES. However, despite the ability to diagnose PNES with high confidence using video-EEG monitoring, the delay in diagnosis is long, averaging about 7–10 years.

The patient's history may suggest the diagnosis. Several clues are useful in clinical practice and should raise the suspicion that seizures may be psychogenic rather than epileptic. One of the first clues is resistance or worsening of seizures to antiepileptic drug trials. The presence of prominent comorbid psychiatric conditions should also raise the suspicion of PNES, particularly the presence of depression, anxiety, or PTSD (mainly secondary to physical or sexual abuse). Psychiatric comorbidities are found in the majority of patients with PNES, with depression being the most common.

In addition, several specific triggers that are atypical for epilepsy may suggest the diagnosis of PNES, such as emotional triggers (whether positive or negative stress), headache or pain, specific sounds or lights. Also, certain situations may trigger PNES, for example, the presence of specific audience and occurrence in the physician's office or waiting room.

A detailed description of events by witnesses is always helpful since specific clinical features have been shown to favor the diagnosis of PNES. Some of these clinical features include eye closure, side-to-side head or body shaking, bilateral asynchronous and often discontinuous movements, crying, speech stuttering, and arching of the back. With convulsive attacks, rapid or short postictal recovery, shallow irregular, and soft postictal breathing pattern also favor PNES. Despite the fact that urinary incontinence, tongue biting, bodily injuries can be commonly seen in both epileptic and nonepileptic seizures, serious injuries and tongue biting at the side are more typical for epileptic seizures.

PNES diagnosis requires video-EEG recording of typical events. Withdrawal of antiepileptic drugs is also essential for excluding a concomitant

diagnosis of epilepsy, which can be seen in up to 10% of patients suffering from PNES. A formal psychiatric evaluation with additional neuropsychological testing is also an integral part of the initial assessment.

Treatment of PNES is targeted toward specific psychiatric conditions and is often very individualized. Therapy typically includes psychotherapy and the use of adjunctive medications to treat coexisting depression or anxiety.

Successful treatment and seizure freedom may be a challenging task, and in several instances hard to reach. Some of the common treatment obstacles include effective delivery of the diagnosis, acceptance of the diagnosis and patient commitment to therapy and follow-up. In general, patients who accept their diagnosis and follow through with therapy are more likely to experience a successful outcome.

Genetic Analysis of Epilepsies

13

Sara K. Inati

Background

An ever larger number of gene mutations have been discovered to have a major effect on susceptibility to seizures and epilepsy. Epilepsy associated with a single gene mutation (Mendelian or monogenic inheritance) is thought to occur in approximately 1–2% of patients with epilepsy. Up to 40% of epilepsies are thought to involve polygenic or complex genetic inheritance, involving multiple possibly interacting genes and/or environmental influences [1, 2]. Genetic generalized epilepsies (formerly idiopathic generalized epilepsies), where generalized seizures are the predominant feature, show mostly complex inheritance. However, specific mutations have been associated with a variety of other epilepsy syndromes, most notably early-onset epileptic encephalopathies, syndromes associated with febrile seizures, several familial focal epilepsy syndromes, as well as symptomatic epilepsy syndromes, in which seizures are only part of a more widespread CNS disorder [3].

There are several types of genetic changes that may contribute to the development of seizures and epilepsy. Small deletions, insertions, and point mutations can lead to problems in neuronal metabolism, network development, and membrane and synaptic signaling. Contiguous gene syndromes are microdeletions leading to loss of several neighboring genes. Chromosomal abnormalities involve larger deletions, duplications, and translocations, usually causing polygenic dysfunction and producing severe symptoms such as mental retardation and/or growth failure. These are most frequently found in epilepsy patients with coexisting multiple congenital abnormalities and/or intellectual disability. Most involve de novo parental germ-cell mutations, but familial rearrangements such as balanced translocations can occur. Once they reach a certain number, trinucleotide repeat expansions may also lead to diseases associated with epilepsy [4].

Multiple methods are available to test for different types of genetic changes. Standard karyotyping and high-resolution chromosome analysis can be used to identify chromosomal abnormalities such as Trisomy 21 or ring chromosome 20. Array-comparative genomic hybridization (aCGH) can detect submicroscopic chromosomal rearrangements (deletions or duplications, also called copy number variations or CNVs) and can investigate multiple loci simultaneously. Single nucleotide polymorphism (SNP) arrays can assess known SNPs throughout the genome. Testing for pathogenic CNVs using aCGH and SNP arrays is also known as molecular karyotyping. These tests identify CNVs that are felt to be causative in approximately 15–20% of patients with intellectual disability [5], and 8% of patients with early-onset epileptic encephalopathies [6], and are becoming widely used in these settings. Other techniques, such as fluorescent in situ hybridization (FISH) and

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multiplex ligation probe amplification (MLPA), are also widely used [1].

Utility of Genetic Testing in Epilepsy

When ordering genetic testing, it is important to be aware of factors that may affect the clinical validity and utility of a given test in a specific clinical situation. Clinical validity describes the ability of a test to determine whether a person is or will become affected with a given disorder. Clinical utility of a test refers to the risks and benefits of a positive or negative test on patient care.

Clinical validity is determined by many factors. Genetic testing may be performed in several types of laboratories. Clinical laboratories in the USA that are certified under the Clinical Laboratory Improvement Act (CLIA) are required to meet federal quality standards. Tests can also be carried out in research laboratories, which do not require CLIA certification and perform analyses for research only. There is also direct-to-consumer genetic testing, usually ordered over the Internet for a fee. This has the advantage of easy access and privacy, but is not subject to the same quality control measures as clinical laboratories, and generally does not include genetic counseling or adequate epidemiological data about baseline genetic variation to assist with interpretation of the results [2].

The appropriate type of test must also be ordered, as a given test will miss changes that it is not designed to detect (a mutation in a given gene may not affect a test for a particular SNP or CNV but still contribute to a disease). For each test, a negative result is most definitive if a positive result was obtained from an affected family member. Additionally, the source of DNA affects the validity of a test. A germ-line mutation may be absent in a parent's somatic cells (leading to negative genetic testing), but can still be passed on to offspring. Somatic mosaicism (more than one genotype in the body) may lead to negative testing from one tissue and positive testing from another [2].

Clinical validity is also impacted by the sensitivity and specificity of the test and the type of genetic change that is identified. When a mutation in a single gene produces different epilepsy phenotypes in different individuals, this is referred to as variable expressivity and reduces the positive predictive value of the test. For example, missense mutations in SCN1A can be associated with phenotypes ranging from no seizures or simple febrile seizures (GEFS+) to severe epileptic encephalopathy (Dravet syndrome) [7].

Genetic (or locus) heterogeneity occurs when a single clinical phenotype can result from mutations in different genes (e.g., in GEFS+ due to different sodium and/or GABA receptor mutations), or when different genetic mechanisms can produce the same disease (e.g., IGE can show autosomal dominant or complex inheritance). Additionally, families with a given syndrome may not have mutations in any previously identified genes. Patients without affected relatives are also less likely to have a mutation in previously identified genes [2]. In such cases, a positive result may be informative, but a negative result is not helpful clinically.

Reduced penetrance describes when individuals with a mutation remain unaffected. Penetrance for AD epilepsy is usually approximately 70% [2]. This lowers the positive predictive value of testing and can present significant difficulties in predictive testing in asymptomatic individuals. Also, gene–environment interactions may play a role in the expression of a trait. Each of these factors may lead to decreased clinical validity of a genetic test.

Clinical utility depends on the clinical validity of a test, but also on specific features of a given clinical situation. The relative risks and benefits of testing depend on the availability of an effective treatment, cost and accessibility of testing, severity of the disease, age of onset (particularly as it may affect reproductive choices), family history and the implications of testing on other family members, and potential ethical, legal, and social implications of genetic testing. The Federal Genetic Information Non-Discrimination Act (GINA) passed in May 2008 prohibits discriminatory use of genetic information by employers and health insurers, but does not extend to life insurance, disability

insurance, or long-term case insurance [8]. All of these issues should be addressed in pretest and posttest genetic counseling, and informed consent should be obtained before ordering a genetic test [2].

Clinical Application of Genetic Testing in Epilepsy

Genetic testing in patients with epilepsy can be diagnostic or predictive. Diagnostic testing is done in a patient with epilepsy to clarify the diagnosis and/or prognosis, to save a patient from further evaluation/testing, and rarely to affect clinical management. It can also provide families with information about the risks of recurrence and can help with reproductive decision-making. Ideally, this testing may also lead to targeted therapy.

Predictive testing is performed to predict the onset of epilepsy in asymptomatic patients (usually offspring or siblings of patients with epilepsy). This also includes prenatal diagnostic testing. The risk of epilepsy in relatives of patients with epilepsy is increased if there is an earlier age of onset (<35 years old), idiopathic epilepsy, an increased number of affected relatives, and if a parent is affected, particularly the mother [9]. Particularly for prenatal diagnostic testing, epilepsy risk is increased if a parent is a carrier of a balanced chromosomal translocation, if the mother is a carrier of an X-linked or mitochondrial mutation, if both parents are carriers for an autosomal recessive condition, or if a parent carries an autosomal dominant disorder [1]. Many severe pediatric neurogenetic conditions result from de novo or spontaneous mutations. If parents have negative genetic testing, the risk of recurrence in future offspring is <1% and would likely be attributable to undetectable gonadal mosaicism [1].

Options for parents at high risk who desire additional children include adoption, use of a donor egg or sperm (depending on which parent carries the mutation), prenatal testing (chorionic villous sampling or amniocentesis), or preimplantation genetic diagnosis (which requires in vitro fertilization). Of note, for women carrying a mitochondrial mutation, the risk of recurrence cannot be accurately predicted and prenatal testing is not accurate. The only way to guarantee avoidance of recurrence is the use of a donor egg [1].

In order to perform appropriate genetic testing, a full history must be obtained, including a three-generation pedigree focused on seizures and other seizure mimics, neurodevelopmental and psychiatric conditions, ancestral origins, outcomes of all pregnancies, and consanguinity. Full neurologic examination, developmental assessment, and appropriate further testing such as EEG, MRI, and/or metabolic workup can also contribute to appropriate genetic counseling and test selection [1].

For the epilepsies, the total number of genes in a differential diagnosis is often large and available tests are rapidly changing, so it is important to know genetic diseases with a high risk for epilepsy and to become familiar with online references such as GeneTests and OMIM [2]. Gene panels are also becoming more widely available. Tables 13.1 and 13.2 are a selected list of genes that have been identified in idiopathic and symptomatic epilepsies. These represent a synthesis of information from the referenced articles, and the reader is referred to epilepsy textbooks and the references at the end of this section if a more complete list is desired.

The clinical utility of performing these tests remains highly variable. Identification of mutations in patients with early-onset epileptic encephalopathies such as Dravet syndrome (SCN1A), epilepsy limited to females with mental retardation (EFMR) (PCDH19), and infantile spasms (ARX in boys, CDKL5 in girls) can be very useful, as they can limit further (often invasive) diagnostic testing, inform the prognosis, at times guide treatment, and provide useful information for genetic counseling for the family [3].

In other clinical situations, genetic testing has less clinical utility. Although very useful in the setting of a baby with possible Dravet syndrome, testing for SCN1A mutations in a family with GEFS+ has limited clinical utility due to the widely variable phenotype, so that testing cannot

Table 13.1 Genes identified in idiopathic epilepsy syndromes

Syndrome	Genetic test	Inheritance	Comment
(a) Syndromes beginning in the 1st year of life			
Benign familial neonatal seizures	KCNQ2 KCNQ3	AD	M-channel subunit of voltage-gated potassium channel Seizure onset often day of life 2–3 Diagnosis often clear without testing Benign outcome
Benign familial neonatal-infantile seizures	SCN2A	AD	Sodium channel subunit Seizures from 2 days to 6 months, normal development
Ohtahara syndrome	STXBP1 ARX	Various	Onset <6 months of age, tonic spasms, suppression burst on EEG
Early-onset spasms	CDKL5 (consider aCGH, TSC1/2, etc.)	X-linked	In girls (possibly lethal in males) Hypermotor-tonic-spasms
X-linked infantile spasms	ARX	X-linked	In boys
(b) Syndromes with prominent Febrile seizures			
Generalized Epilepsy with Febrile Seizures plus (GEFS+)	SCN1A SCN1B GABRG2	Can be AD or oligogenic	Sodium channel and $GABA_A$ receptor subunits Early-onset febrile seizures and/or variable afebrile seizure types including absence
Dravet syndrome (or severe myoclonic epilepsy of infancy—SMEI)	SCN1A	AD	Sodium channel subunit Early febrile and then various afebrile seizure types; psychomotor delay usually apparent during 2nd year of life
Childhood absence epilepsy with febrile seizures	GABRG2	AD	$GABA_A$ receptor subunit
Epilepsy and mental retardation limited to females	PCDH19	X-linked (present only in heterozygous females)	Protocadherin Early-onset seizures, autism, developmental delay Affects only heterozygous females
(c) Idiopathic generalized epilepsies			
Early-onset absence epilepsy	SLC2A1	AD	GLUT1 (glucose transporter type 1) Can also see mutation in early-onset refractory seizures, movement disorders Treat with ketogenic diet
Juvenile myoclonic epilepsy	GABRA1 EFHC1	AD	$GABA_A$ receptor EF hand motif protein
(d) Focal epilepsies			
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	CHRNA4 CHRNA2 CHRNB2	AD	Nicotinic acetylcholine receptor subunits Nocturnal clusters of brief motor seizures
Autosomal dominant partial epilepsy with auditory features (ADPEAF)	LGI1	AD	Also called autosomal dominant lateral temporal lobe epilepsy (ADLTLE) Simple partial seizures with mainly acoustic hallucinations

Table 13.2 Genes identified in symptomatic epilepsy syndromes

Syndrome	Genetic test	Inheritance	Comment
(a) Progressive myoclonic epilepsies			
Myoclonic epilepsy with ragged red fibers (MERRF)	Mitochondrial DNA evaluation (tRNA)	Mitochondrial	Best diagnosed by muscle biopsy
Unverricht-Lundborg	EPM1 (CSTB: cystatin B)	AR	
Lafora disease	EPM2A, NHLRC1 (EPM2B)	AR	PME with rapidly progressive dementia Proteins: laforin and malin Lafora bodies present on biopsy
Neuronal ceroid lipofuscinosis (NCL)	CLN1-8 PPT1	Adult onset Kufs—AD All others AR	With visual failure Lysosomal storage disease
Sialidosis	NEU	AR	Increased urinary oligosaccharides
Dentatorubral-pallidoluysian atrophy (DRPLA)	ATN1	AD	Trinucleotide repeat disorder
(b) Epilepsies related to cortical malformations			
Lissencephaly	LIS1 (PAFAH1B1)	AD	Posterior predominant Developmental delay, hypotonia, seizures
X-linked lissencephaly/double cortex syndrome/subcortical band heterotopia	DCX (XLIS)	X-linked dominant	Males: lissencephaly, epilepsy, MR Females: broad heterotopic zone, frontally predominant
Periventricular nodular heterotopia (PNH)	FLNA ARFGEF2	X-linked dominant (FLNA) AR (ARFGEF2)	ARFGEF2: PNH and microcephaly
(C) Other			
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Mitochondrial DNA evaluation (tRNA-Leu)	Mitochondrial	Seizures initially with metabolic disarray, later due to structural lesions
Alpers syndrome	POLG1	AR	Nuclear gene for DNA polymerase gamma Intractable seizures, developmental arrest, liver dysfunction
Tuberous sclerosis	TSC1 TSC2	AD, variable penetrance	CNS, renal, cardiac, dermatologic, pulmonary, eye abnormalities Proteins: hamartin and tuberin Can have infantile spasms, MR, autism
Fragile X syndrome	FMR1	AD	Trinucleotide repeat disorder
Rett syndrome	MECP2	X-linked	Seizures and other "spells," regression
Trisomy 21	Classical cytogenetics		Epilepsy in up to 12 %, variable seizure presentation including West syndrome and Lennox–Gastaut syndrome
Angelman syndrome	DNA methylation analysis UBE3A		Severe mental retardation, ataxic jerky movements, hypotonia, inappropriate laughter, absence of speech, microcephaly

accurately predict prognosis or necessarily inform treatment or genetic counseling. Testing for KCNQ2 and 3 in benign familial neonatal seizures, although highly accurate, is also of limited usefulness clinically. The diagnosis is often clear based on the history, as this disorder is autosomal dominant with high penetrance. In addition, the prognosis is favorable, so diagnosis is unlikely to alter reproductive choices [2].

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Epilepsy Secondary to Specific Mechanisms

14

Amar Bhatt

Autoimmune Epilepsy

Epilepsy related to cerebral autoimmune disease has recently gained increased recognition. These are not "zebras" and remain an important, treatable cause of epilepsy. Antiepileptic drugs (AEDs) alone will not suffice as treatment, and a protracted course of multiple immunotherapies may be needed (often over weeks or months). The evidence basis for diagnosis and treatment of autoimmune epilepsy is limited to expert opinion and case series [1, 2].

Autoimmune epilepsy should be considered early in cases of limbic encephalitis, new-onset refractory epilepsy, or new-onset status epilepticus. Features that favor autoimmune epilepsy include encephalopathy, cognitive decline, personality changes, a movement disorder, or prominent psychiatric symptoms (psychosis, catatonia, and agitation). Additional "red flags" include autoimmune stigmata (type 1 diabetes mellitus, thyroid disease, celiac disease, and vitamin B12 deficiency) or a history of cancer (or strong cancer risk factors). Stiff person syndrome, type 1 diabetes mellitus, and autoimmune encephalitis can all be associated with anti-glutamic acid decarboxylase (GAD) antibodies.

In any suspected cases, antibody testing and malignancy screening are necessary. Antibodies should be tested in both serum and CSF, though they may be found more consistently in the CSF. Routine CSF studies (cell counts, oligoclonal bands, and IgG index) are usually normal. MRI should be performed with contrast, but this can also be normal. Cancer investigation should include whole-body PET/CT; in select cases, ultrasound, endoscopy, or mammography may be needed.

Antibody testing in the serum and CSF is available both commercially and through private universities. Newer and rarer antibodies may not be available commercially or may not be included on the commercial panels. Antibodies can be classified as cellular ("onconeural") or cell membrane. The cellular antibodies have a stronger association with cancer, though these are thought to represent an epiphenomenon and are not necessarily pathogenic. Cellular antibody-mediated diseases may be poorly responsive to immunotherapy and require an exhaustive search for malignancy. A recent review [3] has an excellent discussion of the most common antibodies, their classifications, and common cancer associations. A brief overview is given in Table 14.1.

One important set of antibodies is directed against the voltage-gated potassium channel (VGKC) complex. This complex was previously implicated in Isaac syndrome (neuromyotonia) which at times was paraneoplastic. These antibodies are associated with non-paraneoplastic autoimmune limbic encephalitis, presenting with

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Table 14.1 Common antibody-related autoimmune epilepsies and associated presentations

Antibody/target	Symptoms (other than seizures/limbic encephalitis)	Associated cancer(s)
VGKC complex[a]	Personality or behavioral changes, myoclonus (CJD-like picture), neuropathy, and hyponatremia	SCLC, thymoma
NMDA receptor	Psychosis, extrapyramidal disorders (e.g., choreoathetosis), and dysautonomia	Ovarian teratoma
GAD	Stiff person syndrome, ataxia, brainstem encephalitis, parkinsonism, and diabetes (DM-1)	Thymoma Breast adenocarcinoma
Ma1, Ma2	Brainstem encephalitis	Testicular
ANNA-1 (Hu)	Brainstem encephalitis, autonomic or sensory neuropathy	SCLC
CRMP-5	Dementia, personality change, chorea, ataxia, and neuropathy	SCLC Thymoma
Amphiphysin	Dementia, myelopathy, and neuropathy	SCLC Breast adenocarcinoma
Antibody/target	GABA receptor; Symptoms: encephalopathy; Associated cancer(s)	SCLC, thymoma
Antibody/target	ANNA-2 (Ri); Symptoms: brainstem encephalitis, cerebellar ataxia; Associated cancer(s)	SCLC, breast, gynecological
Antibody/target	AMPA receptor; Symptoms: psychiatric; Associated cancer(s)	multiple solid cancers

[a] Multiple antibody targets in this complex (LGI1, CASPR2, and contactin-2)
VGKC, voltage gated potassium channel; SCLC, small cell lung cancer; CJD, Creutzfeld-Jakob disease; NMDA, N-methyl-D-aspartate; GAD, glutamic acid decarboxylase; DM, diabetes mellitus; ANNA, anti-neuronal nuclear antibody; CRMP, collapsin response mediator protein; GABA, gamma-aminobutyric acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

seizures, confusion, amnesia, and myoclonus (thus mimicking Creutzfeldt–Jakob disease). There is often associated hyponatremia. Both seizures and MRI abnormalities (T2 hyperintensity, restricted diffusion, or contrast enhancement) are typically in the temporal regions, though generalized seizures may also occur. Variations in presentation may relate to the different antibody targets within the VGKC complex; laboratory results may be reported by the specific target (CASPR2, LGI1, and contactin-2). LGI1-associated disease may present with faciobrachial dystonic seizures (FBDS), characterized by repetitive, brief episodes of facial twitching and ipsilateral arm dystonia, with or without EEG correlation. FBDS may occur before, during, or after the development of cognitive impairment, which can delay diagnosis.

Another important autoimmune epilepsy is related to anti-*N*-methyl-D-aspartate receptor (NMDA-R) antibodies. This is classically described as a paraneoplastic syndrome associated with ovarian teratoma, though it is often non-paraneoplastic. Typical symptoms include seizures, confusion, catatonia, amnesia, choreoathetosis, and dysautonomia. Anti-NMDA-R antibody titers may correlate to disease severity. The course may be protracted, have relapses, and require hospitalization for weeks or months to control drug-resistant seizures or immunotherapy-resistant symptoms. A recent study suggests that the "extreme delta brush" pattern on EEG may be a unique finding in anti-NMDA-R encephalitis [4].

Management has a four-part approach: first, an aggressive workup including MRI, EEG, CSF, antibody testing, and cancer screening; second, early immunotherapy; third, concomitant AED treatment; and fourth, management of systemic complications. First-line immunotherapy is usually 3–5 days of IV methylprednisolone, IV immunoglobulin, or both. If there is good response, the treatment may be tapered and replaced with mycophenolate or azathioprine. In resistant cases, cyclophosphamide or rituximab may be considered.

Brain Tumors and Epilepsy

Intracranial tumors are a common cause of adult —and childhood-onset epilepsies. In general, the following tumors are more epileptogenic: adult-onset tumors (which tend to be supratentorial, as opposed to pediatric tumors), lower grade tumors, cortical tumors, and tumors closer to sensitive networks, such as hippocampus or motor cortex [5]. Parietal tumors have the strongest association with seizures, followed closely by temporal tumors.

Seizure semiology depends on tumor location, but certain pathologies have stronger association with seizures. Nearly all dysembryoplastic neuroepithelial tumors will cause seizures, followed by gangliogliomas and low-grade astrocytomas; higher grade or fast-growing tumors (such as glioblastoma multiforme [GBM] or primary CNS lymphoma) do not cause seizures as often [6]. A characteristic GBM is shown in Fig. 14.1. Additionally, hypothalamic hamartomas cause gelastic seizures. Regardless of tumor type, a seizure as the initial symptom of tumor presentation may increase the risk of recurrent seizures and refractory seizures, possibly independent of treatment.

Epileptogenicity may relate to both peritumoral (non-neoplastic) tissue as well as genetic factors. Higher grade tumors may have central necrosis and be electrically silent, whereas surrounding hemosiderin or edematous tissue may be epileptogenic. One example of a genetic correlation is the absence of LGI1 gene product in GBM, due to gene translocation [5]. This is a tumor suppressor gene, but two non-neoplastic epilepsies relate to LGI1: autosomal dominant lateral temporal lobe epilepsy with auditory features caused by LGI1 gene mutation and autoimmune epilepsy related to antibodies against an LGI1 gene product (VGKC complex).

The American Academy of Neurology (AAN) guidelines recommend strongly against AED prophylaxis in brain tumor patients *without* a history of seizures, since prophylaxis does not prevent the first seizure [7]. AED prophylaxis may be used peri- and post-operatively, but usually only for one week. Once seizures have occurred, AEDs must be chosen carefully due to interactions with chemotherapy and corticosteroids, as well as additive risk of bone marrow suppression. Thus, agents such as levetiracetam and lacosamide may be preferred.

The goal of seizure freedom must be balanced with tumor prognosis; seizure freedom may not be a goal with unresectable tumors. Surgical treatment must be divided into "tumor surgery" (curative) or "epilepsy surgery" (palliative). Poor prognostic factors for seizure control include longer epilepsy duration, lower tumor grade, seizures at time of tumor diagnosis, and incomplete resection. Surgery can be considered even in low-grade tumors with resistant epilepsy, even if stable on imaging. Imaging alone should not guide surgery, since peritumoral tissue can be epileptogenic. Video-EEG, electrocorticography,

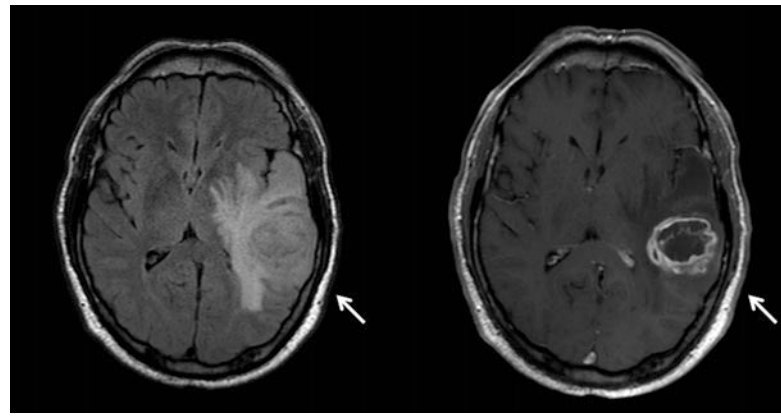

Fig. 14.1 Left temporal glioblastoma multiforme, on T2 FLAIR and T1-contrasted MRI

and functional mapping (e.g., language or motor function) should be used to guide resection.

Malformations of Cortical Development

Classification and understanding of malformations of cortical development (MCDs) continues to evolve. Most definitions are based on genetics, imaging, molecular biology, and pathology [8, 9]. Stem cells not only differentiate into neurons and glia, but they also migrate radially outward from the germinal matrix in the deep forebrain and periventricular regions. They also organize into "cytoarchitectonic" patterns, creating the six layers of neocortex. Any disruption in this process can lead to MCDs (i.e., normal cells in the wrong place, or abnormal cells in the right place).

Many MCDs are named based on descriptive anatomic terms and do not indicate a specific disease or genetic cause *per se*; in fact, many have overlapping pathology. Some occur in isolation as well as in the context of larger syndromes, such as hemimegalencephaly (HMEG). HMEG is characterized by a triad of intractable partial seizures from infancy, hemiparesis, and developmental delay; imaging readily identifies an enlarged, dysmorphic cerebral hemisphere. HMEG may occur in neurocutaneous syndromes, such as tuberous sclerosis complex (TSC) or neurofibromatosis. Functional hemispherectomy can improve seizure control and quality of life.

Lissencephaly (LIS) and subcortical band heterotopia (SBH) are two distinct phenotypes that may share similar genetic features. LIS is characterized by a "smooth brain" with absent or decreased convolutions (so-called agyria or pachygyria). SBH consists of an extra band of gray matter within the white matter (also known as "double cortex"). The classical form of LIS has a thickened, four-layer cortex and may have associated SBH. The autosomal dominant form of LIS is caused by LIS1 gene mutation and is typically more severe posteriorly, whereas the X-linked form is usually caused by DCX ("doublecortin") gene mutation and is typically more severe anteriorly. The X-linked inheritance has important implications; males have the more severe phenotype of LIS, whereas females have the milder phenotype of SBH (e.g., mild developmental delay and seizure onset in teenage years).

Polymicrogyria (PMG) is characterized by excessive, small gyri. It may present as bilateral perisylvian polymicrogyria syndrome, consisting of seizures, aphasia, and oromotor dysfunction. Schizencephaly (SCZ) and porencephaly (POR) are both characterized by parenchymal "clefts"; SCZ typically has gray matter along the clefts (which is often PMG), whereas POR has a white matter lining. When SCZ is associated with optic nerve hypoplasia and absence of the septum pellucidum, this is known as septo-optic dysplasia (de Morsier syndrome), and screening for hypopituitarism is important.

Periventricular nodular heterotopia (PVNH) consists of gray matter nodules along the lateral ventricles due to failed neuronal migration (Fig. 14.2), often causing intractable focal seizures. PVNH may be associated with abnormal overlying cortex; there is debate as to whether both the nodule and cortex should be resected. PVHN must be differentiated from the subependymal nodules of TSC (Table 14.2).

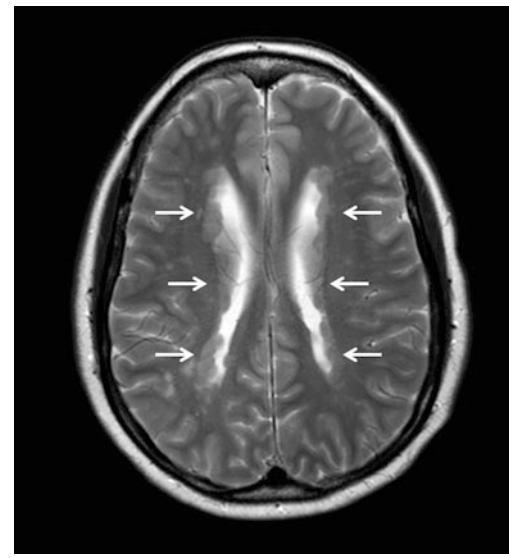

Fig. 14.2 Bilateral periventricular nodular heterotopia, as seen on T2-weighted MRI

Table 14.2 Comparison of periventricular lesions in two distinct neurological disorders

Tuberous sclerosis complex (subependymal nodules)	Periventricular nodular heterotopia
Smaller	Larger
Less in number	More in number, often bilateral
Heterogeneous	Homogeneous
Calcified	Not calcified
White matter intensity on MRI	Gray matter intensity on MRI

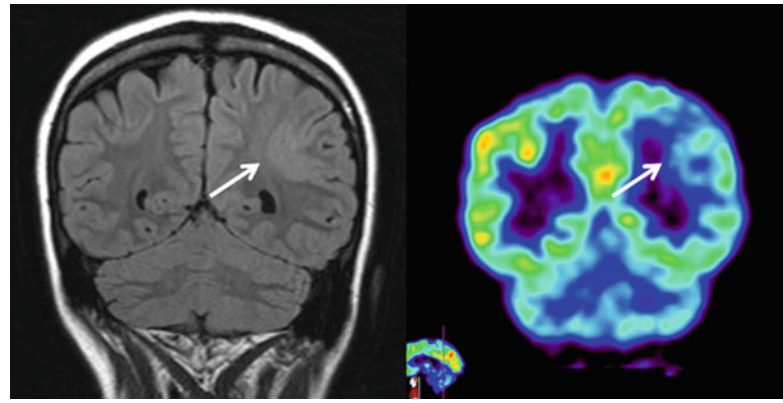

Fig. 14.3 Left parietal focal cortical dysplasia, with thickened cortex on T2 FLAIR and concordant region of hypometabolism on FDG-PET

PVNH can be familial, most often due to the X-linked FLNA (filamin A) gene mutation. Genetic cases are typically female and have bilateral PVNH (presumably the mutation is lethal in males).

Focal cortical dysplasias (FCDs) can also cause intractable focal seizures. Typical MRI findings include blurred gray–white junction, thickened cortex (Fig. 14.3), or the transmantle sign (a band of T2 hyperintensity extending radially between the cortex and ventricle). Many FCDs are subtle or not visible on MRI and may be found on functional imaging (PET or interictal SPECT, see Fig. 14.3). FCDs can be classified by pathological severity [10, 11]; more severe pathology has better prognosis, possibly due to being more visible on MRI or due to having better defined resection margins [12]. The mildest type is known as microdysgenesis. The intermediate type (Type I) may or may not be seen on MRI. The most severe type (Type II) can have "balloon cells" on pathology (Type IIb). Type III refers to dual pathology (FCDs associated with other lesions, such as tumors or mesial temporal sclerosis).

Post-traumatic Epilepsy

Head trauma is a leading cause of epilepsy, especially in young adults. The challenge lies in differentiating post-traumatic epileptic seizures from psychogenic non-epileptic events (PNES), though both may coexist in the same patient. Post-traumatic seizures are classified as early (within the first week) and late (after the first week).

A single late unprovoked post-traumatic seizure is nearly synonymous with epilepsy, and the terms may be used interchangeably. In one study, the risk of seizure recurrence after a single late seizure was 86% within two years [13]. Therefore, only one late seizure is necessary to diagnose epilepsy and strongly consider AED treatment. Approximately 10% of patients with early post-traumatic seizures develop epilepsy; however, multivariate analysis has shown that this can be explained by factors other than the early seizures themselves [14]. Also, early status epilepticus may have a higher risk for late seizures.

Head trauma may be classified as mild, moderate, or severe (Table 14.3). The presence of early seizures *in combination* with moderate or severe head trauma increases the risk of developing epilepsy [15]. Early seizures in mild head trauma do not necessarily increase that risk. In fact, there may be an association between mild head trauma and PNES. In children under five years of age, early seizures after head trauma are more common, but these are less predictive of epilepsy as compared to adults.

Assuming that a past head injury is the cause of seizures can be detrimental; one may miss non-epileptic events or a diagnosis of idiopathic/genetic generalized epilepsy. The cost may be more severe in veterans; PNES is associated with significantly more cumulative AED exposure and delay in diagnosis in veterans as compared to civilians [16]. Epileptiform discharges on EEG are not necessarily predictive of epilepsy and can be misleading, particularly when events are unwitnessed or the history is vague. Video-EEG remains the gold standard in the diagnosis of post-traumatic seizure-like events, and it should be considered in any patient who is medication-resistant after one year of treatment. Video-EEG with AED withdrawal is important, since some patients have both epileptic seizures and PNES.

Prophylactic treatment is only recommended in certain situations, and the evidence is strongest for prevention of early seizures in adults; data in children is insufficient. The AAN guidelines recommend phenytoin prophylaxis in adults with severe brain injury, but only for the first week; evidence does not suggest benefit of longer duration of prophylaxis in preventing late seizures [17]. Per a Cochrane review, the number needed to treat in preventing early seizures is ten, though maintaining first-week seizure freedom does not reduce mortality, disability, or late seizures [18]. There is no evidence for the use of steroids to prevent seizures.

Stroke and Epilepsy

Pediatric and adult epilepsy related to cerebrovascular disease differs in many regards. Seizure as the presenting symptom of stroke is very common in neonates (about 80%), relatively common in children (about 30%), and rare in adults; epilepsy risk after pediatric stroke can be up to 40%, whereas the risk in adults is less than 5% [19].

Post-stroke seizures are classified as early (within the first week) or late (after the first week), similar to post-traumatic seizures. Even one late unprovoked post-stroke seizure has a high recurrence rate (>50%), and AED treatment should strongly be considered. Therefore, as in head trauma, late post-stroke seizures are nearly synonymous with epilepsy.

Predictors of post-stroke epilepsy in adults include cortical location, presence of hemorrhage, and stroke severity (based on examination and NIH stroke scale) [19]. The EEG is not consistent in predicting epilepsy after stroke. Lateralized periodic discharges (LPDs, formerly known as periodic lateralized epileptiform discharges or PLEDs) are considered a classic finding in stroke and may be predictive of seizures, but they are not common, and may only predict early seizures and not necessarily later epilepsy. The most common finding is slow activity (focal or generalized), which is non-specific and not predictive of seizures. A recent Cochrane review [20] has not found strong

Table 14.3 Definitions of the severity of head trauma

	Mild	Moderate	Severe
Duration of loss of consciousness, amnesia, or coma	<30 min	30 min–24 h	>24 h
Presence of structural brain injury	None	Skull fracture without contusion or intracranial hemorrhage	Brain contusion, intracranial hemorrhage, or dural penetration

evidence that treating early post-stroke seizures prevents the development of epilepsy, although only one of the studies reviewed met inclusion criteria as a randomized controlled trial designed to address this question.

Mesial Temporal Sclerosis

Mesial temporal sclerosis (MTS), also known as hippocampal sclerosis, is one of the most common causes of adult-onset epilepsy, especially refractory epilepsy. However, it has been found in up to 14% of adults without epilepsy [21]. Classic semiology can include abdominal auras (nausea, pressure, butterflies, and epigastric rising), fear, an unpleasant taste or smell, oroalimentary or (ipsilateral) limb automatisms, and autonomic phenomenon. The typical ictal EEG pattern consists of anterior temporal rhythmic theta or alpha activity, which often exceeds 5 Hz within 30 s of seizure onset [22, 23]. Though many cases may have bilateral temporal onset on scalp (bisynchronous or independent), this does not necessarily rule out surgery. However, since seizures may start elsewhere and spread to the mesial temporal region, a primary extratemporal localization may be the source of seizures, even when semiology and ictal EEG patterns are predominantly temporal.

The most common MRI finding in MTS is hippocampal hyperintensity on T2-weighted sequences (e.g., FLAIR). However, this is not very reliable. Hippocampal atrophy is the most specific finding, usually noted on T1-weighted, thin cut imaging (Fig. 14.4) [24]. When comparing hippocampal volumes, asymmetry of the temporal horns of the lateral ventricle should not be over-interpreted as MTS. Additionally, even if MRI is normal, PET may show temporal hypometabolism suggestive of MTS. A recent study found good surgical outcomes after temporal lobectomy in patients with PET-positive, MRI-negative temporal lobe lesions [25], comparable to the typical MRI-positive MTS patients.

The cause of MTS is unclear. There may be a relationship between MTS, early complex febrile seizures, and childhood head trauma, but cause and effect remain controversial. Often there is a latent period between the injury and seizure onset, but it is not clear whether the MTS noted on imaging was either not previously present, not apparent since the brain was still developing, or not able to be studied by current imaging techniques.

Histopathology in MTS usually involves neuronal loss and gliosis in the CA1, CA3, and CA4 hippocampal regions, with relative sparing of CA2. Surgical experience has noted two important areas outside the hippocampus that usually require resection to achieve a good seizure outcome: the parahippocampal gyrus and the amygdala. Because MTS is so common, and so amenable to surgical resection, new-onset temporal lobe epilepsy at any age warrants evaluation for MTS. Dual pathology (MTS with coexistent neoplasms, MCDs, or vascular lesions) may require resection of both lesions for a good outcome.

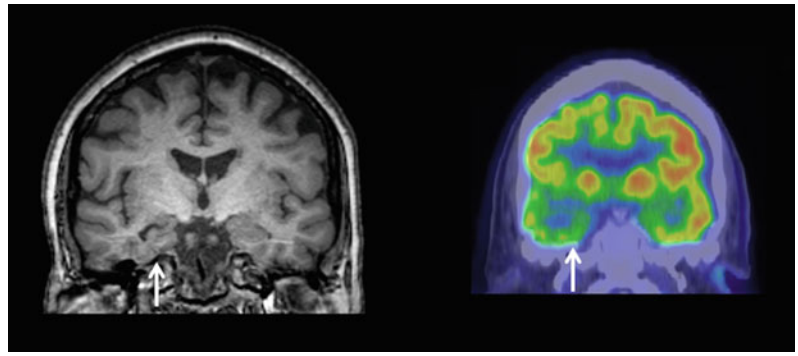

Fig. 14.4 Right mesial temporal sclerosis, with hippocampal atrophy on T1-weighted MRI and anterior temporal hypometabolism on FDG-PET

Predictors of good postsurgical outcomes include later age at onset, shorter duration of epilepsy, presence of febrile seizures, positive MRI (or positive PET with negative MRI), unilateral findings on PET, concordant data (matching of localization based on semiology, EEG, functional imaging, and anatomical imaging), and the lack of need for intracranial monitoring. In a typical case of MTS, the chance of seizure freedom after resection is approximately 60–70%. Surgical options include selective amygdalohippocampectomy, tailored temporal lobectomy (sparing dominant eloquent function), hippocampal laser ablation, and standard anterior temporal lobectomy.

Vascular Malformations

Epilepsy is most strongly associated with arteriovenous malformations (AVMs) and cavernous malformations (CMs). Developmental venous anomalies (DVAs) are usually incidental findings and not epileptogenic. In most vascular malformations, the surrounding hemorrhage, gliosis, and encephalomalacia are the epileptogenic tissues; the vascular lesions themselves are silent since they do not contain neuronal structures. Surgical management should have dual goals of seizure freedom and hemorrhage prevention. Electrocorticography-guided resection may have better seizure outcomes, as opposed to pure structural lesion-guided resection, especially in temporal CMs [26]. Stereotactic radiosurgery is also an option in AVMs.

An AVM is a direct connection between arteries and veins, without capillaries in between. These appear as a small collection of signal void on MRI. CMs are also known as cavernous angiomas or cavernomas, consisting of small bundles of brittle vascular endothelium (not true vessels) that lead to recurrent bleeding. On MRI, they are heterogeneous, with a core of mixed signal intensity surrounded by a T2 or gradient-echo hypointense rim (presumably hemosiderin). Familial CM syndromes have been reported, usually with autosomal dominant inheritance; some patients also have cutaneous and retinal involvement.

In a recent large population study [27], risk of new-onset seizure over five years in patients with incidental AVMs was 8%, but the risk increased to 23% if the AVM had previously caused hemorrhage or a focal neurological deficit. On the other hand, this study noted that CMs carried a similar risk (4–6%) of new-onset seizure, whether the CM was incidental or symptomatic. There was a suggestion that AVMs (but not CMs) in the temporal lobe were more likely to cause seizures.

Venous angiomas and DVAs rarely cause seizures or hemorrhage and are most often incidental. Resection should probably be avoided, as the epileptogenic focus may be unrelated to these lesions. A recent review of fifteen studies (with a combined 714 patients at the time of DVA diagnosis) found that 61% of DVAs were incidental findings, 6% were associated with focal neurologic deficits, 6% with symptomatic bleeding, and 4% with seizures; the presenting symptoms were unclear in the remaining 23% [28]. This study also prospectively analyzed an adult DVA population in Scotland, noting that 98% of DVAs (in 93 patients) were incidental.

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Multiple Choice Questions for Part III

1. Which of the following is shared by Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS+)?

   A. Lamotrigine is helpful in both conditions
   B. Both result from mutations in SCN1A
   C. EEG shows multifocal spikes and slowing
   D. Seizures decrease by late childhood
   E. All of the above

2. During video-EEG monitoring, which of the following features are suggestive of nonepileptic psychogenic seizures?

   A. Epigastric rising sensation, lip smacking, and confusion
   B. Visual hallucination, nystagmus, confusion, and vomiting
   C. Eye closure, confusion, and speech stuttering
   D. Head turning, confusion, and bicycling
   E. Brief staring, unresponsiveness, and subtle facial automatism

3. The rate of GLUT1 deficiency in early-onset absence epilepsy is closest to:

   A. 1%
   B. 10%
   C. 50%
   D. 75%
   E. 100%

4. Which of the following is true about familial lateral temporal lobe epilepsy with auditory features?

   A. Autosomal recessive inheritance
   B. Typical seizure onset in early childhood
   C. Typical seizure onset in early childhood
   D. Related to mutations in the leucine-rich glioma-inactivated (LGI) gene on chromosome 10q
   E. Epilepsy surgery is curative.

5. A 6-month-old-male infant has a hemiclonic convulsion lasting 5 min in the context of a fever. He continues having monthly febrile seizures. Around 12 months of age, he develops myoclonic seizures and generalized tonic clonic seizures. His development is noted to be delayed by 18 months of age. Which of the following is true?

   A. Genetic testing for mutations in a sodium channel is indicated.
   B. Seizures are easily controlled with the first antiseizure medicine.
   C. Nonconvulsive status epilepticus is very rare.
   D. Gait remains normal in all patients.
   E. Vaccination has never been reported as a trigger.

6. Mutations in which of the following genes are associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)?

   A. STXBP1
   B. LGI
   C. SCN1A
   D. KCNQ2
   E. nicotinic acetylcholine receptor

7. The risk of SUDEP in patients with drug-resistant convulsive epilepsy is:

   A. 1/100000
   B. 1/10000
   C. 1/1000
   D. 1/100
   E. 1/10

8. Which of the following is true about childhood absence epilepsy (CAE)?

   A. Ethosuximide and valproate are equally tolerable
   B. Lamotrigine and ethosuximide are equally efficacious
   C. Children with CAE are cognitively intact
   D. GABA receptor mutations have been identified
   E. It is more frequent in boys

9. Convulsive psychogenic seizures are more likely to show the following except:

   A. Closed eyes
   B. Side-to-side head movements
   C. Asynchronous motor activity
   D. Back arching
   E. Postictal regular and noisy breathing

10. Mutations of the cystatin B gene are associated with which of the following progressive myoclonus epilepsies (PME)?

    A. Lafora body disease
    B. Jansky–Bielschowsky disease
    C. Unverricht–Lundborg disease
    D. Sialidosis
    E. Batten disease

11. Which of the following is true about epilepsy with myoclonic absences?

    A. Ethosuximide must be avoided
    B. Seizure frequency increases in the afternoon and evening
    C. Brain MRI may show abnormalities
    D. Tonic seizures do not occur
    E. It is more frequent in girls

12. A 3 month-old full-term baby presents with upper respiratory tract symptoms and one simple febrile seizure. His work-up should include:

    A. EEG
    B. LP
    C. Brain MRI/MRA
    D. Bronchoscopy
    E. None of the above

13. Mutations of which of the following genes are not associated with generalized epilepsy with febrile seizures plus (GEFS+)?

    A. GABRG2
    B. PCDH19
    C. SCN1B
    D. SCN1A

14. Which of the following statements is true regarding seizures after stroke?

    A. Neonatal strokes are more likely to present with focal neurologic deficits rather than seizures
    B. Adult onset stroke is more likely to lead to epilepsy as compared to pediatric stroke
    C. At least two late seizures are necessary to diagnose post-stroke epilepsy and consider treatment

D. Focal slowing on EEG is not predictive of epilepsy after stroke
E. Strokes are not correlated with seizures

15. Which of the following is true about Doose syndrome?

A. Positive family history of idiopathic generalized epilepsy
B. Grand mal seizures are rare
C. Brain MRI often shows abnormalities
D. Glut-1 deficiency is identified in 50% of cases
E. Dietary therapies are not effective

16. A 6-year-old male is seen for occasional nocturnal seizures consisting of strange throaty noise and contraction of the left face. The yield of the EEG will be highest during:

A. Photic stimulation
B. Sleep
C. Wakefulness
D. Hyperventilation
E. Studying

17. Which of the following does not have an autosomal dominant inheritance?

A. Early-onset absence epilepsy (due to GLUT-1)
B. Juvenile myoclonic epilepsy (due to GABA-A receptor)
C. Lateral temporal lobe epilepsy with auditory features (due to LGI1)
D. Dentatorubral-pallidoluysian atrophy (due to trinucleotide repeats)
E. Sialidosis (due to Increased urinary oligosaccharides)

18. Which of the following is true regarding seizures after traumatic brain injury?

A. Prophylaxis of seizures should continue for one month after severe brain injury
B. Risk of epilepsy decreases with time after the injury, especially after the first two years
C. At least two late seizures are necessary to diagnose post-traumatic epilepsy and consider treatment
D. A history of mild head trauma and abnormal EEG warrants anticonvulsant treatment
E. All of the above are correct

19. Which of the following is true about Lennox–Gastaut syndrome (LGS)?

A. Infantile spasms precede LGS in >50% of cases
B. The EEG shows spike-wave discharges at 3–5 Hz
C. Sleep normalizes the EEG
D. EEG background is often normal
E. 70% of the patients have structural/metabolic causes

20. A 26 year old lady with two-year history of diarrhea and weight loss, presented with new onset seizures. Which of the following can help most with the diagnosis?

A. Pelvic CT scan
B. D-Xylose test
C. Sural biopsy
D. Urine epinephrine test
E. None of the above, EEG is the only helpful test

21. A 16-year-old girl with intractable partial epilepsy has a brain MRI which reveals periventricular lesions. Which of the following radiologic features is more likely to suggest periventricular nodular heterotopia, rather than the subependymal nodules of tuberous sclerosis complex?

    A. Unilateral lesion
    B. Calcified lesion
    C. Homogenous lesion
    D. White matter intensity lesion
    E. Ventricular lesion

22. Which of the following is an identifiable pathology in continuous spike-and-wave during sleep (CSWS)?

    A. Polymicrogyria
    B. Porencephaly
    C. Thalamic lesions
    D. Migrational disorders
    E. All of the above

23. A 6-month-old boy has epileptic spasms, hypotonia, and difficulty feeding. His MRI reveals lissencephaly. Which genetic mutation is also known to be responsible for a milder phenotype, especially in girls?

    A. LIS1 on chromosome 17
    B. DCX (doublecortin) on the X chromosome
    C. FLNA (filamin A) on the X chromosome
    D. TSC2 (tuberin) on chromosome 16
    E. WD 40

24. Which of the following would NOT be an appropriate treatment for this patient (in question 23), if started within the first 4 days of onset?

    A. Vigabatrin
    B. Carbamazepine
    C. Ketogenic diet
    D. Oral corticosteroids
    E. ACTH

25. A 17-year-old high school student presented with recurrent weekly episodes of odd behavior at night. During these episodes, he would wake up 3 h after falling asleep, walk through the dormitory, or be sitting quietly in the kitchen room. His classmates report that he would appear confused and clumsy and afterward has no recollection of the event. Which of the following is the most likely diagnosis?

    A. Nocturnal absence seizures
    B. Confusional arousal disorder
    C. Frontal hypermotor seizures
    D. Sleep-induced syncope
    E. Early-onset dementia

26. Which of these tumor types is most likely to be associated with seizures?

    A. Primary CNS lymphoma (PCNSL)
    B. Dysembryoplastic neuroepithelial tumor (DNET)
    C. Meningioma
    D. Astrocytoma
    E. Schwannoma

27. Which of the following is true about juvenile myoclonic epilepsy (JME)?

    A. Photosensitivity is noted in 75%
    B. Family history is positive in <20%
    C. Inheritance is likely polygenic
    D. Mutations in myoclonin1/EFHC1 have been identified in 50%
    E. All of the above

28. A 65-year-old male is referred for the evaluation of frequent nocturnal stereotyped events of brief violent motor activity. EEG recording during these events is normal. His brain MRI is also normal. Which neurological condition is likely associated with this sleep disorder?

    A. Alzheimer's dementia
    B. Parkinson's disease

C. Multiple sclerosis
D. Pompe's disease
E. Tuberous sclerosis

29. Pallister-Hall syndrome (GLI3 gene mutation) is associated with which of the following?

A. Autosomal dominant temporal lobe epilepsy
B. hypothalamic hamartoma
C. Juvenile myoclonic epilepsy
D. Electrical status epilepticus during sleep
E. None of the above

30. Glucose transporter type I deficiency syndrome (Glut1 DS) is associated with which of the following?

A. Infantile onset seizures
B. Microcephaly
C. Ataxia
D. Mixed-type seizures
E. All of the above

31. Which of the following reduces the likelihood of remission in psychogenic seizures?

A. Normal neuropsychological testing
B. Longer duration of illness
C. Frequent events
D. Willingness to seek psychiatric help
E. All of the above

32. In primary brain tumors, which of the following factors is least likely to have higher association with seizures?

A. Adult onset of brain tumor
B. Tumor situated near the hippocampus
C. Tumor situated near primary motor cortex
D. High-grade tumor pathology
E. All the above have similar seizure association

33. A 46-year-old woman has been suffering of frequent complicated attacks of migraines since her early teens. She has no history of epilepsy. If she undergoes an EEG, the tracing may show the following:

A. Normal background
B. Generalized slowing
C. spikes
D. Enhanced photic drive
E. All of the above

34. A 55-year-old man presents with a one-month history of progressive cognitive decline and episodes of unresponsiveness (which are diagnosed as nonconvulsive seizures by video-EEG monitoring). Despite cessation of seizures after treatment with four anticonvulsants, he becomes comatose. On examination, he is noted to have myoclonic jerks. Laboratory studies reveal hyponatremia. Which serum antibody is most likely to be positive in his condition?

A. N-methyl-D-aspartate receptor (NMDA-R) antibody
B. LGI1 antibody (voltage-gated potassium channel [VGKC] complex)
C. Glutamic acid decarboxylase (GAD) antibody
D. Anti-Amphiphysin antibody
E. Anti-cardiolipin antibody

35. Which of the following statements is false regarding early seizures after traumatic brain injury?

A. Early seizures occur within the first week after injury
B. Early seizures may be associated with increased occurrence of late seizures/epilepsy
C. Early status epilepticus may be associated with increased occurrence of late seizures/epilepsy

D. Early seizures should be treated in order to lower the risk of late seizures/epilepsy
E. All of the above are correct

36. A 5-year-old girl is seen in first seizure clinic after a nocturnal episode of vomiting, pallor, behavioral irritability, then eye deviation to the right and unresponsiveness, followed by a generalized tonic clonic seizure. The total duration of the episode was 5 min. Her development has been normal and there is no family history of seizures. Which of the following is true?

A. This epilepsy syndrome has a poor prognosis for seizure control.
B. Treatment typically includes corticosteroids and vigabatrin.
C. Most patients with this disorder have major structural brain malformations.
D. Trauma is a frequent antecedent of this epilepsy syndrome.
E. The EEG likely will show paroxysms of occipital spikes.

37. A 2-year-old boy presented with occasional episodes of generalized stiffness and tonic spasms since birth. His development, neurological examination, and EEG are normal. Which of the following is true about this boy's condition?

A. Inhibitory glycine receptor mutation
B. LGL1 gene mutation
C. Calcium T-channel disfiguration
D. Leucine antibodies
E. Anti-Gad antibodies

38. Glucose transporter type I deficiency syndrome (Glut1 DS) is associated with which of the following except?

A. Dysarthria
B. Episodic weakness
C. CSF glucose <40 mg/dl
D. Medications are effective in about half of the cases
E. Dietary therapies are ineffective.

39. A 46-year-old woman presents with new-onset episodes of cold sweat, pallor, and heart racing lasting for few minutes. Occasionally, these episodes are associated with loss of consciousness. She had a normal neurological examination and negative prior routine EKG, EEG, and brain imaging. She was started on lacosamide with partial relief. Which of the following test is most likely to provide a definitive diagnosis?

A. Inpatient video-EEG monitoring
B. Tilt-table testing
C. Cardiac Holter monitoring
D. Lumbar puncture
E. 24-hour urine metanephrine

40. An 8-year-old boy has epilepsy and partial blindness. He has a history of events where he feels palpitations and lightheadedness, falls down, and passes out for 30–45 s. An EEG during the event reveals generalized slow activity. MRI shows clefts in the cortical tissue and the absence of the septum pellucidum. What is the most appropriate test to order in this patient?

A. Continuous video-EEG monitoring
B. Tilt-table testing
C. 24-hour cardiac rhythm monitoring
D. Serum cortisol level
E. Sedimentation rate

41. A 43-year-old woman is being evaluated for intermittent convulsions. Which feature would be more suggestive of epileptic seizures as opposed to psychogenic nonepileptic seizures?

A. Tongue biting at the side
B. Opisthotonic posturing
C. Side-to-side head movements

D. Postictal shallow and rapid breathing
E. Ictal eye closure

42. A 4-year-old boy has severe oral and facial dysfunction since birth, associated with difficulty feeding. He has intractable partial epilepsy with bihemispheric epileptiform discharges on EEG. His MRI shows excessive, small convolutions in the bilateral frontal and temporal opercular regions. What is his diagnosis?

A. Polymicrogyria
B. Lissencephaly
C. Schizencephaly
D. Pachygyria
E. Septum pellucidum

43. Anti-NMDA receptor encephalitis is associated with which of the following except?

A. A prodrome of viral-like illness
B. Ovarian teratoma
C. Mildly elevated protein in CSF
D. CSF rarely shows signs of inflammation
E. Anti-NMDA receptor antibodies in both serum and CSF

44. Propofol infusion syndrome is more common:

A. Children
B. Critically-ill patients
C. Concomitant use of catecholamines
D. Prolonged infusions
E. All of the above

45. Which of the following characteristics is most associated with a good outcome in psychogenic nonepileptic seizures?

A. Prominent motor features
B. Male gender
C. Longer duration of illness
D. Older age at diagnosis
E. Lower educational achievement

46. A patient with a brain tumor has never had a seizure and is requesting anticonvulsant prophylaxis when being admitted for her tumor resection. The most appropriate response is:

A. Anticonvulsant prophylaxis is not recommended before the first seizure, and it is also not recommended perioperatively.
B. Anticonvulsant prophylaxis is not recommended before the first seizure, but it is recommended for the first six months postoperatively.
C. Anticonvulsant prophylaxis is not recommended before the first seizure, but it is recommended for the first one week postoperatively.
D. Anticonvulsant prophylaxis is recommended before the first seizure, and it also should be continued indefinitely postoperatively.
E. Steroids are the anticonvulsant of choice

47. In a child presenting with seizures, CSF analysis can be helpful if which of the following is suspected?

A. Nonketotic hyperglycinemia
B. Alpers' syndrome
C. Pyridoxamine 5′-phosphate oxidase (PNPO) deficiency
D. Primary cerebral folate deficiency
E. All of the above

48. A 4-month-old full-term baby has periodic episodes of arching of the back and stiffening every 2–3 h. His neurological examination and EEG between attacks is normal. He has not been gaining weight at the expected pace and has occasional vomiting. The treatment of choice is:

    A. Pyridoxine
    B. Vigabatrin
    C. ACTH
    D. Omeprazole
    E. Observe

49. A 35-year-old woman without a history of epilepsy is hospitalized with confusion and psychosis. EEG reveals frequent partial seizures, resistant to four anticonvulsants. She is noted to have choreiform movements on examination. Which test is most likely to provide a specific diagnosis?

    A. PET-CT of abdomen and pelvis
    B. LGI1 antibody (voltage-gated potassium channel complex)
    C. MRI of the brain with contrast
    D. Continuous video-EEG monitoring
    E. Lumbar puncture

Answers

1. (B). Dravet syndrome presents in infancy with convulsive seizures often triggered by fever. It also includes other seizure types such as myoclonic, atonic, focal dyscognitive seizures, and nonconvulsive status epilepticus. Development slows in the second year. Intellectual disability and intractable seizures ensue. In Dravet, ~75% of subjects have mutations in the voltage-gated sodium channel gene, SCN1A (95% of which are de novo). Sodium channel agents, such as lamotrigine, tend to worsen the seizures. In 10% of familial GEFS+, there are mutations in the SCN1A gene; others have GABRG2 mutations affecting the GABA channel.
2. (C). For the diagnosis of nonepileptic psychogenic seizures, several clinical features are helpful in confirming this diagnosis. Highly predictive features include eye closure, out of phase or discontinuous motor activity, and forward pelvic thrusting, among others. Confusion is not helpful in distinguishing epileptic from nonepileptic seizures.
3. (B). Most cases of absence epilepsies of childhood have complex inheritance. In one study, only 12% of screened patients with early-onset absence epilepsy had mutations in SLC2A1, the gene encoding the GLUT1 glucose transporter. Some mutations are familial and others are de novo.
4. (D). Familial lateral temporal lobe epilepsy with auditory features is autosomal dominant with seizure onset in adolescence or early adult life. Typical aura is a simple auditory hallucination with the evolution to dyscognitive and grand mal seizures. It is associated with mutations in the leucine-rich glioma-inactivated (LGI) gene on chromosome 10q.
5. (A). This is a classical description of an infant with Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI). More than 70% of patients have mutations in SCN1A, although girls with negative testing should undergo analysis of PCDH19. Seizures are very difficult to control. Many recommend avoidance of seizure medicines that act on sodium channels. Nonconvulsive status epilepticus is not uncommon. Deterioration in gait patterns has been noted in studies of older patients. Vaccinations (especially those containing whole-cell pertussis) have been reported as a trigger in case series.
6. (E). Mutations in CHRNA2, CHRNA4, and CHRNB2, genes encoding the nicotinic acetylcholine receptor, are seen in patients with autosomal dominant nocturnal frontal lobe epilepsy. Please refer to Table 12.1 for other details.
7. (D). The risk of Sudden Unexpected Death in Epilepsy (SUDEP) in patients with drug-resistant epilepsy is about 1/100, while

the risk of SUDEP in community-based epilepsy patients is 1/1000.

8. (D). CAE is more frequent in girls, and in some cases mutations in GABA receptor (GABRG2, GABRA1), calcium channels, and non-ion channel proteins have been identified. A double-blinded, randomized, comparative clinical trial compared ethosuximide, lamotrigine, and valproate in CAE and found that ethosuximide provided the best combination of seizure control and fewest attentional side effects, making it the optimal initial monotherapy in CAE. Ethosuximide provided better seizure control compared to lamotrigine and fewer attentional effects compared to valproic acid. Although CAE is often perceived as "benign," many children with CAE have cognitive deficits and long-term psychosocial problems.
9. (E). When evaluating convulsive attacks, several clinical features favor the diagnosis of psychogenic nonepileptic seizures. Most studied features include eye closure, side-to-side head and body movements, asynchronous motor activity, and postictal irregular shallow breathing.
10. (C). PME is characterized by myoclonic and grand mal seizures, as well as progressive cognitive dysfunction deterioration and ataxia. Unverricht–Lundborg disease is associated with mutations of the cystatin B gene, Lafora body disease with mutations of EPM 2A (coding for laforin) and EPM2B (coding for malin) genes, and sialidosis with mutations of NEU1 gene that codes for neuraminidase. A number of gene mutations have been identified in neuronal ceroid lipofuscinosis of which Jansky–Bielschowsky disease and Batten disease are subtypes.
11. The majority (70%) of children with epilepsy with myoclonic absences are boys. Neuroimaging abnormality, mainly some degree of diffuse atrophy, is seen in 17% of patients. Frequent seizures may occur on awakening. Tonic contractions, particularly elevation of the arms, are often noted, which can be asymmetric. Treatment options include valproate and ethosuximide.
12. (B). Infants younger than five months of age presenting with febrile seizures should undergo a thorough infectious work-up including a lumbar puncture to rule out CNS infections. chest Xray, urine testing and
13. (B). Please refer to Table 13.1.
14. (D). Unlike adult stroke, pediatric stroke more commonly presents with seizure as the presenting symptom and has higher risk for developing epilepsy. In fact, about 80% of neonatal strokes present with seizure (as opposed to with focal neurological deficits). Similar to post-traumatic epilepsy, even one late unprovoked post-stroke seizure has a high recurrence rate and is tantamount to post-stroke epilepsy. Predictors of post-stroke epilepsy include cortical stroke location, presence of hemorrhage, and examination severity, but not presence of focal slowing (a nonspecific finding).
15. (A). In 15–32% of subjects with Doose syndrome, there is strong family history of idiopathic epilepsy. GTC is usually the first seizure and is seen in 75–95% of patients. Neuroimaging is typically normal. Glut-1 deficiency is identified in about 5% of children with Doose syndrome. Treatment options include valproate, lamotrigine, ethosuximide, topiramate, levetiracetam, and the ketogenic diet.
16. (B). The age and description of the seizures is consistent with benign epilepsy with centrotemporal spikes (BECTS) also known as benign rolandic epilepsy. Onset of seizures occurs between the ages of 4–10 years. Clinically, seizures are common during sleep (80% of times) consisting of unilateral tonic or clonic activity of the face and excessive salivation often followed by secondarily generalization.
17. (C). Contrary to all listed conditions, Sialidosis is inherited in an autosomal recessive pattern.
18. (B). Prophylaxis is recommended only for the first week after severe traumatic brain

injury. Recurrence risk of seizures after one late post-traumatic seizure is high; therefore, this is essentially considered to be epilepsy, and treatment should be strongly considered. Early seizures in combination with moderate or severe head trauma increase risk of developing epilepsy, but mild head trauma in combination with abnormal EEG is not diagnostic of epilepsy, particularly if the clinical events are not convincingly epileptic by history. Video-EEG monitoring should be considered in such cases, as non-epileptic events are in the differential diagnosis.

19. (E). The peak age of onset of LGS is 3–5 years, and infantile spasms precede LGS in 10–25%. EEG features of slow background with generalized slow spike-wave discharges at 1.5–2 Hz, multifocal discharges, and generalized fast activity at 10–25 Hz in sleep. LGS results from structural/metabolic causes in 70–78%.
20. (B). Common clinical signs and symptoms of Whipple's disease include diarrhea, steatorrhea, abdominal pain, weight loss, and migratory arthropathy. In about 10–30% of patients, CNS symptoms of dementia, movement disorders or seizures may occur. D-Xylose test can help with confirming intestinal malabsorption syndrome. Overall, duodenal biopsy is considered the gold standard for diagnosis.
21. (C). Both tuberous sclerosis complex (TSC) and periventricular nodular heterotopia (PVNH) can present with seizures and periventricular lesions. The lesions of PVNH are typically not calcified, are homogenous, are gray matter (by definition), and may be bilateral (particularly in familial cases, which are usually X-linked).
22. (E). CSWS manifests as global regression in cognition and behavior. The majority of patients have seizures. CSWS is sometimes associated with identifiable pathology, e.g., neuronal migrational disorders, polymicrogyria, shunted hydrocephalus, porencephaly, and thalamic lesions. Family history of seizure is reported in 10–15%.
23. (B). LIS1 gene mutation causes the autosomal dominant form of lissencephaly; the DCX gene mutation has an X-linked inheritance pattern which may present with (milder) subcortical band heterotopia phenotype in girls. FLNA is related to periventricular nodular heterotopia, and TSC2 is related to tuberous sclerosis complex.
24. (B). A recent evidence-based guideline outlined the evidence for different treatments for infantile spasms (Go et al., Neurol 2012;78:1974). Of all the treatments listed, carbamazepine would not be expected to lead to resolution of the spasms. Earlier onset of treatment is associated with better outcomes.
25. (B). The history of stereotyped nocturnal odd behavior occurring during the first half of the night, and amnesia of the events is suggestive of confusional arousal disorder. Sleep deprivation, excessive stress, or alcohol intake can trigger these episodes. EEG recording during these events may be normal or show generalized slowing of background activity.
26. (B). Of the primary brain tumors, DNET has the highest association with seizures (nearly 100%), followed by gangliogliomas and astrocytomas. Higher grade or fast-growing tumors such as glioblastoma or PCNSL have a lower association with seizures.
27. In JME, photosensitivity is noted in about 30% of patients. Family history of epilepsy is reported in 40–50%. Inheritance is unclear, likely polygenic, but both autosomal dominant and recessive inheritance have been reported. Gene mutations identified in some families include GABRA1 (GABA-A receptor gene on chromosome 5q34), CLCN2 (chloride channel 2 gene on chromosome 3q26), and myoclonin1/EFHC1 (EH-hand motif protein on chromosome 6p12; found in 9% of JME).
28. (B). The clinical description is most consistent with REM behavior disorder. This sleep

disorder has been closely linked to the development of Parkinson's disease.

29. (B). Hypothalamic hamartoma is usually sporadic but is rarely associated with autosomal dominant Pallister–Hall syndrome (GLI3 gene mutation).
30. (E). Glut1 is found in microvessels and astrocytes, and it facilitates glucose transport into the brain. Initial patients with Glut1 DS had refractory epilepsy (infantile onset), encephalopathy, acquired microcephaly, cognitive impairment, and motor abnormalities (spasticity, ataxia, and dystonia). Clinical features include seizures, movement/gait disorders, and cognitive/behavioral disturbances. Seizure starts in infancy (average age of onset 8 months). GTC, absence, myoclonic, and focal seizures may occur. Only 8% will be seizure free with medications alone.
31. (B). Longer duration of illness, abnormal neuropsychological testing, and presence of psychiatric comorbidities are the predictors of negative outcome in psychogenic nonepileptic seizures.
32. (D). Tumors in adults, tumors near sensitive or irritable structures and networks (limbic pathways, motor cortex), and tumors that are low grade (e.g., those without central necrosis) are more likely to be associated with seizures.
33. (E). Patients with history of migraines may have normal EEGs or nonspecific EEG changes including generalized slowing (or focal in hemiplegic migraines), loss of normal alpha rhythm, enhanced photic drive, and attenuated beta activity. Occipital spikes can also be seen in basilar migraines. In the absence of suspicion for epilepsy, there is no justification in obtaining EEGs for migraineurs.
34. (B). The presence of rapid cognitive decline and myoclonus could suggest Creutzfeldt–Jacob disease, but new-onset intractable seizures more strongly suggest autoimmune epilepsy. Hyponatremia is typical of VGKC-complex antibody-mediated disease, of which LGI1 is a common target. NMDA-R antibody-mediated disease often presents with associated movement disorder and ovarian teratoma; GAD antibody-mediated disease may also present with type I diabetes mellitus or stiff-person syndrome; anti-Amphiphysin antibody-mediated disease often presents with neuropathy and can be associated with small cell lung cancer or breast adenocarcinoma.
35. (D). There is no evidence that treating early post-traumatic seizures lowers the risk of developing epilepsy/late seizures, although treating and preventing early seizures may help with acute recovery, as early seizures could lead to further brain injury. Although multivariate analyses have shown that early seizures do not themselves increase risk of late seizures, early seizures are associated with development of late seizures due to confounding factors that increase risk for both early and late seizures (brain contusion, subdural hematoma, and loss of consciousness or amnesia > 24 h).
36. (E). The patient has benign occipital epilepsy or idiopathic childhood occipital epilepsy (most likely Panayiotopoulos syndrome). The symptoms and signs described in the question are classic for this diagnosis. The EEG classically shows occipital spikes that are best brought out by darkness but other types of epileptiform activity have been noted, as well. Because the frequency of seizures is low, many patients do not need to be treated with antiseizure medicines.
37. (A). Age and clinical description are consistent with the diagnosis of hyperekplexia or stiff baby syndrome. It consists of a triad of generalized stiffness, nocturnal myoclonus, and tonic spasms that are usually triggered by auditory or tactile stimuli. It is caused by gene mutations affecting the inhibitory glycine receptor (GLRA1 and GLRB). The treatment of choice is clonazepam.
38. Glut1 deficiency is associated with spastic or ataxic gait, dystonia, chorea, tremor,

exertional dyskinesia, and episodic weakness (triggered by fasting and exercise). Cognitive and behavioral disturbances including learning/intellectual disability, language deficit (predominantly expressive), and dysarthria are common. The diagnosis of Glut1 DS is based on hypoglycorrhachia with normoglycemia and low-to-normal CSF lactate. CSF glucose is <40 mg/dl (2.2 mmol/L); in all reported cases, CSF glucose is <60 mg/dl (3.3 mmol/L). CSF: blood glucose ratio is <0.4 (fasting state). Gene mutation (SLC2A1 gene on chromosome 1p35-31.3) is identified in about 90% of patients. 90% is de novo mutation; ~10% AD; rare AR. Erythrocyte glucose uptake assay may be used to confirm the diagnosis. The ketogenic diet is effective. Only 8% will be seizure free with medications alone.

39. (A). The initial symptoms are suggestive of presyncope but the associated change in awareness and the partial relief on lacosamide are both suggestive of epileptic seizures. Normal routine EEG and brain imaging do not exclude the diagnosis of epilepsy. An inpatient video-EEG monitoring with lacosamide withdrawal is the gold standard test, in addition to full cardiac telemetry will be valuable too.
40. (D). The constellation of partial blindness, epilepsy, schizencephaly, and an absent septum pellucidum suggests septo-optic dysplasia (de Morsier syndrome). Optic nerve hypoplasia may also be seen. This is typically associated with hypopituitarism, and the events described are probably syncope and not seizures. Therefore, a serum cortisol level is most likely to give a specific diagnosis. Although the remaining answer choices may suggest a cause of syncope, screening for pituitary dysfunction should not be overlooked.
41. (A). During convulsions, tongue biting (especially at the side of tongue) is more likely to occur with epileptic seizures. The remaining features are highly suggestive of psychogenic nonepileptic seizures.
42. (A). This is a classic description of bilateral perisylvian polymicrogyria syndrome; the perisylvian localization explains the symptoms, EEG findings, and imaging abnormalities. Schizencephaly can be seen with polymicrogyria but is not typically part of this syndrome; the MRI would show parenchymal clefts in schizencephaly. Pachygyria and lissencephaly are seen in combination with each other, and the MRI description is inconsistent with these two options.
43. (D). Anti-NMDA receptor encephalitis may present with a prodrome of viral-like syndrome precedes psychiatric and behavioral problems. The symptoms progress to altered mental state, seizures, dyskinesia, choreoathetosis, and breathing and autonomic instability. CSF shows signs of inflammation in over 90% of patients. Lymphocytic predominant pleocytosis, mildly elevated protein, and oligoclonal bands may be present. The diagnosis of anti-NMDA receptor encephalitis is made by the demonstration of anti-NMDA receptor antibodies in serum and CSF. The level of antibody in CSF correlates with symptom and outcome. Anti-NMDA receptor encephalitis may be associated with ovarian teratoma in females.
44. (E). Propofol infusion syndrome is a rare syndrome which affects patients undergoing long-term treatment with high doses of propofol. This can lead to cardiac failure, metabolic acidosis, rhabdomyolysis, and kidney failure, and is often fatal. The syndrome occurs more commonly in children, and critically ill patients receiving glucocorticoids and catecholamines.

45. (B). Several characteristics were shown to be associated with good outcomes (event resolution) in psychogenic nonepileptic seizures. These include male gender, younger age at onset, short duration of illness, higher educational and socioeconomic status, and minimal motor involvement during events.
46. (C). The American Academy of Neurology guidelines recommend anticonvulsant treatment only after a seizure has occurred. Prophylaxis in brain tumor patients without a history of seizures is only recommended for one week post-operatively; longer-term prophylaxis in patients (regardless of operative history) has not been shown to prevent the first seizure.
47. (E). Glycine encephalopathy (also known as nonketotic hyperglycinemia) is an autosomal recessive condition caused by defect in the glycine cleavage system (intramitochondrial enzyme complex) resulting in excess glycine in all tissues, especially CNS. Glycine is both excitatory (cortex) and inhibitory (brainstem and spinal cord) neurotransmitter in the CNS. Infants presented with neonatal hypotonia, seizures (often myoclonic), encephalopathy or coma, and hiccups. The diagnosis of glycine encephalopathy is confirmed by elevated glycine in plasma and CSF, and CSF to plasma glycine ratio >0.08. Seizures occur in 35–60% of patients with mitochondrial disorder. Examples include MERRF (myoclonic epilepsy and red ragged fibers), Alpers syndrome [POLG1 (polymerase gamma) mutation: explosive focal epilepsy, EPC or status epilepticus, and predominant occipital discharges on EEG may suggest the diagnosis], and MELAS (mitochondrial myopathy encephalopathy, lactic acidosis and stroke-like episodes). Elevated plasma and/or CSF lactate suggests mitochondrial disorder but normal lactate does not rule out the diagnosis. Elevated alanine level may indicate mitochondrial disorder. Pyridoxal 5′ phosphate (PLP) is an essential cofactor in the synthesis of dopamine and serotonin. Pyridoxamine 5′-phosphate oxidase (PNPO) deficiency, caused by mutation of PNPO on chromosome 17q21.32 and inherited as autosomal recessive trait, results in the decreased synthesis of PLP and clinically manifests with severe refractory neonatal epileptic encephalopathy with prenatal seizures. EEG may show burst-suppression pattern. CSF neurotransmitter metabolite levels are abnormal: low HVA and 5-HIAA concentration (degradation products of dopamine and serotonin, respectively), and high L-dopa (precursor of dopamine), 5-hydoxytryptophan (precursor of serotonin), and 3-ortho-methyldopa concentrations. CSF PLP level is reduced. Patients respond to pyridoxal phosphate but not to pyridoxine.Primary cerebral folate deficiency results from defect in transport of folate across blood-CSF/blood–brain barrier. There are 2 possible causes for the transport defect: blocking auto-antibodies against folate receptors of the choroid plexus and folate receptor gene mutation (FOLR1). Clinically symptoms start at 4–6 months of age with irritability and disturbed sleep. Slow head growth, ataxia, choreoathetosis, and ballistic movements are additional features. By 2 years of age, mental retardation, ataxia, involuntary movements, and spastic diplegia will ensue. Later visual disturbance and progressive sensorineural hearing loss occur. About a third of patients have seizures which includes myoclonic-atonic, absence, and GTC seizures.
48. (D). The clinical description is most consistent with the diagnosis of Sandifer syndrome or infantile gastroesophageal reflux disease. Since he has been losing weight and vomiting, a trial of antacids such is omeprazole is needed. This condition usually resolves after the age of 6 months.
49. (A). The patient most likely has anti-NMDA receptor encephalitis, characterized by new-onset refractory seizures, prominent psychiatric features, and a movement

disorder. This can be associated with ovarian teratoma. Testing for malignancy (PET-CT or ovarian ultrasound) is indicated. MRI and EEG can be abnormal but are not likely to reveal a specific diagnosis or etiology. Anti-LGI1 (VGKC-complex) encephalitis can have a similar presentation but may have hyponatremia, myoclonus, and faciobrachial dystonic seizures and in most cases is not paraneoplastic.

Part IV
Management of Epilepsy

Principles of Epilepsy Diagnosis and Management

15

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Epidemiology

Epilepsy is a fairly common condition compared to other neurological disorders. Approximately 3.1 % of the US population (about 9 millions) suffers from epilepsy. About 5 % of the US population (about 15 millions) will have a seizure at some time in their lives and only just a bit more than half of those will progress into epilepsy. Incidence rate for epilepsy is about 44 per 100,000 in the US. This rate is 61 for first unprovoked seizures, 39 for acute symptomatic seizures, and 100 for all seizures including seizures from epileptic patients Hauser et al. [1]. The incidence of epilepsy tends to be higher in males and is highest at or after age 75. The most common known etiology is cerebrovascular disease at 11 %, followed by neurologic deficits from birth, mental retardation, or cerebral palsy at 8 % Hauser et al. [1].

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First Seizure

i. **Provoked seizures:**

This term is often misinterpreted as all seizures are provoked. However, in epilepsy, the term "provoked seizure" often implies the presence of a simple fixable cause for the seizure. The term "provoked seizure" is mostly used for a selected group of seizures. These are the seizures triggered by some reversible process, such as electrolyte abnormality, severe sleep deprivation, or a medication adverse effect. A provoked seizure is preventable after reversing the provocation. In contrast, intractable epilepsies are often caused either by a cortical malformation, hippocampal sclerosis, or some other structural abnormalities such as acute cerebral insults. These are called symptomatic seizures (related to a structural abnormality) rather than provoked seizures. Even when we cannot identify a clear etiology, we assume there is always a reason for seizures including genetic causes.

ii. **First unprovoked seizure:**

This is defined as a seizure with no clearly identified provocation or etiology at the initial work up.

iii. **Appropriate work up for the first unprovoked seizure:**

There is level B evidence supporting the use of EEG and brain imaging mainly MRI for the initial

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work-up of a first unprovoked seizure. MRI is usually preferred over CT scans because of its higher resolution for soft tissue and malformations. In one pooled analysis of 928 subjects with brain MRI after first seizure, 15 % were found to have brain MRI abnormalities. In the same study, 51 % of 1766 patients (pooled analysis) had an abnormal initial routine EEG. An additional 35 % were identified to have abnormalities on the second sleep-deprived EEG. An abnormal EEG predicts a higher recurrence rate, and a normal EEG predicts a lower recurrence rate but does not rule out epilepsy. On average, about 50 % of individuals clinically diagnosed with a seizure have a normal first routine EEG. Laboratory testing, such as complete blood counts, blood glucose, and electrolyte panels (particularly sodium), cerebrospinal fluid analysis, and toxicology screening may be helpful as determined by the specific clinical scenario based on history, physical, and neurologic examination, but there are insufficient data to support or refute recommending any of these tests for the routine evaluation of adults presenting with an apparent first unprovoked seizure (Krumholz et al.).

In one study by King et al., brain MRI abnormalities were seen in 14 % (38 of 277) of patients with a first unprovoked seizure. Tumors were the most commonly identified etiology for seizures followed by developmental anomalies then hippocampal pathologies and vascular malformations King et al. [2]. In another similar study done 15 years later, 23 % (177 of 764) of patients had MRI abnormalities. This time developmental anomalies were equally common as tumors. The higher yield was attributed to the use of 3 T MRIs as opposed to 1.5 T in the original study Hakami et al. [3].

iv. **Seizure recurrence after first unprovoked seizure:**

The recurrence rate after the first unprovoked seizure averages around 40 % within the first two years. This was concluded based on three large pivotal studies:

Meta-analysis (USA) in 1991 which found a 36 % recurrence by the two years.

Table 15.1 Seizure recurrence rates

	Recurrence rate (%)
After first unprovoked seizure	40
After two unprovoked seizures	73
After three unprovoked seizures	76
After treating first unprovoked seizure	15

FIRST Trial (Italy) in 1993 found a 51 % recurrence by two years.

UK (MESS Trial) in 2005 found 39 % recurrence by two years.

The recurrence rates were higher years after a remote symptomatic and after having two or more seizures (Tables 15.1 and 15.2). Treatment after the first seizure decreases the recurrence rate by 30–60 % but does not eliminate the risk completely (Table 15.3).

v. **Seizure recurrence after the first unprovoked seizure according to etiologic factors and EEG findings Berg and Shinnar [4]:**

Etiology
Idiopathic 32 %
Symptomatic 57 %
EEG
Normal 27 %
Epileptiform 58 %
Etiology + EEG
Idiopathic + Normal 24 %
Symptomatic + Abnormal EEG 65 %

Focal onset seizures had higher risk of recurrence than generalized-onset seizures. A first seizure occurring during sleep also had higher risk for recurrence than a seizure occurring during wakefulness. The other risk factors for seizure recurrence included status epilepticus as first seizure, abnormal interictal neurological examination, abnormal brain imaging, multiple or clustered seizures at onset, and strong family history of seizures.

Treatment decision after first seizure

This subject has always been controversial as scholars usually differ in their practices of treating or not treating the first seizure. In general,

Table 15.2 Risk of seizure recurrence after first symptomatic seizure (Hesdorffer et al.)

	Acute (%)	Remote (%)
Stroke	33	71.5
TBI	13.4	46.6
CNS Infection	16.63	63.5

Acute: within one week, remote: after one week

Table 15.3 Seizure recurrence rates at 6 and 24 months, after treatment or no treatment

		Seizure rate	
		Untreated (%)	Treated (%)
Italian FIRST study 1993 (n = 397)	**6 months**	**41**	**17**
	24 months	**51**	**25**
UK MESS study 2005 (n = 1443)	**6 months**	**26**	**18**
	24 months	**39**	**32**

about 60 % of the patients who had their first seizure will never have another one. In this case, it is appropriate to give the facts to the patient and let them make their decisions. If the patient prefers not to be treated and understands the risk of receiving no treatment, it is perfectly acceptable not to treat. Some patients will insist on being treated since they do not want to risk another seizure. In this case, treatment is offered for these patients provided that they understand the seizure recurrence risk is decreased but not necessarily eliminated with treatment. After an acute or remote symptomatic (cerebral insult) seizure in a clinically unstable patient, treatment is usually indicated without waiting for a second seizure. Selecting an appropriate antiepileptic (AED) is quite challenging task in most cases. This is due to the presence of multiple AED options and very little predictability of good response. In addition, efficacy and tolerability of AEDs may strongly differ among individuals.

There are several available factors that could help us make an educated decision of what AED would be best to start with. The spectrum of a particular AED (narrow or broad) is one of these factors (Table 15.4). In general, narrow spectrum AEDs are reserved for seizures with known. When seizure classification is unclear, it is wiser to initiate a broad spectrum agent AED. The reason for this approach is that most narrow spectrum AEDs will not benefit patients with generalized-onset seizures or generalized epilepsies. On the contrary, some narrow spectrum AEDs could cause worsening of seizures if given to a patient with generalized-onset seizures (see Table 15.4).

Mechanism of action (MOA) is another factor that may influence the selection of an AED (Table 15.5). However, the role of MOA is very limited, and the existing data do not support consideration of MOA as a major criterion in choosing an AED. Many AEDs have multiple MOAs, and some have unknown MOAs. This makes it even more difficult to make a judgment based on MOA alone [5, 6]. According to a study by Deckers CL et al., there is some evidence showing that AED polytherapy based on MOA may enhance effectiveness. In particular, combining a sodium channel blocker with a drug enhancing GABAergic inhibitor could be an advantageous combination. Combining two GABA mimetic drugs or combining an AMPA antagonist with an NMDA antagonist may enhance efficacy, but tolerability may be reduced with this combination.

Other Factors Influencing AED Selection

- Seizure type/classification
- Epilepsy syndrome
- Established drug efficacy for a particular seizure type or epilepsy syndrome

Table 15.4 Grouping of AEDs according to their spectrum of activity

Broad spectrum AEDs	Narrow spectrum AEDs
Valproate	Phenytoin*
Felbamate	Ezogabine*
Phenobarbital#	Perampanel*
Lamotrigine	Lacosamide*
Topiramate	Carbamazepine~
Zonisamide	Gabapentin~
Levetiracetam	Pregabalin~
Benzodiazepines	Tiagabine~
Primidone	Oxcarbazepine~
	Vigabatrin@
	Rufinamide
	Ethosuximide

Rufinamide is minimally effective against focal seizures, Ethosuximide is only approved for absence seizures, * = Spectrum not yet fully identified or mixed, ~ = May exacerbate some generalized seizures such as myoclonus and absence, @ = Considered narrow spectrum but exceptionally useful in infantile spasms, # = May trigger absence seizures or worsen Lennox-Gastaut syndrome or myoclonic epilepsies

- Safety
- Tolerability profile
- Co-morbidities (weight, cognition, psychiatric, other)
- Side-effect profile
- Metabolic status (renal, hepatic)
- Drug-drug interactions
- Drug formulations
- Ease of administration/titration
- Pregnancy or contraception
- Prior allergies and cross reactivity
- Cost
- Availability

Available AEDs: Currently, there are about 25 FDA-approved AEDs in the USA. The graph below lists AEDs in chronological order (Fig. 18.1). Commonly used abbreviations, brand names, and common side effects of current AEDs are listed in Table 15.6.

Older (Classic) Versus Newer AEDs

The classic AEDs include Phenobarbital, Phenytoin, Primidone, Ethosuximide, Benzodiazepines, Carbamazepine, and Sodium Valproate. There were no new AEDs during the period of 1978 (approval of VPA) until 1993 (approval of Felbamate). The AEDs which came after 1993 are considered to be newer AEDs. The newer AEDs have shown comparable efficacy to older ones. However, newer AEDS offer numerous advantages over the older AEDs. These include minimal drug-drug interactions, better pharmacokinetic profiles, and minimal or no long-term side effects. They are often associated with less teratogenicity and less immediate side effects. Most importantly, they usually do not need routine blood level monitoring because of low protein binding and negligible hepatic induction or inhibition properties. The availability of generic formulations of some of the newer AEDs helped boost their use. AED selection is still determined on a case-by-case basis but overall, the newer AEDs mostly replaced the older ones as first choice AEDs.

FDA Indications

Drug trials primarily aim to prove superiority over placebo, or no inferiority (conversion to monotherapy studies). Drug trials tend to use

Table 15.5 Mechanism of action of AEDs

AED	Enhancement of GABA-mediated excitation	Blockade of sodium channels	Blockade of calcium channels	Inhibition of glutamate	Other
Benzodiazepines[&]	+	+[*]			
Carbamazepine		+			
Ethosuximide			+ (T-type)		
Phenobarbital[&]	+	+		+	
Phenytoin		+			
Valproate	+	+	+ (T-type)		+
Gabapentin			+ (L-type)[$]		
Pregabalin			+ (L-type)[$]		
Felbamate	+	+		+	
Lamotrigine		+	+ (L-type)		
Levetiracetam					+[@]
Oxcarbazepine		+	+ (L-type)		
Tiagabine[^]	+				
Topiramate[~]	+	+	+ (L-type)	+	+
Zonisamide[~]		+	+ (L-type)	+	+
Lacosamide	+[#]				
Rufinamide	+[#]				
Vigabatrin[%]	+				

[+]= a documented mechanism of action, [*] = at high benzodiazepine concentrations, [%] = GABA transaminase inhibitor, [#] = enhancers of slow inactivation of sodium channel, [~]=Carbonic anhydrase inhibitors, [^] = GABA reuptake inhibitor, [@] = acts on synaptic vesicle 2A receptors, [$] = acts on alpha-2-delta receptors, [&] = GABA-A receptor enhancers (Phenobarbital causes sustained opening of GABA channels, benzodiazepines cause frequent opening of GABA channels

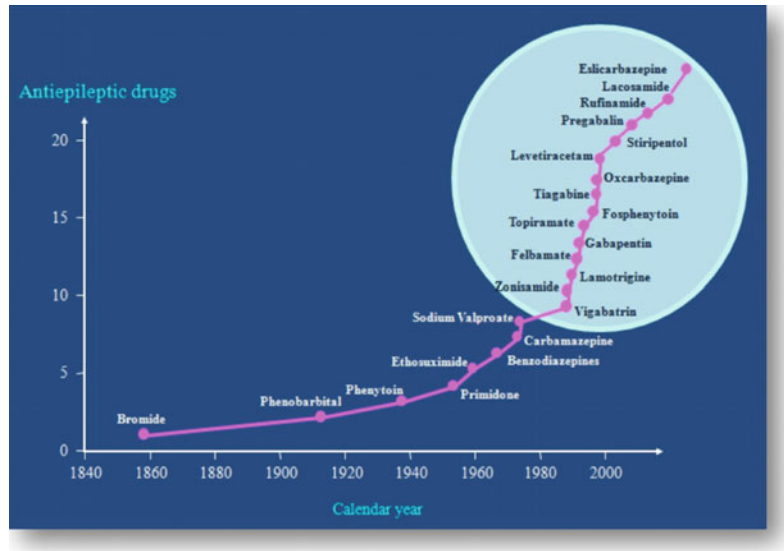

Fig. 15.1 There are about 25 FDA-approved AEDs in the USA. This graph lists AEDs in chronological order. *Adapted from Brodie MJ. Seizure 19 (2010) 650–655. Since this graph was created three additional AEDs got approved by FDA (Clobazam, Ezogabine, Perampanel, and eslicarbazepine)*

Table 15.6 Commonly used abbreviations, brand names, and most frequent side effects of AEDs

ABR	Generic	Brand	Watch for
Older (Classic) AEDs			
PHB	Phenobarbital	(Luminal)	Sedation, rash, liver failure, aplastic anemia, osteopenia, CT d/o
PHT	Phenytoin	(Dilantin)	SJS, blood dyscrasia, liver failure, gingival hyperplasia, hirsutism, osteopenia
PRM	Primidone	(Mysoline)	Metabolized to phenobarbital
ESX	Ethosuximide	(Zarontin)	Stomach upset, abdominal pain/cramps
CLZ	Clonazepam	(Klonopin)	Somnolence, lethargy, sexual dysfunction, tolerance is an issue
CZP	Clorazepate	(Tranxene)	Somnolence, lethargy
DZM	Diazepam	(Valium)	Not for prevention, can be used as abortive medication (watch for resp suppression)
LRZ	Lorazepam	(Ativan)	Not for prevention, can be used as abortive medication (resp suppression)
CBZ	Carbamazepine	(Tegretol)	Sedation, ↓WBC, ↓Na, bradycard, SJS, agranulo, hepatic fail, pancreatitis
VPA	Valproate	(Depakote)	Weight gain, tremor, ↓Plt, pancreatitis, liver failure, ↑ammonia, hair loss
Newer AEDs			
VGB	Vigabatrin	(Sabril)	Permanent visual field deficit 30–40 %, reversible subcortical edema
ZNS	Zonisamide	(Zonegran)	Cross reacts with sulfa, hypohidrosis, renal stones
LTG	Lamotrigine	(Lamictal)	Nonsedating, insomnia, SJS (needs very slow titration), myoclonus
FBM	Felbamate	(Felbatol)	Aplastic anemia, liver failure, weight loss, ↑PHT, VPA, PHB
GBP	Gabapentin	(Neurontin)	Sedation, weight gain, myoclonus
TPM	Topiramate	(Topamax)	Weight loss, severe cognitive slowing, dysesthesias, glaucoma, renal stones
TGB	Tiagabine	(Gabitril)	Sedation, cognitive slowing, worsens gen szs (myoclonic, absence)
OXC	Oxcarbazepine	(Trileptal)	↓Na in elderly, ↓OCP levels, sedation, rash
LEV	Levetiracetam	(Keppra)	Irritability (hateful, anger issues, Vit B6 100 mg/day may help), depression
PGB	Pregabalin	(Lyrica)	Sedation, swelling in lower extremities, blurred vision
RFM	Rufinamide	(Banzel)	Loss of appetite, aggravated seizures, status epilepticus
LCM	Lacosamide	(Vimpat)	Dizziness, fatigue
ESL	Eslicarbazepine	(Aptiom)	Nausea, Dizziness, diplopia, hyponatremia (1–2 %)
CLB	Clobazam	(Onfi)	1, 5-benzodiazepine, somnolence, lethargy, (less addiction potential)
EZG	Ezogabine	(Potiga)	Urinary retention, tremors, bluish skin coloration
PER	Perampanel	(Fycompa)	Ataxia, severe mood issues (hostility, homicidal ideation, aggression)

higher doses to reach higher efficacy. Tolerability at these higher doses tends to be lower. Table 15.7 summarizes studies and level of evidence for each seizure type and epilepsy syndrome adopted from a special report by the International League Against Epilepsy.

Reference Studies on AED Selection

In one study, Mattson et al. compared CBZ, PHB, PHT, or PRM in partial seizures and secondarily generalized tonic-clonic seizures

Table 15.7 Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	**Level A: CBZ, LEV, PHT, ZNS** Level B: VPA Level C: GBP, LTG, OXC, PHB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	**Level A: OXC** Level B: None Level C: CBZ, PHB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	**Level A: GBP, LTG** Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized-onset tonic–clonic seizures	0	0	27	**Level A: None** Level B: None Level C: CBZ, LTG, OXC, PHB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalized-onset tonic–clonic seizures	0	0	14	**Level A: None** Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	**Level A: ESM, VPA** Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	**Level A: None** Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	**Level A: None** Level B: None Level C: None Level D: TPM, VPA

(SGTCS). This was a multi-center double-blind trial for initiation monotherapy. A total of 622 adult epilepsy patients were recruited. Treatment success was highest with CBZ or PHT, intermediate with PHB, and lowest with PRM (Mattson et al. 1985). In another multi-center double-blind study, VPA was compared to CBZ for the treatment of complex partial seizures and SGTCS in adult patients. Both drugs were equally effective in controlling SGTCS. For complex partial seizures, outcome measures favored CBZ which also had less adverse effects (Mattson et al. 1992). Glauser et al. compared ESX, VPA, and LTG monotherapies for the treatment of childhood absence epilepsy in a double-blind randomized controlled trial. This study was done on 453 children with newly diagnosed absence epilepsy. ESX and VPA had similar efficacy which was better than LTG. ESX had fewer attentional dysfunction than VPA. ESX was re-established as the first choice drug in the childhood absence epilepsy despite the availability of multiple newer AEDs. No prospective double-blind controlled study

Table 15.8 Indication

Indication	Try	Avoid
Seizure type		
Focal or secondary generalized	LTG, LEV, OXC, LCM, TPM > CBZ, > VPA, ESL, PHT	
Primary Generalized (GTC)	VPA, LEV, LTG, TPM, ZNS	
Primary Generalized (Absence)	ESX, VPA > LTG	PHT, CBZ, GBP, TGB, VGB
Primary Generalized (Myoclonic)	LEV, VPA, CLZ	PHT, CBZ, GBP, TGB, VGB, PGB
Rolandic (centrotemporal)	LEV, OXC	
Other factors		
Young women	LTG, LEV, LCM	VPA > > CBZ, PHT
Depression	LTG	PHT, PHB, PRM,
Labile, impulsive	VPA, CBZ, LTG, OXC, TPM	LEV
Liver disease	LEV, LTG, PGB	VPA, PHT, CBZ
Obesity	TPM, ZNS	VPA, GPN, PGB
Pain	GBP, PGB, CBZ, OXC	
Headache	TPM, VPA, GBP, PGB	
Type A personality (baseline irritability)		LEV
Polytherapy (non AEDs)	LEV, PGB, GBP	Enzyme Inducers
Asian (Han Chinese or Taiwanese)		CBZ, OXC (if have to use **check HLA-b 1502**)

showed superior efficacy of newer drugs compared to the older ones. Several studies showed better tolerability and less discontinuation rates with newer AEDs. In one study, PGB had similar tolerability but inferior efficacy to LTG for the treatment of newly diagnosed partial seizures in adults Kwan et al. [7]. Another study demonstrated PGB to be non-inferior to LTG in the treatment of refractory partial seizures. In a meta-analysis by Costa J. et al., clinical comparability of the newer AEDs in refractory partial epilepsy was analyzed. A total of 62 randomized controlled trials comparing a new AED to a placebo as adjunctive therapy, and 8 randomized controlled trials comparing a new AED to another AED as add were reviewed. In this meta-analysis, LEV shined as the AED with high responder rate as well as low withdrawal rate. Looking at the results overall, TPM and LEV had the highest responder rates. GBP and TGB had the lowest responder rates. Withdrawal rate was highest with OXC and TPM and lowest with GBP and LEV Costa et al. [8]. Table 15.8 summarizes ideal AED(s) selection based on seizure type and comorbidities.

Drug-Resistant Epilepsy and Polytherapy

Drug resistant epilepsy is defined as failure to achieve seizure freedom after adequate trials of two appropriately chosen AEDs used as therapeutic levels in monotherapy or combination therapy (2010 consensus document by ILAE, Kwan et al. 2010). Overall, about one third of all epilepsies prove to be drug resistant. Among all epilepsies, symptomatic or cryptogenic epilepsies have higher rate of drug resistance compared to idiopathic epilepsies Kwan et al. [9]. Drug resistance also tends to be higher in patients who had more than 20 seizures prior to starting

Table 15.9 Specific rash cross-sensitivity rates (Hirsch et al. 2008)

AEDs	Cross-sensitivity rates (%)
CBZ – OXC	33–71
CBZ – PHT	42–57
CBZ – PHB	27–66
PHT – ZNS	21

treatment. When the initial AED fails, adding a second AED or switching to another AED did not differ statistically; however, common practice favors the combination therapy Kwan et al. [9]. Wide range of combinations of two or perhaps three AEDs can be effective in some patients. With the available 25 different AEDs, about 300 possible double therapy regimen and more than 2000 triple therapy regimens can be achieved. While choosing an appropriate AED combination, drug-drug interactions should be avoided. Enzyme inducing AEDs will increase their own clearance as well as most of the other AEDs (Table 15.10). For example, combining PHB and VPA would increase sedation and weight gain; combining PHT and CBZ would result in increased side effects such as dizziness and diplopia and bidirectional induction of metabolism would make it difficult to maintain therapeutic blood levels. VPA may triple LTG blood levels and result in increased chances of allergic reactions. If used cautiously, VPA and LTG combination therapy is shown to be one of the most successful combinations in generalized epilepsy. Also it is recommended to avoid combination of AEDs with similar side effects such as dizziness, imbalance, and diplopia common to sodium channel blockers. In particular, these combinations include CBZ + LTG, CBZ + LCM, OXC + LCM, or LTG + LCM. In one study, 1617 seizure-free epilepsy patients on polytherapy were identified. The majority of seizure-free patients (81.3 %) on polytherapy were on two AEDs only. With 64 effective dual therapy regimens, VPA and LTG combination was the most commonly successful combination at 24.3 %. About 17.5 % of seizure-free patients were on three AEDs. There were 57 effective triple therapy regimens, and the most commonly successful combinations were (LTG + TPM + VPA) or (LEV + LTG + VPA) Stephen et al. [10].

One should also consider the specific rash cross-sensitivity rates among AEDs (Table 15.9). There is no known specific cross-sensitivity between LTG and other AEDs. AEDs with low risk of rash include VPA, GBP, PGB, LEV, and TPM.

Eliminating AEDs which are deemed ineffective is necessary to decrease the drug burden, to allow higher doses of more effective drugs, and also to avoid drug-drug interactions. There may be certain patients who would have increased seizures even when an ineffective drug is decreased or stopped. These patients usually end up on multiple AEDs up to six or seven without seizure control. Withdrawal seizures should not discourage clinician to simplify AED regimens. If needed, epilepsy monitoring unit could be used to safely taper the ineffective AED.

Table 15.10 P450 enzyme modulation of several AEDs

Enzyme inducing AEDs (strong)	Enzyme inhibiting AEDs (strong)
Phenobarbital **Primidone** **Phenytoin** **Carbamazepine** **Oxcarbazepine (doses > 900 mg)** **Lamotrigine (weak)**	Valproic acid Topiramate (weak)

80–90 % of all existing medications will be affected by the enzyme inducing AEDs above. In particular efficacies of steroids, estrogens, digoxin, warfarin, furosemide, and doxycycline will be decreased

Stopping AEDs When Seizure Freedom Achieved

About 70 % of epilepsy patients will eventually achieve seizure freedom with AEDs. There is often an illusion of cure after seizures are controlled for long term. However, this is not the case in most patients. In general, depending on the seizure or epilepsy and etiology, 11–41 % of patients will relapse after the AED discontinuation. The relapse rate tends to be lower in children (~ 20 %) and higher in adults (~ 40 %). In one large study, patients in long-term remission were randomized either to withdraw or continue the treatment. In the first two years, 41 % of the patients coming off the treatment relapsed versus 22 % of the patients continuing on medication. Most relapses occurred within the first year of treatment reduction or AED withdrawal. The more severe and long lasting a patient's active epilepsy was before remission, the greater the risk of relapse. Diagnosis of Juvenile myoclonic epilepsy (JME) or the presence of a structural lesion underlying the epilepsy also increased the relapse risk (MRC Antiepileptic Drug Withdrawal Group (1991).

Clinicians should choose a patient specific approach in discontinuing AED therapy. Also, the epilepsy classification and seizure type should be considered. Relapse rate in rolandic epilepsy is about 2 %, so the threshold to withdraw the treatment after long-term remission should be low. On the other hand, the relapse rate in JME is about 85 %, so there should be a much higher threshold to withdraw the treatment in these patients. Young women with 2–3 year seizure freedom could prefer drug withdrawal during pregnancy. Some patients have intolerable side effects which may necessitate drug withdrawal. Some patients have difficulty finding a job while on AEDs, and we may chose to taper AEDs off in these patients. In general 2–5 years of seizure freedom is needed. And the tapering of the AEDs should be slowly spread over 6–12 months.

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Old Generation Antiepileptic Drugs 16

Bassel Abou-Khalil

Phenobarbital

The first of old-generation antiepileptic drugs (AEDs) that are currently marketed was phenobarbital, which came into clinical use in 1912. Its initial use was as a sedative and sleep aid. Its efficacy against seizures was discovered later (Table 16.1).

Phenobarbital exerts its action by binding to the GABA-A receptor and enhancing chloride currents by prolonging the opening of the chloride channel. It may also have other actions including blocking high-voltage-activated calcium channels and AMPA subtype glutamate receptors.

Phenobarbital is available as oral preparations as well as parenteral solution. Its oral availability is greater than 90%. Its protein binding is about 45%. Its volume of distribution is approximately 0.6 L/kg. Phenobarbital is mostly metabolized in the liver but 20–25% is eliminated unchanged in the urine. The half-life in adults is 80–100 h. The half-life is longer in newborns and shorter in young children. Phenobarbital is a potent inducer of P4 50 enzymes. It does accelerate the metabolism and reduces the levels of anti-epileptic drugs processed by this enzyme system. For example, phenobarbital reduces serum concentrations of valproate, ethosuximide, lamotrigine, and others. It reduces the serum concentration of carbamazepine but may increase the carbamazepine epoxide to carbamazepine ratio. It reduces the efficacy of warfarin, steroids, and the oral contraceptive.

Phenobarbital has a variable effect on phenytoin concentration; while it may induce phenytoin metabolism, it may also compete with phenytoin for metabolic enzymes CYP 2C9 and 2C19. Phenobarbital serum concentration may be increased by the inhibitors valproate and felbamate.

The main adverse effects of phenobarbital are sedation, mood changes (particularly depression), hyperactivity and irritability in children, and decreased memory and concentration. It also has long-term adverse effects. Long-term use of phenobarbital is associated with decreased bone density and some connective tissue disorders, particularly Dupuytren's contractures, plantar fibromatosis, and frozen shoulder. Phenobarbital is associated with increased risk of cardiac malformations in the exposed fetus and reduced cognitive abilities in the exposed male offspring. It is assigned to pregnancy category D.

Phenobarbital is effective against partial onset (focal) seizures, generalized tonic–clonic seizures, and other generalized onset seizures except for absence. The recommended therapeutic concentration is 50 and 2 14 mg/L. Phenobarbital is not a drug of first choice in developed countries, because of its adverse effects, namely sedation, and because of its enzyme-inducing properties. However, it is inexpensive and widely available, and may be

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Table 16.1 Select pharmacokinetic parameters of main old-generation antiepileptic drugs

AED	Phenytoin	Carbamazepine	Oxcarbazepine MHD	Phenobarbital	Valproate	Ethosuximide
Protein binding[a]	High	Intermediate	Low	Low	High	Low
Half-life[b]	Intermediate (can become long in toxicity)	Intermediate	Short	Long	Intermediate	Long
Metabolism	Extensive, Nonlinear	Extensive	Extensive	>70%	Extensive	Extensive
Enzyme Induction	+++	+++ autoinduction	+ (CYP 2C19)	+++	–	–
Enzyme Inhibition	–	–	+ (CYP 3A4)	–	+++	–

[a]Low < 50%; intermediate: 50–85%, high > 85%
[b]Short < 10 h; intermediate 10–30 h; long > 30 h

the only affordable antiepileptic drug in much of the developing world.

Primidone

Primidone is converted to phenobarbital and phenylethylmalonamide (PEMA), which is also an active metabolite. Unlike phenobarbital, primidone does not have a direct effect on GABA receptors. Primidone and phenobarbital may act synergistically to reduce sustained high-frequency repetitive firing, at clinically relevant concentrations. This is an effect on the sodium channel that neither drug has when used alone. As mentioned earlier, phenobarbital acts at the GABA-A receptor to prolong the opening of the chloride channel. The mechanism of action of PEMA is unknown, and its anti-seizure activity is modest. Primidone is available only as an oral preparation. It is poorly soluble, precluding an IV preparation.

Primidone oral bioavailability is fairly complete. Its volume of distribution is $\sim$0.7 L/kg. Its protein binding is low, less than 10% for primidone and for PEMA.

Primidone is metabolized in the liver. PEMA is the first detected metabolite. When used in monotherapy, about 25% of oral primidone is converted to phenobarbital. After one dose, approximately 64% of primidone is excreted unchanged in the urine. In the presence of enzyme induction, only about 40% is excreted unchanged. In monotherapy, primidone half-life is 10–15 h; it is shorter (6.5–8.3 h) in the presence of enzyme inducers.

In the presence of inducers, particularly phenytoin, the ratio of primidone-to-phenobarbital is reduced due to the acceleration of primidone-to-phenobarbital conversion. Primidone and phenobarbital are potent enzyme inducers, decreasing the efficacy of drugs metabolized by the p450 enzymes system. Since phenobarbital will be present when primidone is used, all phenobarbital interactions are also present by necessity.

Primidone has acute toxic reactions that are different from phenobarbital. It can produce transient drowsiness, dizziness, ataxia, nausea, and vomiting that can be debilitating. These reactions are present even before phenobarbital has appeared as a metabolite. Therefore, a slow titration of primidone is necessary. Tolerance to these acute adverse experiences develops rapidly within hours to days. Otherwise, primidone has similar adverse experiences to phenobarbital, including adverse experiences from long-term use.

Primidone is effective against the same seizure types as phenobarbital. The recommended primidone therapeutic plasma concentration is 5–12 mg/L. A phenobarbital level should also be

monitored. Since about 25% of oral primidone is converted to phenobarbital, the dose of primidone required for a certain level is about 4–5 times the dose of phenobarbital required for that same level. Primidone was found to have equal efficacy but lower tolerability in comparison with phenobarbital, phenytoin, and carbamazepine.

Phenytoin

Phenytoin has been used since 1938 when Houston and Merritt discovered its efficacy in the maximum electroshock animal model. Phenytoin acts by binding to active state of the sodium channel and reducing high-frequency firing (as might occur during a seizure), while allowing normal action potentials to occur.

Phenytoin is available as oral preparations and parenteral solution. There is also a phenytoin prodrug for parenteral administration, fosphenytoin.

Phenytoin absorption is variable. The rate and extent of absorption may also differ among formulations and is affected by a variety of factors including age and food. While oral bioavailability can be greater than 90% in adults, it is decreased in neonates and is also decreased in the presence of nasogastric feedings, calcium, and antacids. There is limited absorption in the stomach. Absorption is primarily in the duodenum where the higher pH increases the phenytoin solubility. The time to maximal concentration is shorter with immediate release preparations and longer with extended-release formulations. The volume of distribution is approximately 0.75 L/Kg. Protein binding is approximately 90%.

The major pathway of elimination of phenytoin is hydroxylation, mediated mainly by the cytochrome p450 enzymes CYP 2C9 and to a lesser extent CYP 2C19. Phenytoin follows nonlinear kinetics. Small changes in CYP 2C9 activity may have clinically significant effects. Some CYP 2C9 alleles are associated with reduced clearance of phenytoin. The importance of CYP 2C19 increases with higher levels. Some inhibitors such as ticlopidine and isoniazid may lead to phenytoin accumulation. Similarly, some alleles are associated with decreased activity leading to accumulation.

The phenytoin half-life is dependent on the serum concentration. The initial half-life is approximately 22 h (with the range of 8–60 h). The half-life increases as the serum concentration increases within and above the recommended therapeutic range (10–20 mg/L).

The mechanism of the nonlinear elimination kinetics is that enzymes responsible for most of phenytoin elimination are partially saturated with concentrations within the recommended range (with individual variation as to the concentration at which this phenomenon first appears). These enzymes are not able to increase their activity in proportion to phenytoin concentration, as the concentration increases in the recommended therapeutic range. Therefore, steady-state phenytoin level increases disproportionately as the maintenance dose is increased within and above the recommended therapeutic range. Below are two examples of the consequences of phenytoin nonlinear kinetics.

Example 1: A daily dose of 300 mg per day results in a concentration of 9 mg/L, with some residual seizures. Increasing the dose to 400 mg per day, a 30% increase in dose would have been expected to increase the steady-state concentration by 30%, to 12 mg/L, if phenytoin were to follow linear elimination kinetics. However, with its nonlinear kinetics, the concentration increases disproportionately, by more than 300%, to 31 mg/L, with associated toxicity. Therefore, when increasing phenytoin dose within the therapeutic range, small increments should be used (e.g., 30–60 mg).

Example 2: A patient presents with phenytoin toxicity and a serum concentration of 40 mg/L. The half-life was previously estimated at 24 h when the serum concentration was 13 mg/L. However, after phenytoin was stopped, it took 3 days for the serum concentration to drop below 20 mg/L. The reason for this is that the half-life was markedly prolonged in the presence of toxicity.

Phenytoin is affected by drugs that decrease absorption (e.g., nasogastric tube feedings) drugs

that compete for protein binding (such as valproate) and by enzyme inducers or inhibitors. Drugs that cause phenytoin accumulation include amiodarone, azoles, fluoxetine/fluvoxamine, and isoniazid. Phenytoin is a potent enzyme inducer that reduces the efficacy of other drugs metabolized by the p450 enzyme system, including a number of other antiepileptic drugs.

Phenytoin protein binding plays an important role in some phenytoin interactions. The protein-free phenytoin level is responsible for its therapeutic effect and for its toxicity. The free fraction increases in the presence of low-protein state, renal failure, hepatic failure, old age, or with co-administration of valproate. Therapeutic decisions are usually made based on the total phenytoin level, assuming that 10% is free. However, a free level should be obtained in clinical situations where an increase in the free fraction is expected.

As an example of the potential consequences of altered protein binding of phenytoin, a patient with epilepsy and renal impairment may be having uncontrolled seizures with a total phenytoin concentration of 15 mg/L. The decision has to be made whether the dose should be increased to improve seizure control or should be decreased because of toxicity causing a paradoxical increase in seizure frequency. The protein-free concentration turns out to be 4.5 mg/L, equivalent to a total phenytoin concentration of 45 mg/L under the condition of normal protein binding. In this case, holding phenytoin was the correct approach. While renal and hepatic failures are frequently associated with the decreased albumin concentration, the reduction in protein binding may also occur as a result of small molecules that compete for protein binding.

Valproate competes with phenytoin for protein binding. In monotherapy, each of phenytoin and valproate are approximately 90% protein-bound, and the free phenytoin level is about 10% of the total level. With concomitant use, each 1 mg/L of valproate increases the free fraction of phenytoin by approximately 0.1–0.2%. At a valproate level of 100 mg/L, the free phenytoin fraction may increase to 20–30%. A phenytoin level of 15 mg/L may actually be toxic with a free level of 3–4.5 mg/L, equivalent to a total level of 30–45 mg/L in the presence of normal protein binding.

When a low-protein state is present as the only factor affecting protein binding, the total phenytoin level can be corrected using the following formula: $Cn = Co/[(0.02 \times \text{albumin}) + 0.1]$, where Cn is the normal total level and Co is the observed total level.

Phenytoin concentration-dependent adverse effects include nystagmus, ataxia, incoordination, diplopia, dysarthria, and drowsiness. In addition, exacerbation of seizures may occur with concentrations above 30 mg/L. Some individuals may experience prominent adverse effects within the recommended therapeutic range, including cognitive adverse effects.

Idiosyncratic reactions may be related to the formation of an arene oxide, the active metabolite that forms due to inadequate epoxide hydrolase activity. Allergic rash occurs in up to 8.5% of patients. Serious severe rash such as Stevens–Johnson syndrome or toxic epidermal necrolysis are much less common. A hypersensitivity syndrome may occur rarely, with rash, fever, lymphadenopathy, eosinophilia, elevated liver enzymes, and renal failure.

Phenytoin also has long-term adverse effects including gingival hyperplasia, hirsutism, acne, cerebellar atrophy (which may also occur after acute intoxication), reduced bone density, reduced folate levels, anemia, and macrocytosis. Phenytoin also has potential teratogenicity and is classified with pregnancy category D.

The IV preparation is associated with local reactions such as pain and burning at the infusion site, phlebitis, cellulitis, or necrosis from extravasation, and the purple glove syndrome with discoloration then petechial rash. Cardiovascular adverse experiences include hypotension, conduction abnormality, and arrhythmia. They are related in part to the vehicle, propylene glycol. They can be avoided with the slowing of the infusion rate, which should not exceed 50 mg/m.

Phenytoin is effective against partial onset (focal seizures) and generalized tonic–clonic

seizures. Efficacy against tonic and atonic seizures is less well established. Phenytoin is not effective against generalized myoclonic or generalized absence seizures and may even exacerbate these seizures.

Phenytoin can be loaded orally (18 mg/kg divided into 3 doses given 2–3 h apart). IV loading dose for status epilepticus is 18–20 mg/kg. Phenytoin should be evaluated in normal saline, not dextrose 5% in water. It should be administered into a large vein with a maximum rate not exceeding 50 mg/min.

Intramuscular injection is not recommended due to slow and erratic absorption as well as crystallization at the injection site causing pain and a sterile abscess.

Fosphenytoin

Fosphenytoin is a water-soluble phenytoin prodrug. It can be given intravenously or intramuscularly. It is rapidly and completely converted to phenytoin by the cleavage of the phosphate group by nonspecific phosphatases. Its conversion half-life is 8–18 min, and the conversion is completed in a little more than 1 h. It is highly bound to serum albumin (95–99%). It displaces phenytoin from protein-binding sites after IV administration, increasing unbound phenytoin concentrations as a function of fosphenytoin concentration. It is indicated for a replacement of oral fosphenytoin or for intravenous or intramuscular loading. It is marketed in phenytoin equivalents, so the loading dose is the same as phenytoin. The maximum rate of intravenous infusion is much higher, at 150 mg/min, in view of the absence of propylene glycol. A therapeutic phenytoin level is usually reached within 10 min after IV loading and within 30 min after intramuscular administration.

Fosphenytoin has a lower incidence of local reactions. However, intravenous administration in the awake individual is commonly associated with paresthesias and itching, most often in the groin and perianal region, as well as the trunk and the back of the head. This adverse experience is related to infusion rate and subsides rapidly after the end of infusion. It is not seen with intramuscular administration.

Carbamazepine

Carbamazepine is a related structure to tricyclic antidepressants. Its mechanism of action is reducing high-frequency neuronal firing through the blocking of the sodium channel in a voltage and use dependent fashion.

It has good bioavailability of 80–90%, and it is lipophilic but poorly water-soluble, making parenteral formulation difficult. Its protein binding is about 75%, usually not of clinical importance.

Carbamazepine is cleared almost entirely via hepatic metabolism. The most important metabolic product is carbamazepine-10,11-epoxide, produced via oxidation through CYP 3A4 and CYP 2C8. It is an active metabolite which is also responsible for some adverse effects. Carbamazepine induces its own metabolism. This process, known as autoinduction, causes increased clearance, shortened half-life, and lower serum concentration of carbamazepine over time. The process typically takes 2–4 weeks. As a result, carbamazepine cannot be started at the target maintenance dose. It has to be titrated gradually.

Carbamazepine is a potent inducer of p450 enzyme system (particularly CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2), increasing the clearance of agents metabolized by these enzymes. The list of drugs affected includes hormonal contraceptives, warfarin, and several antiepileptic drugs, including valproate and lamotrigine.

Carbamazepine is affected by agents that induce or inhibit CYP 3A4. The list includes erythromycin and other macrolide antibiotics (except azithromycin), fluoxetine, propoxyphene, and grapefruit juice among others. The level of carbamazepine epoxide is increased by the concomitant use of valproate, felbamate, oxcarbazepine, and zonisamide.

The most common adverse experiences with carbamazepine are nausea, GI discomfort,

headache, dizziness, incoordination, unsteadiness, vertigo, sedation, tiredness, blurred vision, diplopia, nystagmus, and tremor. Benign leukopenia is common, occurring in 10–20% of instances. It is most often transient and may be persistent though not progressive. This is to be distinguished from the more serious but very rare aplastic anemia. Carbamazepine can cause hyponatremia. Cognitive impairment has been reported on neuropsychological testing. Long-term use is associated with weight gain and decreased bone density. Carbamazepine has been found to increase sex hormone binding globulin and decrease testosterone concentration.

Idiosyncratic adverse experiences include rash, rare Stevens–Johnson syndrome and toxic epidermal necrolysis, as well as very rare hypersensitivity syndrome with fever, rash, end organ involvement. Lupus-like syndrome is rare, as are hepatotoxicity and aplastic anemia (estimated at 1 in 200,000). There is a strong association between the HLA-B1502 allele and carbamazepine-induced Stevens–Johnson syndrome in Asian populations and individuals of Asian descent. The FDA has issued an alert and updated product labeling recommending genetic testing of HLA-B polymorphisms to predict carbamazepine-induced serious skin reactions in individuals of Asian descent.

Carbamazepine has been assigned pregnancy category D due to increased risk of spina bifida when used in polytherapy.

Carbamazepine is effective against partial onset (focal) seizures and against generalized tonic–clonic seizures. However, it may exacerbate absence and myoclonic seizures as well as atonic seizures. The recommended therapeutic range is 4–12 mg/L.

The efficacy and tolerability of carbamazepine, phenobarbital, phenytoin, and primidone were compared in a large, multicenter, double-blind, cooperative veterans administration trial [9]. Six hundred and twenty-two adults with partial and secondarily generalized tonic–clonic seizures were randomly assigned to one of the four drugs and were followed for two years or until the drug failed due to uncontrolled seizures or unacceptable side effects. The overall treatment success was highest with carbamazepine and phenytoin, intermediate with phenobarbital and lowest with primidone. The drugs had overall equal efficacy, and the difference in treatment success was related to tolerability. Primidone caused more intolerable acute toxic effects, mainly nausea, vomiting, dizziness, sedation, decreased libido, and impotence. When specific seizure types were analyzed, control of secondarily generalized tonic–clonic seizures did not differ significantly with the 4 drugs, but carbamazepine provided complete control of partial seizures more often than primidone or phenobarbital. As a result, carbamazepine became the drug against which new antiepileptic drugs were compared.

Oxcarbazepine

Even though oxcarbazepine was first introduced in the USA in 2000, it is listed with the old-generation drugs since it was introduced in some European countries as early as 1963. Oxcarbazepine is structurally related to carbamazepine, but different from carbamazepine in its metabolism and in the induction of metabolic pathways. Oxcarbazepine has a similar mechanism of action to carbamazepine, inhibiting high-frequency repetitive neuronal firing by blocking voltage-gated sodium channels. It also modulates high-voltage-activated calcium channels.

Oxcarbazepine absorption is almost complete with a bioavailability of about 99%. It is very rapidly metabolized to a monohydroxy derivative, an active metabolite responsible for oxcarbazepine activity. Oxcarbazepine protein binding is about 60% while the monohydroxy derivative protein binding is about 40%. The oxcarbazepine half-life is 1–3.7 h. The monohydroxy derivative is further metabolized and has a half-life of 8–10 h. Oxcarbazepine does not induce its own metabolism.

The monohydroxy derivative level decreases in the presence of enzyme-inducing drugs. One major advantage of oxcarbazepine over carbamazepine is that it is not affected by CYP 3A4 inhibitors such as erythromycin, fluoxetine, propoxyphene, and grapefruit juice. Oxcarbazepine does not induce the metabolism of other antiepileptic drugs or warfarin. It weakly induces CYP 3A4 which is responsible for estrogen metabolism, thus reducing the efficacy of the birth control pill at high doses. Oxcarbazepine also weakly inhibits CYP 2C19, thus raising phenytoin level when used at high doses.

The most common adverse effects of oxcarbazepine are somnolence, headache, dizziness, blurred vision, diplopia, fatigue, nausea, vomiting, and ataxia. Rash has been reported in 2–4% of individuals. Oxcarbazepine can cause hyponatremia, which is more likely in older individuals and those taking a diuretic. Oxcarbazepine does not has the effect on sex hormone binding-globulin and testosterone that carbamazepine has.

Oxcarbazepine was assigned pregnancy category C.

Oxcarbazepine is effective against partial onset (focal) seizures. The recommended therapeutic range is 15–35 mg/L. Oxcarbazepine is a narrow spectrum drug that should be avoided in individuals with generalized epilepsy. Oxcarbazepine may exacerbate absence and myoclonic seizures.

Multiple comparative monotherapy trials for new onset partial epilepsy have demonstrated that oxcarbazepine is equal in efficacy to phenytoin and carbamazepine but with superior tolerability [1, 3, 5, 6, 11–13]. Conversion to oxcarbazepine from carbamazepine can be made overnight using a 1.5-to-1 ratio when the carbamazepine dose is 800 mg or less. At higher carbamazepine doses, a slower conversion and a lower ratio are advisable. Conversion from carbamazepine to oxcarbazepine will be accompanied by enzyme de-induction and possible elevation of some medication levels. In addition, sodium level may decrease after conversion from carbamazepine.

Valproate/Divalproex

Valproate discovery was serendipitous as it was used as a solvent for antiepileptic drugs in testing. Valproate is a short chain, branched fatty acid. It has multiple mechanisms of action, including the blocking of sodium channels, gabapentin potentiation, and blocking of T calcium channels. The main form of valproate used clinically is divalproex sodium, a complex composed of equal parts of valproate and sodium valproate. Preparations include immediate release valproate capsules, tablets, and syrup; delayed-release enteric coated tablets of divalproex sodium; divalproex sodium enteric coated sprinkles; extended-release divalproex sodium; and parenteral sodium valproate. The delayed-release enteric coated tablets are rapidly absorbed after the coating is dissolved, or the extended-release divalproex sodium is absorbed slowly. Oral bioavailability is almost complete for most of valproate preparations, but 90% for the extended-release preparation. The time to maximal concentration is very dependent on the preparation. It is 2 h for the syrup and up to 17 h for the extended-release divalproex. The volume of distribution is 0.13–0.19 L/kg in adults. Protein binding is about 90%. The free fraction increases with increasing total concentration and can reach 30% 150 mg/L.

Valproate is extensively metabolized by p450 enzymes, including CYP 2A6, CYP 2B6, CYP 2C9, and CYP 2C19. The half-life in adults is 13–16 h without induction and about 9 h with enzyme-inducing drugs.

Valproate metabolism is induced by phenytoin, carbamazepine, and phenobarbital. Valproate levels will increase after the withdrawal of these enzyme-inducing drugs. Valproate levels increase with coadministration of felbamate and clobazam. Valproate can inhibit the metabolism of phenobarbital, lamotrigine, rufinamide, and carbamazepine epoxide, causing increased serum concentrations. Valproate competes with phenytoin for protein binding (look under phenytoin for potential consequences of this interaction).

Valproate adverse effects include gastric irritation with nausea, vomiting, GI distress, and anorexia. These adverse effects are most likely with the enteric coated preparation and the extended-release formulations. Other adverse effects include tremor, weight gain, hair loss, peripheral edema, thrombocytopenia, and drowsiness/lethargy/confusion. A reversible dementia and brain atrophy have been described in some individuals, particularly in seniors. Encephalopathy may occur when valproate is used in polytherapy. Hyperammonemia may be seen in some individuals. Carnitine deficiency has been reported and associated with tiredness.

Idiosyncratic adverse experiences include fatal hepatotoxicity and pancreatitis. The risk factors for severe hepatotoxicity are polytherapy and young age. Hepatotoxicity is most likely to occur below age 3, with a risk of 1 in 600. Above age 40, the risk is less than 1 in 100,000. Monitoring of liver enzymes is recommended in young children.

Valproate is teratogenic and was assigned pregnancy category D. Valproate teratogenicity is dose-dependent. The risk of major congenital malformations can be higher than 30% at doses greater than 1100 mg per day [15]. At doses below 1000 mg per day, the malformation rate was about 3.2%. In addition in utero exposure to valproate has been associated with reduced verbal IQ and autism [2, 10]. This developmental toxicity is also dose-dependent.

Valproate has a wide spectrum of efficacy against partial onset (focal) and all generalized onset seizures, including absence and myoclonic seizures. It is also FDA-indicated for migraine prophylaxis and bipolar disorder. The recommended therapeutic range is 40–100 mg/L. An important class III comparative study showed that valproate was more effective than lamotrigine and better tolerated than topiramate for the treatment of generalized epilepsy [7]. However, in another cooperative Veterans Administration Study, valproate was less effective than carbamazepine for complex partial seizures, even though the two drugs were equally effective for secondarily generalized tonic–clonic seizures [8]. In addition, carbamazepine was better tolerated.

Ethosuximide

Ethosuximide mechanism of action is blockade of the T-type calcium currents in the thalamus. It has an excellent oral bioavailability (greater than 90%), and volume of distribution is 0.65 L/kg. Protein binding is very low, less than 10%. Ethosuximide is extensively metabolized in the liver with oxidative biotransformation to inactive metabolites, mainly by CYP 3A4 has a long half-life of 30–60 h (shorter in children).

Ethosuximide has no effect on hepatic p450 enzymes and is unlikely to affect other drugs. However, it is susceptible to interactions from inducers and inhibitors of p450 enzyme system. Its clearance is increased with enzyme inducers and may decrease with valproate and isoniazid.

Most ethosuximide adverse effects are dose-related and helped by dividing the dose and administration with meals. Among these, GI side effects include nausea, abdominal discomfort, anorexia, vomiting, and diarrhea; CNS adverse effects include drowsiness, insomnia, nervousness, dizziness, hiccups, fatigue, ataxia, and behavior changes such as aggression, irritability, and hyperactivity; hematologic side effects include granulocytopenia. Headaches, psychosis, depression, and hallucinations (visual or auditory) are not clearly dose-related.

Idiosyncratic adverse experiences include rash, Stevens–Johnson syndrome, SLE, rare aplastic anemia, thrombocytopenia, or agranulocytosis, and rare autoimmune thyroiditis.

Ethosuximide has been assigned a pregnancy category D due to increased risk of birth defects.

Ethosuximide has a narrow spectrum of activity with efficacy limited to generalized absence seizures. It is not effective against any other seizure type. A large, multicenter, double-blind, randomized, controlled trial to compare the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine favored ethosuximide [4]. After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar and higher than the rate for lamotrigine. However, attentional dysfunction was more common with valproic acid than with

ethosuximide. As a result, ethosuximide became the drug of choice for pure generalized absence seizures. The recommended therapeutic range is 40–100 mg/L. It is recommended that a complete blood count be checked before and after 2–3 months of treatment.

Benzodiazepines

Benzodiazepines as a family act mainly on the GABA-A receptor, increasing the frequency of GABA-mediated chloride channel openings. Benzodiazepines have a wide spectrum of efficacy. Among the benzodiazepines most commonly used for epilepsy, diazepam and lorazepam are primarily used for acute seizure emergencies, particularly status epilepticus and acute repetitive seizures, while clonazepam, clorazepate, and clobazam are used mainly for chronic epilepsy management.

Most benzodiazepines have good oral bioavailability (larger than 80%). One exception is midazolam (not discussed in this chapter), which is metabolized in intestinal epithelium, resulting in a bioavailability of about 40% [14]. All benzodiazepines rapidly cross the blood–brain barrier, with diffusion rate and onset of action determined by lipid solubility. Benzodiazepines have large volumes of distribution and are characterized by 2-compartment distribution model; after initial rapid distribution in the blood, benzodiazepines diffuse into a second compartment. For example, diazepam redistributes to adipose tissue after intravenous administration. While the true half-life is 36 h, the redistribution half-life is less than 1 h. Benzodiazepines are also highly protein-bound.

While benzodiazepines are generally similar in absorption and distribution, they vary considerably in their metabolism and elimination rate [14]. Diazepam, clorazepate, and clobazam are converted to active metabolites while lorazepam and clonazepam are converted to inactive metabolites (Table 16.2).

Benzodiazepines have both pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions are dependent on the specific metabolic pathway. Inhibition of the major pathway may cause accumulation, while inhibition of a minor pathway has limited effect. On the other hand, induction of either a major or minor pathway will reduce the benzodiazepine concentration. The clinical effect of induction and inhibition also depends on the presence of active metabolites and metabolic pathways (Table 16.3).

Benzodiazepines have similar adverse experiences, particularly drowsiness, to which tolerance may develop. With higher doses, nystagmus, incoordination, ataxia, and dysarthria may occur. Behavioral disturbances may occur, more commonly in children (aggression, hyperactivity, paranoia). Most benzodiazepines are assigned pregnancy category D. Tolerance may develop to the therapeutic effect of benzodiazepines, so that after a few weeks or months of treatment, efficacy is lost, or any higher dose is required to maintain efficacy. Withdrawal seizures may occur with abrupt discontinuation. Below is specific information on individual benzodiazepines.

Clonazepam has minimal interactions, except that its clearance is increased by inducers. Clonazepam is used for long-term treatment as well as acute seizure management. Only an oral form is available in the USA, while an intravenous formulation is available abroad. It has an official FDA indication for myoclonic seizures. However, it has a wide spectrum of efficacy against partial and generalized seizure types.

Diazepam is metabolized to desmethyldiazepam (DMD). Like other benzodiazepines, it is highly protein-bound. Valproate may increase free diazepam levels due to displacement from protein binding. Diazepam is available in oral tablet and liquid form, rectal gel, and parenteral solution. It is also being investigated for nasal administration. It is used for acute repetitive seizures and for status epilepticus. When used for status epilepticus through intravenous route, an additional agent needs to be administered to maintain seizure control beyond the first 15–30 min, because of diazepam's short duration of action due to redistribution. Diazepam is not usually adequate for chronic use except that a

Table 16.2 Benzodiazepine metabolism (adapted from [14])

Benzodiazepine	Primary metabolic pathway	Active metabolite	T1/2 of parent drug (hrs)	T1/2 of active metabolite (hrs)
Diazepam	Demethylation, hydroxylation, glucuronidation	**Desmethyldiazepam (DMD)**, oxazepam, temazepam	21–70	**DMD: 49–179** Oxazepam: 6–24 Temazepam: 8–24
Lorazepam	Glucuronidation	None	7–26	NA
Clonazepam	Nitroreduction, acetylation, hydroxylation	None	19–60	NA
Clorazepate	Decarboxylation	**DMD**, oxazepam	NA	**DMD: 20–160** Oxazepam: 6–24
Clobazam	Demethylation	N-desmethylclobazam	10–30	36–46

Table 16.3 Enzymes involved in metabolism of select benzodiazepines (adapted from [14])

Enzyme	Diazepam	Lorazepam	Clonazepam	Clorazepate	Clobazam
CYP 2B6	X				X
CYP 2C9	X				
CYP 2C18					X
CYP 2C19	X			X*	X
CYP 3A4	X		X	X*	X
CYP 3A5	X				
UGT		X			
NAT			X		

UGT—uridine diphosphate glucuronosyltransferase
NAT—N-acetyltransferase
*applies to DMD

diazepam course can be used in some syndromes such as Landau–Kleffner syndrome and electrical status epilepticus during sleep (ESES).

Lorazepam is metabolized in the liver through glucuronidation and excreted by the kidneys. It does not have active metabolites. Its clearance is reduced by valproate and other inhibitors. It is available in oral and parenteral forms. It is not appropriate for chronic use. Its main use is for status epilepticus. It has a longer duration of action than diazepam despite its shorter half-life, as a result of less lipid solubility and less redistribution to adipose tissue. Lorazepam can also be used orally to stop mild seizure clusters/acute repetitive seizures.

Clorazepate is a prodrug, as it is rapidly decarboxylated in the stomach to form the active desmethyldiazepam (DMD). It is FDA-approved for management of anxiety disorders and as adjunctive therapy in the management of partial seizures. It is available in oral form only, in immediate and extended-release preparations.

Clobazam was only approved in the USA in 2009, but is listed with the old-generation antiepileptic drugs because it has been used in Europe since 1975. It is the only

1,5–benzodiazepine (referring to position of nitrogen atoms in the heterocyclic ring), while other benzodiazepines are 1,4–benzodiazepines. It is metabolized in the liver to the active N–desmethylclobazam. It is less sedating than 1,4-benzodiazepines. It is available in tablets and syrup. It is FDA-indicated for seizures associated with the Lennox–Gastaut syndrome, but it has a wide spectrum of efficacy as with other benzodiazepines.

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New Generation Antiepileptic Drugs 17

Bassel Abou-Khalil

The new-generation antiepileptic drugs (AEDs) became available in the USA after 1993, following a 15-year hiatus during which no new drugs were introduced for the treatment of epilepsy. In general, the newer AEDs have not improved on the efficacy of carbamazepine, the AED to which they have been most often compared. However, many of the newer antiepileptic drugs have advantages in terms of pharmacokinetics (Table 17.1), interactions, and tolerability [1, 2]. The new drugs will be discussed in the order that they were introduced to the US market. The exceptions are oxcarbazepine and clobazam, which were discussed in the previous chapter.

Felbamate

Felbamate was first approved in the USA in 1993. Felbamate has several mechanisms of action, including NMDA antagonism, enhancing GABA, blocking sodium channels, and blocking high-voltage activated calcium channels.

It has excellent oral bioavailability, greater than 90%. It is only 25% protein-bound, which is not clinically significant. It is metabolized via CYP 3A4. Between 40 and 50% of the absorbed dose appears unchanged in the urine and the rest as inactive metabolites and conjugates. Its half-life in monotherapy is 20–23 h. The half-life is shorter in children and also shorter in the presence of enzyme inducers. Felbamate has many interactions. It is an inhibitor of CYP 2C19, CYP 1A2, and beta-oxidation. As a result, it inhibits the metabolism and increases the serum concentration of phenobarbital, phenytoin, valproate, carbamazepine epoxide, and warfarin. On the other hand, felbamate induces CYP 3A4 and thus decreases carbamazepine level and also reduces oral contraceptive efficacy.

Felbamate is affected by enzyme-inducing antiepileptic drugs which accelerate felbamate clearance and reduce its serum concentration.

Common adverse effects of felbamate are anorexia, nausea, vomiting, and weight loss. Stomach irritation can be improved by administration with food and by the use of H2 blockers or proton pump inhibitors. Felbamate may also cause insomnia, irritability, and headache.

Felbamate was discovered to have serious idiosyncratic potential adverse effects. It may cause aplastic anemia with an estimated risk of 1 in 5000–8000 patients. Aplastic anemia has not been reported below age 13. The onset of aplastic anemia is after 2.5–6 months of treatment. It is highly unlikely to occur after one year of treatment. It has risk factors including prior cytopenia, allergy to or significant toxicity with other antiepileptic drugs, and underlying autoimmune disease [3]. Another serious idiosyncratic potential adverse effect is hepatic failure, with an estimated risk of 1 26,000-1 and 54,000. The

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Table 17.1 Select pharmacokinetic parameters of new-generation antiepileptic drugs

AED	Felbamate	Gabapentin	Lamotrigine	Topiramate	Tiagabine	Levetiracetam
Protein binding[a]	Low	Low	Intermediate	Low	High	Low
Half-life[b]	Intermediate	Short	Intermediate	Intermediate	Short	Short
Metabolism	~50%	None	Extensive	~30%	Extensive	~30% Not hepatic
Enzyme induction	+ CYP 3A4	–	–	+ CYP 3A4	–	–
Enzyme inhibition	+++	–	–	+ CYP 2C19	–	–

AED	Zonisamide	Pregabalin	Lacosamide	Vigabatrin	Rufinamide	Ezogabine
Protein binding[a]	Low	Low	Low	Low	Intermediate	Intermediate
Half-life[b]	Long	Short	Intermediate	Intermediate[c]	Short	Long
Metabolism	~65%	None	~60%	None	Extensive	Extensive
Enzyme induction	–	–	–	+ CYP 2C9	+ UDP–GT	–
Enzyme inhibition	–	–	–	–	+ CYP 2E1	–

AED	Perampanel	Eslicarbazepine
Protein binding[a]	High	Low
Half-life[b]	Long	Intermediate
Metabolism	Extensive	~40%
Enzyme induction	–	+ CYP 3A4
Enzyme inhibition	–	+ CYP 2C19

[a]Low <50%; intermediate: 50–85%; high >85%
[b]Short <10 h; intermediate 10–30 h; long >30 h
[c]Vigabatrin duration of action is longer than predicted by half-life

onset of this toxicity has been after 25–959 days of treatment, with a mean of 217 days. Neither aplastic anemia nor liver failure can be prevented by monitoring of CBC and liver enzymes. Nevertheless, it is recommended to check CBC and liver function tests prior to starting felbamate, then every 2 weeks for 6 months, then every 2–3 months after 6 months, and then every 6 months after the first year.

Felbamate is a wide-spectrum antiepileptic drug, although its efficacy in generalized seizure types of idiopathic generalized epilepsy has not been evaluated in class I studies. The official FDA indications are: "Either monotherapy or adjunctive therapy in the treatment of partial seizures, with or without generalization, in adults with epilepsy and adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children." The FDA indication specifies that "felbamate is not indicated as a first-line treatment; it is recommended only in those who respond inadequately to alternative treatments and whose epilepsy is so severe that the risk of aplastic anemia and/or liver failure is deemed acceptable." A written informed consent is needed.

The suggested felbamate therapeutic range is 40–100 mg/L.

Gabapentin

Gabapentin was first approved in the USA in 1994. The mechanism of action is binding to the alpha-2 delta subunit of voltage-gated calcium channels. This binding reduces the influx of calcium and reduces neurotransmitter release under hyperexcitable conditions. Despite its name, gabapentin does not interact with GABA receptors.

Gabapentin bioavailability is low, with considerable inter-subjective variability. In addition, oral bioavailability decreases with increasing gabapentin dose. For example, bioavailability is 60% after a single 300 mg dose, but only 29% for 1600 mg t.i.d. and 36% for 1200 mg p.o. q.i.d. (bioavailability improves with dividing the dose) [4]. The reason for the above is that gabapentin is transported from the gut into the bloodstream by the L-amino acid transport system, which is saturable. Gabapentin protein binding is minimal at less than 50%.

Gabapentin is not metabolized in humans. It is eliminated unchanged in the urine as a result requires dose reduction with renal impairment. Its half-life is 5–7 h.

Gabapentin has no known interactions, which is predicted by the absence of metabolism, the absence of enzyme induction or inhibition, and the absence of protein binding. However, antacids including aluminum hydroxide or magnesium hydroxide may reduce gabapentin bioavailability if taken within 2 h from gabapentin intake.

Gabapentin adverse effects include sedation, dizziness, ataxia, asthenia, and weight gain. It may cause myoclonus. It may be associated with cognitive slowing in the elderly, and emotional lability or hostility in children. It has been assigned pregnancy category C.

Gabapentin is a narrow-spectrum agent against focal seizures. It failed clinical trials against absence and primary generalized tonic–clonic seizures [5, 6]. It may cause exacerbation of myoclonus [7]. The official FDA indication is for adjunctive therapy for partial seizures. It is also approved for the treatment of postherpetic neuralgia. An extended-release preparation (gabapentin enacarbil) has been approved for the treatment of restless leg syndrome.

Lamotrigine

Lamotrigine was first approved in the USA in 1995, but was licensed in Europe in 1991. Its mechanism of action is blocking sodium channels. This secondarily results in blocking the release of glutamate. Lamotrigine also inhibits high-voltage activated calcium channels.

Lamotrigine has an excellent oral bioavailability of about 98%. The time to maximum concentration is 1–1.5 h with the immediate release preparation and 4–11 h with the extended-release preparation. Its protein binding is only 55%.

Lamotrigine is extensively metabolized in the liver, predominantly by glucuronidation (to lamotrigine 2–*N*-glucuronide), then excreted by the kidney. About 94% is eliminated in the urine, about 10% as unchanged drug, and 90% as glucuronide conjugates. The half-life is about 24 h in monotherapy, 48–60 h when used with valproate, and 12 h when used with an enzyme inducer.

Lamotrigine is associated with a mild autoinduction. It is a weak inhibitor of dihydrofolate reductase (not clinically relevant). Lamotrigine slightly increases topiramate level and slightly decreases valproate level. However, it is markedly affected by some other drugs. Its clearance is increased in the presence of enzyme-inducing drugs, estrogen containing oral contraceptives, and pregnancy. On the other hand, lamotrigine clearance is markedly decreased by valproate.

Dose-related adverse effects include dizziness, ataxia, blurred vision, diplopia, nausea, and vomiting. Headache and tremor may also occur. Rash is seen in about 3%, but the risk is higher in children, with coadministration of valproate, with faster titration, and with higher doses. As a result of increased risk of rash with faster titration, lamotrigine has to be titrated very slowly. The rate of titration is slower in the presence of valproate.

Rare serious idiosyncratic adverse effects include Stevens–Johnson syndrome, toxic epidermal necrolysis, or hypersensitivity syndrome (1 in 4000). It is assigned pregnancy category C.

Lamotrigine is a wide-spectrum antiepileptic drug effective against partial–onset as well as generalized tonic–clonic seizures. It is FDA

indicated as adjunctive therapy or for conversion to monotherapy for partial seizures, adjunctive therapy for generalized tonic–clonic seizures, and adjunctive therapy for Lennox–Gastaut syndrome. Efficacy against generalized absence seizures is less than valproate and ethosuximide. Its efficacy against myoclonic seizures is variable, and lamotrigine may exacerbate myoclonic seizures in some individuals. The recommended therapeutic range for lamotrigine is 2–20 mg/L [8].

Lamotrigine is also FDA indicated for maintenance treatment of bipolar I disorder to delay a mood episode.

Topiramate

Topiramate is a sulfamate-substituted monosaccharide. It was approved in the USA in 1996. It has multiple mechanisms of action including blocking of voltage-gated sodium channels, augmentation of GABA activity, antagonism of AMPA/kainate receptors, inhibition of high-voltage activated calcium channels, and weak inhibition of carbonic anhydrase activity.

Topiramate has a good oral bioavailability of 80–95%. Its protein binding is only 15–40%.

Topiramate is not extensively metabolized. About 70% is eliminated unchanged in the urine. Its hepatic metabolism by the p450 enzyme system is via hydroxylation, hydrolysis, and glucuronidation, to form inactive metabolites. There is evidence of renal tubular reabsorption. The half-life is about 21 h.

Drug interactions are minimal. Topiramate is a mild inhibitor of CYP 2C19, so that it may increase phenytoin levels when used at a higher dose. It is also a mild inducer of CYP 3A4, so that it may reduce the efficacy of the oral contraceptive when used at a dose of 200 mg per day or more. Hyperammonemia may occur when topiramate is used in conjunction with valproate. Enzyme-inducing antiepileptic drugs may reduce topiramate levels by up to 50%.

Topiramate adverse effects include sedation, fatigue, dizziness, and ataxia, which are helped by slower titration. Topiramate may cause cognitive difficulties including memory disturbance, word-finding difficulty, and cognitive slowing. There may be depression. Kidney stones occur in about 1.5% of individuals. Acute myopia and secondary angle-closure glaucoma are reported rarely. Paresthesias in the hands and feet may occur as a result of the carbonic anhydrase activity. Oligohydrolysis, hyperthermia, and metabolic acidosis are more common in children. Weight loss may occur.

Topiramate is assigned pregnancy category D due to increased risk of oral clefts in exposed infants [9].

Topiramate is a wide-spectrum antiepileptic drug. However, it is not effective against generalized absence seizures as demonstrated in a randomized controlled clinical trial [10]. The FDA indications are for initial monotherapy or adjunctive therapy for partial–onset or primary generalized tonic–clonic seizures in adults and children 2 years or older, and as adjunctive therapy for adult and pediatric patients with seizures associated with Lennox–Gastaut syndrome. Topiramate is also indicated for prophylaxis of migraine. Topiramate requires a slow titration to improve tolerability.

Tiagabine

Tiagabine was first approved in the USA in 1997. It is a designer drug, the mechanism of which is inhibition of GABA reuptake at the synapse.

Tiagabine has an excellent oral bioavailability. It is highly protein-bound (96%). It is extensively metabolized in the liver mainly by CYP 3A4. Only 2% is excreted unchanged; 63% is excreted in the feces and 25% in the urine. The half-life is 7–9 h in monotherapy and 2–5 h in the presence of enzyme inducers. As a result of the short half-life, it requires t.i.d. dosing.

Tiagabine does not affect other medications. Even though it is highly protein-bound, its serum concentration is low and it is unlikely to compete for protein binding; in addition, tiagabine dosing decisions are not usually based on serum concentration. Tiagabine metabolism, however, is accelerated by enzyme-inducing drugs.

The most commonly reported tiagabine adverse effects were dizziness, asthenia,

nervousness, tremor, depression, and emotional lability. Adverse effects are more common during titration, and slow titration is thus required. Tiagabine may be associated with dose-related episodes of nonconvulsive status epilepticus or encephalopathy, which may occur even in the absence of epilepsy [11, 12]. It has been assigned pregnancy category C.

Tiagabine is a narrow-spectrum agent effective against focal seizures only. It is not effective against and may exacerbate generalized absence or myoclonic seizures. Its FDA indication is for adjunctive therapy only. It is used off label in the treatment of addiction, to increase proportion of deep sleep, and in the management of spasticity in multiple sclerosis.

Levetiracetam

Levetiracetam was first approved in USA in 1999. Its mechanism of action is binding to the synaptic vesicle protein SV2A. This seems to result in nonspecific decrease in neurotransmitter release. There is a functional correlation between SV2A binding affinity and anticonvulsant potency of levetiracetam analogues.

Levetiracetam is available in oral and IV formulations. It has an excellent oral bioavailability of about 100%. Time to maximum concentration is about 1 h (1.5 h with food). Its protein binding is less than 10%.

Levetiracetam has no hepatic metabolism. It is partly hydrolyzed to inactive compounds; 66% is excreted unchanged in the urine. The half-life is 6–8 h, but shorter in children and longer in the elderly.

There are no known significant pharmacokinetic interactions. However, some studies have suggested lower levetiracetam levels in the presence of enzyme inducers.

Levetiracetam adverse effects include somnolence, dizziness, and asthenia. Irritability and hostility may occur, more commonly in children. Risk factors for these behavioral adverse effects include symptomatic generalized epilepsy, history of psychiatric diagnosis, and faster levetiracetam titration [13]. There have been rare reports of psychosis [14].

Levetiracetam is a wide-spectrum drug. The official FDA indications are adjunctive therapy for partial–onset seizures in adults and children 4 years or older; adjunctive therapy for myoclonic seizures in adults and adolescents 12 years or older with juvenile myoclonic epilepsy; and adjunctive therapy for primary generalized tonic–clonic seizures in adults and children 6 years or older with idiopathic generalized epilepsy. Levetiracetam is not FDA approved for monotherapy in the USA, but it is approved for initial monotherapy in Europe. The optimal therapeutic level is unknown. One study suggested that 11 mg/L may be a threshold concentration for therapeutic response [15]. The upper limit of the therapeutic range is unknown.

Zonisamide

Zonisamide is structurally related to sulfonamides. It was approved in Japan in 1989. However, it was first approved in the USA in 2000.

The mechanism of action is blocking sodium channels, reducing T-type calcium currents, and weak inhibition of carbonic anhydrase activity (it is 100–200 times less potent than acetazolamide).

Oral bioavailability is about 100%. Protein binding is only 40–50%. It is metabolized in the liver by acetylation and reduction, mediated by CYP 3A4, then glucuronidation. Its metabolites are inactive and cleared by renal excretion. It has a long half-life of about 60 h.

Zonisamide is not a hepatic enzyme inducer or inhibitor and has no effect on the pharmacokinetics of other commonly used antiepileptic drugs. However, it is affected by CYP 3A4 inducers or inhibitors. The addition of enzyme-inducing antiepileptic drugs decreases zonisamide half-life and plasma level. On the other hand, zonisamide concentration is increased by CYP 3A4 inhibitors such as ketoconazole or cyclosporine.

Zonisamide adverse effects include sedation, ataxia, dizziness, nausea, fatigue, agitation/

irritability, and anorexia. Weight loss may occur. Cognitive slowing and difficulty with concentration may be seen, particularly at higher doses. Kidney stones occur as frequently as 4%. Rarely, depression and psychosis may occur. Serious rash such as Stevens–Johnson syndrome and toxic epidermal necrolysis occur rarely. Oligohydrolysis, hyperthermia, and metabolic acidosis may occur, more often in children. Zonisamide was assigned pregnancy category C.

Zonisamide is a wide-spectrum antiepileptic drug but has undergone class I trials only for partial–onset seizures. The official FDA indication is for adjunctive therapy in the treatment of partial seizures in adults with epilepsy. In Europe, it is indicated as initial monotherapy for partial seizures. In Japan, it is also indicated as monotherapy for generalized seizures. The suggested therapeutic range is 10–14 mg/L.

Pregabalin

Pregabalin was first approved in USA in 2005. Its mechanism of action is similar to gabapentin. It binds to the alpha-2 delta subunit of voltage-gated calcium channels, reducing the influx of calcium and reducing neurotransmitter release under hyperexcitable conditions.

Unlike gabapentin, pregabalin has very good oral bioavailability, greater than 90%. The bioavailability is also independent of dose. The time to maximum concentration is 1 h, but is delayed up to 3 h when ingested with food. It has no protein binding.

Pregabalin is not metabolized in humans. It is excreted unchanged in the urine, thus requiring dose reduction in patients with renal impairment. Pregabalin half-life is about 6 h.

Pregabalin has no known pharmacokinetic interactions, which is predicted by the absence of metabolism, the absence of enzyme induction or inhibition, and the absence of protein binding. Pregabalin can cause increased appetite and weight gain. There may be peripheral edema. Myoclonus may occur in some individuals, particularly with higher doses. Pregabalin is classified with pregnancy category C.

Pregabalin is a narrow-spectrum drug against partial–onset seizures. The official FDA epilepsy indication is an adjunctive therapy for adult patients with partial–onset seizures. Pregabalin is also indicated for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.

Lacosamide

Lacosamide was first approved in the USA in 2008. Its mechanism of action is enhancing slow inactivation of sodium channels. This is to be distinguished from other antiepileptic drugs that interact with the sodium channel, all of which enhance fast inactivation of sodium channels.

Lacosamide is available in oral and intravenous formulations. The oral bioavailability is about 100%. Protein binding is less than 15%.

Lacosamide is metabolized by demethylation in the liver to inactive *O*-desmethyl metabolite via CYP 2C19. Approximately 95% is excreted in the urine, 40% as unchanged drug, and 30% as *O*-desmethyl metabolite. The half-life is approximately 13 h.

Lacosamide has no known pharmacokinetic interactions despite the CYP 2C19 metabolism. However, it does have pharmacodynamic interactions with other antiepileptic drugs that act on the sodium channel.

The dose-related adverse effects include dizziness, headache, nausea, diplopia, and sedation. All these are more likely when lacosamide is used in conjunction with other sodium channel blockers. It may also cause a small asymptomatic increase in the PR interval.

Lacosamide is a narrow-spectrum antiepileptic drug against partial–onset seizures. The official FDA indication is for adjunctive therapy of partial–onset seizures in patients 17 years or older. The parenteral formulation is indicated as short-term replacement when oral administration is not feasible in patients taking oral lacosamide.

Vigabatrin

Vigabatrin was initially licensed in Europe in 1989, but was first approved in the USA in 2009. Its mechanism of action is irreversible inhibition of GABA transaminase, resulting in the accumulation of GABA.

Vigabatrin has excellent oral bioavailability, which is nearly complete. It has no protein binding.

It is not significantly metabolized and is eliminated unchanged in the urine. The half-life is 10.5 h in young adults and 5–6 h in infants.

Vigabatrin is a weak inducer of CYP 2C9. This results in slight reduction of phenytoin levels with the addition of vigabatrin.

Vigabatrin adverse effects include sedation, fatigue, dizziness, and ataxia. There may be irritability, behavioral changes, psychosis, and depression. Weight gain may occur. The most concerning adverse effect is bilateral concentric visual field constriction, which is progressive and permanent. This occurs in up to 30–40% of individuals [16]. The risk increases with increased daily dose and increased duration of therapy [17]. As a result of the retinal visual toxicity, periodic visual assessment is required at baseline and every 3 months. In cooperative adult and pediatric patients, the monitoring can be accomplished with perimetry. Optional testing includes electroretinography and retinal imaging with optical coherence tomography. MRI changes may occur in treated infants, consisting of increased T2 and restricted diffusion in deep white matter, basal ganglia, thalamus, and corpus callosum. These MRI changes are asymptomatic and reversible. Vigabatrin was assigned pregnancy category C.

Vigabatrin is a narrow-spectrum drug effective against focal seizures. It may worsen absence and myoclonic seizures in idiopathic generalized epilepsy [7]. The official FDA indications are "adjunctive therapy for adults and pediatric patients 10 years of age or older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss" and "monotherapy for pediatric patients with infantile spasms one month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss." Because of the visual toxicity, treatment with vigabatrin should be continued only if there is considerable benefit observed in the first 3 months of treatment.

Rufinamide

Rufinamide was first approved in USA in 2008. Its mechanism of action is binding to the sodium channels, prolonging the inactive state of sodium channels.

Oral bioavailability is about 85% with food, but less without food. Food increases the absorption by more than 30%. Protein binding is about 55%.

Rufinamide is metabolized by enzymatic hydrolysis to an inactive metabolite. This is not dependent on the P450 enzyme system. The inactive metabolites are eliminated by excretion in the urine. The half-life is approximately 6–10 h.

Rufinamide is a weak inhibitor of CYP 2E1 (it increases olanzapine level) and a weak inducer of CYP 3A4 (it decreases oral contraceptive efficacy). Rufinamide is a weak inducer of UDP–GT (it increases the clearance of lamotrigine). The addition of enzyme-inducing antiepileptic drugs increases rufinamide clearance and decreases rufinamide level. On the other hand, the addition of valproate decreases rufinamide clearance and increases rufinamide levels by up to 70%.

Rufinamide adverse effects include dizziness, fatigue, somnolence, and headache. Vomiting may occur in children. Rufinamide may cause a shortening of the QT interval. It was assigned pregnancy category C.

Rufinamide is FDA indicated as adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in children 4 years and older and adults. Although rufinamide was found to be effective for partial seizures, it has not been FDA approved for this indication.

Ezogabine (Known as Retigabine Outside the USA)

Ezogabine was first approved in the USA in 2011. It has a normal mechanism of action as a potassium channel opener. It enhances the activity and prolongs the opening of neuron specific KCNQ2/3 (Kv7.2/7.3) voltage-gated potassium channels, thereby activating the M current. Ezogabine also potentiates GABA-evoked currents in cortical neurons at much higher concentration than that needed to activate potassium currents.

Ezogabine oral bioavailability is about 60%. It is about 80% protein-bound.

Ezogabine is extensively metabolized, primarily via glucuronidation and acetylation. It is metabolized to the active N-acetyl metabolite (NAMR), which is also subsequently glucuronidated. About 85% of the absorbed dose is recovered in the urine, 36% as unchanged ezogabine, and 18% as NAMR. The half-life is 7–11 h for both ezogabine and NAMR.

Ezogabine does not significantly affect other antiepileptic drugs except for a 22% increase in lamotrigine clearance. NAMR may inhibit renal clearance of digoxin. Enzyme-inducing antiepileptic drugs reduce ezogabine levels.

The most common ezogabine adverse effects are dizziness, somnolence, fatigue, confusion, blurred vision, tremor, and nausea, most often during titration. Urinary retention may occur. There may be QT prolongation. Long-term use has been associated with skin, nail, and retinal pigmentation. Weight gain may occur. Ezogabine was assigned pregnancy category C.

Ezogabine is FDA indicated for adjunctive treatment of partial–onset seizures in patients aged 18 years and older. It is not known whether ezogabine is effective against other seizure types.

Perampanel

Perampanel was approved in the USA in 2012. Its mechanism of action is noncompetitive antagonism of AMPA glutamate receptors.

Perampanel has excellent oral bioavailability of about 100%. It is 95% protein-bound.

Perampanel is extensively metabolized by primary oxidation mediated by CYP 3A4, followed by glucuronidation. It is excreted as inactive metabolites, 30% in the urine and 70% in the feces. It has a long half-life of 105 h on average.

Perampanel does not affect other antiepileptic drugs. However, perampanel at a dose of 12 mg per day reduces levonorgestrel by about 40%. This effect is not seen at the dose of 8 mg per day. Enzyme inducers will decrease perampanel levels.

Perampanel adverse effects include dizziness, somnolence, headache, fatigue, ataxia, and blurred vision. Aggression and hostility may occur—at a dose of 12 mg per day, its incidence is estimated at 20%. Perampanel is assigned pregnancy category C.

Perampanel is FDA indicated for the treatment of partial–onset seizures with or without secondary generalization in patients with epilepsy aged 12 years or older. It is not yet known whether perampanel is effective against generalized onset seizures.

Eslicarbazepine

Eslicarbazepine acetate was approved for marketing in the USA in 2014. It is rapidly converted to the active metabolite (S)-licarbazepine by hydrolytic first-pass metabolism. (S)-licarbazepine is the active enantiomer of the monohydroxy derivative, which is the active metabolite for oxcarbazepine. The monohydroxy derivative from oxcarbazepine is a racemic mixture of the active (S)-licarbazepine and the inactive (R)-licarbazepine. Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage-gated sodium channel.

Eslicarbazepine has excellent bioavailability, greater than 90%. Its protein binding is less than 40%.

Eslicarbazepine is metabolized to inactive compounds. About 60% of the absorbed dose is excreted in the urine as unchanged eslicarbazepine,

30% as the glucuronide conjugates, and 10% as other metabolites. The half-life of eslicarbazepine is 13–20 h in plasma and 20–24 h in CSF, justifying once daily dosing used in clinical trials.

Eslicarbazepine is not subject to autoinduction. However, it can induce CYP 3A4, thus decreasing plasma concentrations of estrogen and drugs metabolized by this enzyme. It also has a moderate inhibitory effect on CYP 2C19, potentially increasing plasma concentration of phenytoin and other drugs metabolized by this enzyme. Enzyme inducers may reduce her eslicarbazepine serum concentration.

The most common eslicarbazepine adverse effects are dizziness, headache, diplopia, somnolence, vertigo, nausea, vomiting, fatigue, and ataxia. Hyponatremia (defined as less than 125 mEq per liter) is reported in up to 1.5% of individuals taking 1200 mg per day. Rash occurs in up to 3% of individuals at 1200 mg per day.

Eslicarbazepine is effective against partial–onset (focal) seizures. It is currently FDA indicated as adjunctive treatment for partial–onset seizures. Monotherapy trials have been completed but have not yet been considered to change the FDA indication.

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Dietary Therapies

18

Amy Kao

History

In the Hippocratic medical writings of ancient Greece from 500 BC, fasting was described as the treatment for epilepsy. Then in biblical times, it was again mentioned as an effective *cure* for epilepsy. In 1911, two physicians in Paris used starvation in 20 children and adults and found that the severity of their seizures decreased. In 1921, Wilder at the Mayo Clinic proposed a diet consisting of excessive fat and sparse carbohydrates, which would produce ketones, just as starvation does, and coined the term "ketogenic diet." The ketogenic diet was subsequently extensively used as an epilepsy treatment.

In 1938, the discovery of diphenylhydantoin lessened the interest in the KD. In the late 1980s, after learning about the KD, a family of a 20-month-old boy with refractory epilepsy desperately approached the Johns Hopkins Hospital, requesting the treatment; the KD was effective for him. There was subsequently a Dateline episode on the effectiveness of the KD for this boy, Charlie. The family also established the Charlie Foundation, a nonprofit organization that began providing information to parents and instructional videos to practitioners and dietitians. Further publicizing and supporting the KD was the production of "Do No Harm," directed by Charlie's father and narrated by and starring Meryl Streep in 1997. Reflective of the subsequent increase in interest is the increase in medical literature; there were 2–8 publications per year between 1970 and 2000 on the KD and >40 per year since [1]. There are 102 KD programs listed on the Charlie Foundation Web site (www.charliefoundation.org); the majority are in North America, but centers are also located in Europe, South America, Asia, and Australia.

Overview of Types of Dietary Therapies

Ketogenic Diet ("Classic")

The KD simulates the ketosis seen with starvation while providing necessary calories for growth and development. When a "normal" diet is consumed, glucose is the sole source of energy for the brain; fatty acids do not cross the blood–brain barrier. When carbohydrate consumption is limited, glucose supplies are low, so fat is then used as the alternative source of energy. Specifically, when glucose is low, oxaloacetate is shunted from the Krebs cycle to gluconeogenesis, to produce and maintain glucose levels. This decreases the efficiency of the Krebs cycle to metabolize the abundant acetyl-coA generated from fatty acid metabolism, so acetyl-coA is instead converted to ketone bodies, specifically to acetoacetate, which is then degraded to acetone and also converted to beta-hydroxybutyrate.

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Ketone bodies can cross the blood–brain barrier and so are used instead of glucose for energy [2].

The "classic" KD utilizes long-chain fatty acids (as opposed to medium-chain fatty acids) and is the most widely used dietary treatment. The composition of the diet is calculated using a ratio of the weight of fat (in grams) to the sum of the weight of protein and carbohydrates. Typical ratios are 3:1 or 4:1 (compared to the ratio in a standard North American diet which is 0.3:1). In a 3:1 ratio, there are 3 grams of fat for every 1 g of protein plus carbohydrate combined. The amount of protein is calculated to meet dietary reference intake which is 1 g per kilogram body weight, so a 3:1 ratio is typically used for older children with greater body mass. Calories are also measured, such that they are sufficient to support growth but controlled to prevent excessive weight gain. Roughly 90 % of the calories are obtained from fat consumption in the classic KD.

Historically, caloric restriction, fluid restriction, and an initial fasting period of 24–48 h, until large ketones are demonstrated, have been features of the KD, but there is limited evidence that these are necessary. Initial fasting seems to shorten the time to the first reported seizure reduction, but long-term outcomes are not impacted. A randomized controlled trial comparing fasting versus gradual initiation (gradually increasing ratios from 1:1 to 2:1 to 3:1 to 4:1) showed equivalent efficacy at 3 months, with decreased weight loss, decreased episodes of hypoglycemia, and decreased treatment necessary for acidosis or dehydration in those children initiated without fasting [3].

Medium-Chain Triglyceride (MCT) Diet

In 1971, Peter Huttenlocher at the University of Chicago introduced the MCT Diet. Whereas the classic KD uses standard foods as source of fat, this utilizes MCT oil as a source of medium-chain fatty acids, which is more easily absorbed and delivered directly to the liver; thereby, more efficiently generating ketones and allowing greater consumption of protein and carbohydrates. The MCT diet provides 60–70% calories from fat. The downside of the MCT diet is gastrointestinal side effects including diarrhea, vomiting, and abdominal pain [4]. However, a randomized controlled trial comparing the tolerability and efficacy of the MCT diet versus classical KD showed no significant differences in either [5].

Modified Atkins Diet (MAD)

The MAD was developed at Johns Hopkins Hospital, first reported in 2003, and aimed at children with behavioral difficulties, adolescents, and adults [6]. The standard Atkins diet has a goal of weight loss and includes an induction phase in which there is limitation of carbohydrates to induce ketosis. In the MAD, this initial phase of carbohydrate restriction is continued, and weight loss is not encouraged unless nutritionally indicated.

The fat to protein plus carbohydrate ratio of the MAD is 0.9:1, providing approximately 60–65% of calories from fat, 30% from protein (higher than the KD and "normal" diet), and 10% from carbohydrates (higher than the KD). Based upon the protocol at Johns Hopkins, in children, initial carbohydrate restriction is to 10 grams per day for a month, with liberalization to 15 g, then 20–30 g per day. Adults are started at 15 g of carbohydrates per day and then increased to 20–30 g per day after a month. This initial stricter period is based upon data from a randomized, prospective cross-over design study which showed higher incidence of >50% seizure reduction at 3 months in patients who initially consumed 10 grams per day (60%) versus 20 g per day (10%). The glycemic index of carbohydrates is not controlled. Fiber is subtracted from the total carbohydrate count.

Initiation of the MAD is done as an outpatient process and no weighing of foods is required, although counting carbohydrates is required. Low-carbohydrate multivitamin and calcium supplementation is prescribed. Medications may be changed to lowest carbohydrate formulations. Urine ketones are checked twice per week and

may be elevated to the "large" level, but sometimes are lower than those generated by the KD. Monitoring includes phone follow-up in a month and clinic follow-up at 3 and 6 months, with complete blood count (CBC), complete metabolic panel (CMP), fasting lipid profile at baseline, 3 and 6 months [7].

Low-Glycemic-Index Treatment (LGIT)

This is the least restrictive dietary therapy presently used in epilepsy management and, thus, may be seen as more palatable and better tolerated than the other diets. It is also initiated in the outpatient setting, without weighing of foods. It was first reported in 2005 at Massachusetts General Hospital, based upon the theory that one mechanism of the KD could be stabilization of blood sugar levels. This arose from observations that seizure control of children on the KD can be very sensitive to intake of extra carbohydrates, and that blood glucose levels are extremely stable in children on the KD. The LGIT allows higher carbohydrate intake than the other 2 diets but limits the type of carbohydrates to those that are low in glycemic index, foods that result in lower postprandial blood sugar and insulin profiles. Larger particle size, less gelatinization of a starch, presence of fat, higher acidity, and increased fiber content lead to lower glycemic indices. The type of starch is also a factor. In LGIT, fat contributes 60% of calories, protein 20–30%, and carbohydrates are limited to 40–60 g per day. All carbohydrates are foods with glycemic index less than 50 [8].

Patient Selection

In December 2006, the Charlie Foundation commissioned a panel of 26 pediatric epileptologists and dietitians from 9 countries with expertise in the KD, to create a consensus statement on the clinical management of the KD. It was endorsed by the Child Neurology Society and serves as an excellent reference for a wide breadth of issues regarding the KD including the practical details of management.

This consensus statement states that the "KD should be strongly considered in a child who has failed 2–3 anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies." In addition, the committee members reviewed publications on efficacy in particular conditions. For the KD to be considered as having *probable benefit* in that condition, the existence of at least 2 publications was required; those included myoclonic astatic epilepsy, Dravet syndrome, tuberous sclerosis, Rett syndrome, and infantile spasms. Formula feeding through gastrostomy tube or bottle would also be a favorable factor, as it would simplify food preparation and minimize chances of intolerance.

Also, based upon specific metabolic abnormalities, there are 2 conditions in which the KD could be considered *treatment of choice*, to be used before 2 or 3 antiseizure medications have failed. Those would be glucose transporter deficiency syndrome, in which glucose transport across the blood–brain barrier is impaired, and pyruvate dehydrogenase deficiency in which pyruvate cannot be metabolized into acetyl-coA.

Other conditions in which the KD may *possibly* be beneficial (based upon single case report or case series) include such conditions as Landau Kleffner syndrome, Lafora body disease, subacute sclerosing panencephalitis, mitochondrial respiratory chain complex disorders, phosphofructokinase deficiency, febrile infection-related epilepsy syndrome (FIRES)/status epilepticus, Lennox-Gastaut syndrome, hypoxic-ischemic encephalopathy, and focal malformations of cortical development.

Contraindications are essentially disorders that involve fatty acid metabolism defects due to various enzyme deficiencies. Long-chain fatty acids are shuttled across the outer and inner mitochondrial membranes by carnitine, facilitated by first carnitine palmitoyltransferase I, then carnitine translocase, then CPT2, after which beta oxidation occurs within the mitochondrion, generating acetyl-coA, which then enters the Krebs cycle or forms ketones. Pyruvate

carboxylase converts pyruvate to oxaloacetate, so deficiency impairs Krebs cycle function. Thus, contraindications include primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, Beta-oxidation defects (medium-chain acyl dehydrogenase deficiency or MCAD, long-chain acyl dehydrogenase deficiency or LCAD, short-chain acyl dehydrogenase deficiency or SCAD), and pyruvate carboxylase deficiency. The lack of carbohydrates in the KD can also exacerbate acute intermittent porphyria. Relative contraindications include "failure to thrive," an identifiable surgical focus, and predictors of noncompliance such as lack of supervision, access to or tendency toward forbidden foods, and lack of parental readiness and commitment [9].

Typically, an outpatient clinic visit is where screening and patient selection takes place. Nutritional history is obtained, complicating medical factors and other potential barriers to success are identified, education regarding the particular diet is given, and expectations and goals are discussed. Laboratory testing is performed to screen for metabolic contraindications; these may include complete blood count, electrolytes, magnesium, phosphorous, zinc, selenium, liver and kidney function tests, fasting lipid profile, urinalysis, urine calcium/creatinine, urine organic acids, serum amino acids, and acylcarnitine profile.

The concomitant use of carbonic anhydrase inhibitors is *not* a contraindication. Topiramate and zonisamide may increase the likelihood of profound acidosis and associated lethargy and vomiting during the period of initiation of the KD. However, they do not need to be discontinued before initiation of the KD. Daily enteral citrate may be administered to counteract this acidosis.

Mechanisms

The exact mechanisms by which dietary therapies treat seizures have not been precisely delineated. Much research, including animal model studies, has investigated this. Proposed mechanisms have included numerous processes, such as direct anticonvulsant effect of ketones/free fatty acids, antioxidant/anti-inflammatory effects by decreasing reactive oxygen species, action on mitochondrial uncoupling proteins, increase of mitochondrial biogenesis, decrease of glutamate, and increase of GABA.

Duration

When the KD is the effective, evidence of benefit occurs fairly quickly. The range of time until benefit is 1–65 days and is typically within the first 2 weeks after initiation. Similarly, in a prospective study in adults on the MAD, median time to improvement was 2 weeks (range 1–8 weeks) [10]. Based on these data, continued KD administration for 3 months is encouraged before deciding if the KD should be resumed or discontinued.

If seizure freedom is obtained on the KD, weaning and discontinuation of the KD is considered after 2 years, similar to the approach with antiseizure medications. If seizure freedom is not obtained, but improved seizure control occurs, the balance between benefit and long-term risks needs to be considered when discussing duration of the KD.

Complications

Short-term complications of the KD may include vomiting, dehydration, hypoglycemia, and excessive acidosis. Therefore, patients are typically hospitalized for initiation of the KD. Constipation is a frequent side effect, which is treated by increasing hydration, giving conducive foods such as avocado, or using bulk-forming laxatives.

Monitoring for long-term side effects of the KD must take place on a standard basis, at least every 3 months. This includes measurements and laboratory testing for weight and height, hyperlipidemia (fasting lipid profile), nutritional and electrolyte deficiencies (electrolytes with bicarbonate, calcium, magnesium, phosphorous,

complete blood count with platelets, free and total carnitine, zinc selenium, liver function tests, vitamin D), and kidney stones (urinalysis, urine calcium and creatinine). Also, as urine ketone testing is less accurate than serum testing, serum beta-hydroxybutyrate levels may be drawn to correlate with home urine results. Bone mineral density scan, to assess for osteopenia/osteoporosis, may be considered, particularly in patients who are high risk (immobile, multiple antiseizure medications, history of fractures) and on the KD longer than 2 years.

Evidence of longer-term adverse events with the *MAD* is limited. In theory, risk of growth limitation, kidney stones, dyslipidemia, and gastroesophageal reflux would be less common than with the KD. Approximately, 25–50 mg/dl increases in total cholesterol have been noted. Blood urea nitrogen also has been shown to increase, likely related to increased protein intake [7(p39)].

Outcomes

A Cochrane Review in 2012 yielded 4 randomized controlled trials (versus no randomized controlled trials in a similar review in 2003). These trials were heterogeneous, namely one compared 3:1 and 4:1 ratios of the KD, one compared MCT and classical KD, one KD versus no diet, one fasting versus gradual initiation, and one MAD with 10 versus 20 grams of carbohydrates. However, taken together, all showed that at least 38% of patients had a 50% decrease in seizures at 3 months, with the benefit maintained at 1 year.

Modified Atkins Diet

Efficacy of the MAD may be comparable to the KD in children and adults. In two studies including children, 43–65% had at least >50% reduction of seizures at 6 months, with 35–36% having >90% seizure reduction [7(p38)]. Meta-analysis of existing literature as of 2008 showed 45% of patients on the MAD with 50–90% seizure reduction and 28% with >90% seizure reduction. In an adult study, efficacy was quick if present (median 2 weeks), with 47% experiencing >50% seizure reduction by 3 months and 33% by 6 months [7(p39)].

Low-Glycemic-Index Treatment

Review of 60 patients has shown 38% of patients with a >50% decrease in seizures at 1 month, with 24% having >90% seizure decrease. Of the patients who continued on LGIT through 6 months, 60% had a >50% seizure decrease, and 38% had a >90% decrease in seizures [8(p43)].

Future Directions

The use of the KD is being investigated in several neurologic conditions beyond epilepsy, and in traumatic brain injury, Alzheimer's disease, amyotrophic lateral sclerosis, autism, glial tumors, diabetic nephropathy, and Parkinson's disease. In addition, in development is 2-deoxy-(D)-glucose (2-DG), an agent which is a non-metabolizable glucose analog that inhibits glycolysis.

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19 Other Pharmacological Therapies: Investigational Antiepileptic Drugs, Animal Models of Epilepsy, Hormonal Therapy, Immunotherapy

Bassel Abou-Khalil

Investigational Antiepileptic Drugs

The investigation of antiepileptic drugs (AEDs) includes trials of new routes of delivery for marketed drugs, trials of marketed drugs for new indications, and trials of novel compounds.

New routes of delivery are being tested in particular for benzodiazepines, in the treatment of seizure clusters by family members and other nonmedical caregivers. A large pivotal trial was completed for intramuscular diazepam administration by autoinjector, demonstrating intramuscular diazepam to be superior to placebo in preventing additional seizures and in obviating the need for other rescue treatment or emergency room visit [1, 32]. Intranasal midazolam and intranasal diazepam are also in testing for the treatment of seizure clusters by nonmedical caregivers [7, 12, 16, 34]. Intramuscular midazolam by autoinjector was tested as a prehospital treatment of status epilepticus by emergency medical personnel. Intramuscular midazolam was found to be noninferior to intravenous lorazepam; in fact, patients treated with midazolam more often had stopped seizing upon arrival to the emergency department [33]. One important advantage of intramuscular midazolam is faster delivery, with a shorter time to active treatment than for intravenous lorazepam. Another marketed product that is being tested for an alternate route of delivery is intravenous carbamazepine [24].

A number of new AEDs have become available in extended release formulations. The list includes gabapentin (for restless leg syndrome), lamotrigine, topiramate, levetiracetam, and oxcarbazepine [2, 3, 5, 9, 11, 28, 29, 35]. These formulations allow the convenience of once daily dosing or steadier serum concentrations with twice-daily dosing [20].

Several new AEDs are in trials for use in monotherapy (lacosamide and eslicarbazepine) or for use in primary generalized tonic-clonic seizures (lacosamide and perampanel). Intravenous lacosamide is undergoing investigation for use in nonconvulsive seizures or nonconvulsive status epilepticus.

While there are many experimental drugs in testing, the ones in phase 3 trials will be discussed mainly. Brivaracetam is an analogue of levetiracetam which has a sodium blocking mechanism in addition to its SV2A binding [27]. It appears to have a similar profile to levetiracetam in general, with a higher potency. Two novel compounds are, in advanced stages of testing, VX765 (an anti-inflammatory agent) and YKP3089 (an agent with unknown mechanism, probably an inhibitor of slow inactivated state of sodium channels which may also facilitate the release of GABA).

It is worthwhile pointing out a couple compounds that are still in early testing. Cannabidiol, a nonpsychoactive compound derived from

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cannabis, is undergoing early trials in epilepsy after a media campaign based on anecdotal reports of efficacy in various epilepsy syndromes, including Dravet syndrome [8]. Intravenous allopregnanolone, a neurosteroid that modulates synaptic and extrasynaptic $GABA_A$ receptors, is undergoing testing in super-refractory status epilepticus, where there is a decreased synaptic expression of benzodiazepine-sensitive $GABA_A$ receptors [31].

Animal Models of Epilepsy

The development of AEDs has depended considerably on animal models of epilepsy (Table 19.1). Perhaps, the most important application was historically screening of compounds for anti-seizure activity. The two main animal models used in the screening of antiepileptic drug candidates were the maximal electroshock (MES) model and the subcutaneous pentylenetetrazole (PTZ) model [21]. In the MES model, electrical stimulation is applied, usually through the cornea, with an intensity sufficient to elicit tonic hind limb extension in all control animals [4]. The electrical stimulus is 50–60 Hz in frequency, 0.6 ms in pulse width, and 0.2 s in stimulus train duration. The usual intensity needed is 50 mA for mice and 150 mA for rats. In the PTZ model, PTZ is injected subcutaneously at a dose known to induce at least 5 s of clonic seizure activity in 97% of the animals. The MES model has been said to be predictive of efficacy against generalized tonic-clonic seizures, whereas the PTZ model has been thought to be predictive of efficacy against absence seizures. However, these models may miss some effective AEDs, most notably levetiracetam. In addition, these models have been criticized for being models of seizures in healthy animals, rather than models of epilepsy.

One animal model that is predictive of efficacy against partial (focal) seizures is the kindling model. In this model, repeated electrical stimuli are applied to the amygdala or hippocampus of rats, resulting in permanent lowering of the seizure threshold, so that stimuli that initially produced only subclinical after discharges eventually result in full-fledged generalized tonic-clonic seizures [10]. Though laborious, this model has been increasingly used in the preclinical testing of candidate drugs. However, this model has also been criticized for the absence of spontaneous seizures that are typical of human epilepsy.

True animal models of epilepsy should have spontaneously recurrent seizures. Such models may have genetic or acquired epilepsy. Commonly used genetic models are DBA/2 mice with audiogenic seizures and the genetic absence epilepsy rats from Strasbourg (GAERS) [22, 23]. Efficacy in DBA/2 mice with audiogenic seizures helps predict efficacy against human generalized tonic-clonic seizures, while efficacy on GAERS helps predict efficacy against human generalized absence seizures. Animal models of acquired chronic epilepsy include post-status epilepticus models, in which chemically or electrically induced status epilepticus is followed by spontaneously recurring seizures.

Because newly introduced AEDs have had limited impact on the proportion of patients with drug-resistant epilepsy, it is now recognized that there is a need for animal models of epilepsy that are drug-resistant [21]. One such model is the 6-Hz psychomotor seizure model in mice. In this model, 6-Hz pulses of 0.2-ms duration are delivered through the cornea for 3 s, resulting in a seizure that resembles limbic seizures in humans. At an intensity of 44 mA (twice that necessary to produce seizures in 97% of mice), many AEDs become ineffective [21]. The methylazoxymethanol acetate (MAM) rat model of cortical dysplasia can also serve as a model of pharmacoresistant epilepsy. In this model, MAM in utero exposure to results in a cortical dysplasia-like lesion, and seizures induced in these rats by kainate are resistant to several AEDs. Pharmacoresistant epilepsy can also be produced by exposure to low doses of lamotrigine during kindling or by selection of subgroups of rats that are resistant to specific AEDs from a large group of epileptic rats.

All the currently marketed AEDs are used as symptomatic treatment to suppress seizures.

Table 19.1 Select animal models of seizures/epilepsy and the proposed corresponding human seizure/epilepsy type that is modeled

Animal model	MES	PTZ	Kindling	DBA/2 mice	GAERS rats
Human seizure/epilepsy type	Generalized tonic-clonic seizures	Generalized absence seizures	Partial seizures (limbic)	Generalized tonic-clonic, reflex seizures, SUDEP	Generalized absence seizures

Animal model	6-Hz psychomotor seizure model in mice	MAM seizure model	Post-status epilepticus model in rats
Human seizure/epilepsy type	Pharmacoresistant limbic seizures	Pharmacoresistant seizures, cortical dysplasia	Chronic focal epilepsy

There is no clear evidence that any current AED is effective in the prevention of epilepsy. There is increasing interest in the identification of disease modifying treatments that could prevent the development of epilepsy after an insult or prevent the progression of epileptogenesis. Chronic animal models of epilepsy can be used to study potential anti-epileptogenic treatments. The most commonly used models in this setting are the kindling model and the post-status epilepticus model [21].

Hormonal and Immunological Treatment

Hormonal therapy may be considered in women with catamenial epilepsy, in whom seizures seem to follow a cyclical pattern related to the menstrual cycle [13, 15]. Three patterns of catamenial epilepsy have been described: C1 pattern where seizures increase in frequency just before and during menses, C2 pattern where seizures increase around the time of ovulation, and C3 pattern where seizures occur with anovulatory cycles. Catamenial epilepsy is thought to be related to progesterone and estrogen fluctuations. Estrogen appears to be proconvulsant, and progesterone appears to be anticonvulsant. In catamenial epilepsy, seizures are more likely to occur when the ratio of progesterone to estrogen decreases, as seen around the time of menstruation and the time of ovulation. The C1 pattern of catamenial epilepsy responds to progesterone 200 mg tid administered on days 14–28 of the cycle [14]. Synthetic progestins and clomiphene citrate have also been reported beneficial as treatments for catamenial epilepsy in small studies.

Ganaxolone is a derivative of allopregnanolone that lacks hormonal activity. It has been tested in a number of clinical trials. There was a suggestion that women with catamenial epilepsy were a subgroup that benefited in particular [30]. Ganaxolone was also tested in infantile spasms and found helpful in some patients [19]. It is not known if this compound will eventually be available for clinical use.

ACTH and steroids are first-line short-term treatments for infantile spasms/West syndrome. They help control seizures and improve behavior and EEG. They are most effective in the idiopathic syndrome. A high dose seems to be more effective. When it comes to ACTH, one approach is to begin with 40 IU per day for 1–2 weeks and increase to 60 or 80 IU per day thereafter if the response is incomplete. If it is effective, it is then tapered over 1–4 months. ACTH and steroids are less commonly used to treat Lennox–Gastaut syndrome and Landau–Kleffner syndrome.

Steroids and IVIG may be considered in the treatment of Rasmussen's syndrome and other epilepsies suspected to be of immune origin, to treat the underlying cause of epilepsy. Limbic encephalitis, usually autoimmune, is increasingly recognized as a cause of chronic epilepsy. An immune basis of epilepsy should be considered when there is no other clear etiology, the onset was acute or subacute, and there is a prior history of autoimmunity (or autoimmunity is present in a

first-degree relative), in the presence of a neoplasm, when there is CSF or imaging evidence of inflammation, and when neuronal autoantibodies are detected [36]. Faciobrachial dystonic seizures are brief seizures that predominantly affect the arm and ipsilateral face. They are an early sign in anti-LGI1 encephalitis that should prompt investigation for immune etiology and early immune therapy [17, 18]. The autoantibodies most commonly associated with immune epilepsy are anti-LGI1 antibodies (anti-voltage-gated potassium channel complex antibodies), anti-GAD antibodies, and anti-thyroid antibodies [25, 26]. Anti-NMDA antibodies are associated with a distinctive limbic encephalitis syndrome that usually includes seizures, but is unlikely to be a cause of pure chronic epilepsy [6]. When an immune origin is confirmed, first-line immunotherapies include oral or IV steroids (IV methylprednisolone 1000 mg daily for 3–5 days, then weekly for 4–6 weeks), IVIG (0.4 g/kg/day for 3–5 days then weekly for 4–6 weeks), or plasmapheresis [36]. If there has been incomplete benefit and there is strong evidence of autoimmune etiology, chronic immunosuppression could be considered with mycophenolate mofetil, azathioprine, or rituximab [36].

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Epilepsy Management in Special Populations

20

Amir M. Arain

Epilepsy in Individuals with Intellectual and Developmental Disability

Individuals with intellectual disability, a lifelong condition, are dependent on others for their daily care needs. Intellectual and developmental disability (IDD) is defined by mental retardation (MR) and can be mild, moderate, or severe. Individuals with mild MR, with IQs between 50–55 and 70, are considered the educable mentally retarded and are placed in special classes. Individuals with moderate MR, with IQs between 35–40 and 50–55, are often institutionalized, and their training is focused on self-care rather than development of intellectual skills. Finally, those with severe MR, with IQs between 20–25 and 35–40, cannot care for themselves, have major problems with communication, and are often listless and inactive.

Individuals with IDD have higher incidence of epilepsy in comparison with those with normal intellect. Incidence of epilepsy increases with the severity of mental retardation, but it varies depending on epidemiological methodologies. In population-based studies, 21% of those with mild MR had epilepsy [1]. Another study reported epilepsy in 11% of subjects with mild MR and in 23% in those with severe MR [2]. On the other hand, in institution-based studies including patients with severe MR, the prevalence of epilepsy varies from 32–34% [3].

Regarding the seizure semiology in patients with IDD, a population-based study reported generalized tonic-clonic (GTC) seizures to be the most common type [2]. However, in institution-based studies, focal dyscognitive (complex partial) seizures with or without secondary generalization were reported to be the most common [3]. Other seizure types, such as tonic, atonic, myoclonic, and atypical absence seizures are also seen. Seizure types are also age-related with GTC and focal dyscognitive seizures becoming predominant at later ages. Only one-third of the individuals with IDD have seizures that can be classified per ILAE classification [3]. The reason for this is partly the fact that such individuals may have complex non-epileptic behaviors that are confused with epilepsy, and only video-EEG monitoring can discern the nature of such behaviors. This constitutes a major problem in these individuals because often antiseizure medications are added, or their dosages increased, to treat non-epileptic behaviors, impacting the patient's quality of life.

About two-thirds of institutionalized patients with IDD have stereotypical behaviors, including head movements, rocking, and jerking [4]. Other motor behaviors may result from medication adverse events, including tardive dyskinesia, which may be confused with seizures. Video-EEG monitoring is often very helpful in confirming the diagnosis [5]. Caregivers can be advised to make a home video of the spells in

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question as a first screening tool. Several factors have an impact on the caring of individuals with intellectual disability such as maladaptive behavior of the patients [6], severity of intellectual disability, presence of multiple disabilities, and level of social support. Caregivers of individuals with IDD are at-risk of stress [7].

Seizure control is often brittle in this population. Seizure exacerbations occur with fever, infections, metabolic abnormalities [8, 9], or any stressful condition. At times, change in caregivers or environment may have detrimental effect on seizure control. Patients with IDD and epilepsy have risks of morbidity and mortality, including a higher incidence of vitamin D deficiency. Their limited mobility and the effects of antiepileptic drugs (AEDs), especially older generation ones, can worsen their bone health. Patients with epilepsy and IDD have a higher risk of fractures. The risk of mortality individuals with IDD and epilepsy exceeds that of individuals with epilepsy alone, which, in turn, exceeds that of the healthy population.

Treatment principle in the population is to improve their seizure control without compromising their quality of life. Excessive sedation is not an acceptable cost for seizure control. At times, patients may not like the color or taste of medicine. Caregivers should be astute enough to try different formulations. AEDs available as liquid, in soluble or granular form, or as powder may be useful. Caregivers of these patients are the most important liaison between the physician and the patient as often these patients are nonverbal. In these patients, assessment of treatment is often hampered by lack of communication. CNS side effects of AEDs may be masked. Caregivers should be tuned to assess any change in their behavior as drowsiness or mood changes may be a manifestation of side effects.

Patients with IDD and epilepsy who have been seizure-free for several years may undergo AED medication tapering trial. However, the risk of seizure recurrence is high. Predictors of successful discontinuation of AED include history of few documented seizures, no gross neurological abnormalities, and normal EEG before and after AED discontinuation [10].

Epilepsy in the Elderly

The incidence of epilepsy increases with age, with a steep rise after age 60 [11, 12]. Epilepsy has higher incidence (134/100,000 person-years) in the elderly than Alzheimer's disease (123/100,000 person-years). Seizures may present with staring, disorientation, and subtle lip smacking. Atypical presentations are also common in the elderly, including altered mental status, memory lapses, and intermittent confusion. In addition, auras are less common while postictal states can be prolonged mimicking dementia.

The most common causes of seizures in the elderly are stroke, dementia, and head trauma [13]. Other risk factors for epilepsy include major depression, hypertension, and sleep apnea. Both ischemic and hemorrhagic cerebrovascular events increase the incidence of epilepsy [14, 15]. Epilepsy was a concomitant diagnosis in 10% of individuals with Alzheimer's disease in an autopsy-verified study, and seizures can occur at any stage of Alzheimer's disease [16]. In treating patients with dementia and epilepsy, it is important to keep in mind that acetylcholinesterase inhibitors may worsen seizures [17]. Hypertension is another independent risk factor for developing epilepsy in the elderly patients [18]. Aggressive treatment of hypertension in elderly patients, particularly with diuretics, may have a protective effect [19].

Depression in the elderly is associated with an increased risk of developing seizures. In a study of patients aged 55 or older, there was a sixfold increased risk of unprovoked seizures [20]. Similarly, sleep apnea can be a risk factor for new onset seizures or seizure exacerbations in the elderly. Treating comorbid sleep apnea in elderly patients with epilepsy may improve seizure control. In a study of elderly patients with epilepsy evaluated by polysomnography, patients with new onset or worsening seizures had significant high Apnea–Hypopnea Index compared to stable or seizure-free patients [21].

Diagnosis of epilepsy in elderly can be challenging because of higher percentage of partial seizures than generalized tonic-clonic seizures

that can be readily diagnosed. Moreover, the extratemporal lobe seizures with subtle features and prominent postictal confusion are more common in elderly. Misdiagnosis may also result from difficulties in history taking, comorbidities, polypharmacy, and the fact that the EEG is less helpful for diagnosis than in younger individuals. Epilepsy in elderly can be delayed because of these factors. Physicians treating elderly patients should have epilepsy in their differential diagnosis.

Once the diagnosis of epilepsy is established, then the treatment should be started as the risk of recurrence after the first unprovoked seizure is ~80% [22]. Clinicians should have a low threshold in starting AEDs. Physiological changes of aging may affect AED pharmacokinetics. These include decreased albumin, decreased liver metabolism, and decreased glomerular filtration and excretion. These changes result in longer half-lives of the medication and greater risks of drug–drug interactions [23]. Several AEDs including carbamazepine, phenytoin, and valproate are highly protein bound and will compete with other medications, including digoxin, for adherence to serum proteins resulting in toxicity. Changes in protein binding result in misleading measurements of total AED concentration. Checking free levels of phenytoin and valproate is recommended to the elderly. Elderly patients are more sensitive to side effects of AEDs, including peak toxicity. Thus, extended release formulations can be helpful as they result in lower peaks.

Older generation AEDs have higher incidence of drug–drug interactions with other medications. Many AEDs induce liver enzymes, thus lowering the levels of other medications. Administration of carbamazepine, for example, can lower simvastatin level [24]. Newer AEDs have relatively better pharmacokinetics profile with less potential for drug–drug interactions. Grapefruit juice can increase the level of many medications, including carbamazepine, resulting in dizziness, lack of coordination, sedation, and other side effects.

It is recommended that newer AEDs be started in elderly patients with epilepsy because of their favorable pharmacokinetic profiles. Medications must be initiated at a low dose and slowly titrated up. Older AEDs with enzyme-inducing properties should be avoided, and newer generation AEDs with significant cognitive adverse events, including topiramate and zonisamide, should also be avoided [25]. Valproate may be a good choice in elderly, but one has to keep in mind the potential side effects of parkinsonism (which is usually reversible) and dementia [26]. Lamotrigine, gabapentin, and levetiracetam are appropriate medications to be started as monotherapy in elderly patients with epilepsy [27, 28]. Seizures in the elderly can often be well controlled with monotherapy. In patients with refractory epilepsy, epilepsy surgery must be considered.

Women with Epilepsy

Women with epilepsy have some unique characteristics that can significantly affect the course and management of epilepsy. Epilepsy and female hormones reciprocally influence one another. Similarly, AEDs and female hormones also influence one another. Such interactions can affect seizure control and medication adverse events. The specific issues in women with epilepsy warrant special attention to their menstrual cycle regularity, fertility and ovulatory function, sexuality, hormonal contraception, pregnancy and breast-feeding, and bone health. Unfortunately, the awareness to these issues is not prevalent among healthcare providers [29].

Estrogen and progesterone have different effects on epilepsy. Estrogen may be proconvulsant as it may reduce inhibition at the $GABA_A$ receptor and also inhibits the synthesis of GABA. On the other hand, progesterone may be anticonvulsant as it enhances inhibition at the $GABA_A$ receptor and increases the GABA synthesis [30]. Progesterone also may attenuate the action of the brain's major excitatory neurotransmitter, glutamate, in the hippocampus. Thus, the hormonal fluctuations of the menstrual cycle may result in fluctuation in seizure frequency. This pattern is seen in catamenial epilepsy, which is present in approximately half of all women

with epilepsy. In these patients, exacerbations of seizure frequency occur at certain points in the menstrual cycle, either before the start of their menstruation, during menses, or around the time of ovulation possibly because of higher estrogen-to-progesterone ratios [31].

Some AEDs may affect the female hormones and contraception. Enzyme-inducing AEDs, such as phenytoin, carbamazepine, phenobarbital, primidone (and at higher doses, oxcarbazepine >900 mg/day and topiramate >200/day), can reduce the levels of contraceptives [32, 33]. In such situations, alternative or supplementary contraceptive methods should be used. On the other hand, estrogen decreases lamotrigine level by about 50%. Dosage adjustments of lamotrigine may be necessary to maintain appropriate response when starting or stopping estrogen—containing oral contraceptives in these women.

Fertility issues are common in women with epilepsy. In epidemiologic studies, women with epilepsy are approximately two-thirds less likely to have children than women without epilepsy. Factors that may contribute to the lower fertility rates in women with epilepsy include decreased libido, reduced marriage rates, increased anovulatory menstrual cycles, menstrual disorders such as amenorrhea or oligomenorrhea, and increased early miscarriages. AEDs, specifically enzyme-inducing ones, may also have an effect on fetal survival. Moreover, women with epilepsy are more likely to have polycystic-ovary-syndrome-like ovulatory dysfunction with clinical evidence of hyperandrogenemia, a risk that is increased by valproic acid treatment [34].

Pregnancy can affect seizures, and although it is a high progesterone state, some women may have worsening of seizures during pregnancy. This worsening could be an effect of pregnancy itself or because of decreasing AED levels as the pregnancy progresses. The risk of congenital malformations may be increased by epilepsy. Teratogenicity can be worsened by AEDs, and the rates of major congenital malformations (ranging from 4.6% with carbamazepine to 10.7% with valproate monotherapy) are 2–3 times higher than in untreated women with epilepsy (~3%) [35]. Besides anatomical teratogenicity, there is a risk of cognitive teratogenicity with valproic acid. In a study that assessed cognition in 3- and 6-year-old children who were exposed in utero to AEDs, those who were exposed to valproate had significantly lower IQ scores than those exposed to other medications [36, 37]. Thus, valproate must be avoided in monotherapy or polytherapy during the first trimester of pregnancy. However, other authors suggest that if it is imperative to use valproate during pregnancy, then a low dose of the extended release formulation should be used, starting with 500 mg per day and not exceeding 1000 mg per day [38]. It is recommended to use AEDs in monotherapy rather than polytherapy as the risk of major congenital malformations is increased by polytherapy. Based on the data, the probable safest medications are lamotrigine, levetiracetam, oxcarbazepine, zonisamide, gabapentin followed by carbamazepine and phenytoin [39]. Folic acid supplementation is recommended to women with epilepsy prior to pregnancy. There is still controversy on the optimal dose of folic acid. For healthy women, a dose of 0.4 mg/day is optimal, while for high-risk patients, especially ones with the previous history of major congenital malformations, a dose of 4–5 mg/day is recommended [40]. Prenatal testing, at 14–20 weeks of gestation, should be considered in pregnant women with epilepsy. Since then by seizure medication levels drop during pregnancy, checking the levels on a monthly basis is recommended.

Breast-feeding risks and benefits should be assessed for every individual patient. AED excretion into breast milk is adversely proportional to the degree of protein binding, with higher protein binding resulting in less excretion into breast. Phenobarbital and other AEDs may cause sedation or poor feeding. The American Academy of Neurology encourages breast-feeding in conjunction with close observation for any excessive sedation or irritability [41].

Bone health is another important aspect of epilepsy in women. AEDs, especially enzyme-inducing ones, can worsen bone health and predispose to fractures [42]. Valproate, although not an enzyme inducer, can cause osteopenia [43–45]. Among newer generation AEDs, oxcarbazepine and topiramate at high doses can adversely affect

the bone health [46, 47]. Dual-energy X-ray absorptiometry scan can be used to diagnose osteoporosis and low bone mineral density in women with epilepsy at risk. Women at risk should be counseled to take vitamin D and calcium supplementation. If female patients are on AEDs that worsen bone health, then switching them to other medications may reduce the risk of ongoing bone loss. Otherwise, a referral should be made to their primary care providers for possible institution of bisphosphonates or calcitonin.

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Multiple Choice Questions for Part IV

1. Which of the following antiepileptic drugs would be the best initial choice in an adolescent girl with juvenile myoclonic epilepsy?

   A. Carbamazepine
   B. Pregabalin
   C. Lacosamide
   D. Valproic acid
   E. Levetiracetam

2. A 26-year-old female had frequent episodes of focal left hand shaking followed by generalized tonic–clonic seizure activity. On two occasions, she broke her jaw and her right shoulder. Routine EEG is normal, and brain imaging is unremarkable. Which would be most appropriate antiepileptic drug for this patient?

   A. Oxcarbazepine
   B. Lamotrigine
   C. Topiramate
   D. Phenobarbital
   E. Valproate

3. Which is true about animal models of epilepsy?

   A. The PTZ model helps predict efficacy against absence seizures
   B. The kindling model typically has spontaneously recurring seizures
   C. The audiogenic seizure model in mice predicts efficacy against focal seizures
   D. Levetiracetam was effective in both MES and PTZ models
   E. The 6 Hz model is predictive of efficacy against absence seizures

4. The cooperative VA studies showed:

   A. Carbamazepine and phenytoin were overall more efficacious than phenobarbital and primidone
   B. Phenobarbital and primidone were less well tolerated than carbamazepine and phenytoin
   C. Phenobarbital was more efficacious than primidone
   D. Primidone was better tolerated than phenobarbital
   E. Primidone was more efficacious than phenobarbital

5. Which of the following is not a 1,4 benzodiazepine?

   A. Diazepam
   B. Clonazepam
   C. Lorazepam
   D. Clobazam
   E. Clorazepate

6. Which of the following benzodiazepines has important active metabolites?

   A. Clonazepam
   B. Clobazam
   C. Diazepam
   D. B and C
   E. All the above

7. Dupuytren's contractures and plantar fibromatosis are chronic adverse effects of

   A. Tiagabine
   B. Phenobarbital
   C. Vigabatrin
   D. Clobazam
   E. Clorazepate

8. Simvastatin efficacy is reduced with:

   A. Lamotrigine
   B. Carbamazepine
   C. Levetiracetam
   D. Pregabalin
   E. Ezogabine

9. An adolescent boy with epilepsy presents with overheating and fever following exercise. The likely cause is as follows:

   A. Levetiracetam
   B. Lamotrigine
   C. Zonisamide
   D. Valproate
   E. Phenobarbital

10. The following antiepileptic drug is FDA approved for once-daily dosing:

    A. Perampanel
    B. Zonisamide
    C. Ethosuximide
    D. Clobazam
    E. Topiramate

11. Urinary retention is most likely to occur with

    A. Perampanel
    B. Levetiracetam
    C. Ezogabine
    D. Felbamate
    E. Pregabalin

12. Which is not likely to happen with the addition of felbamate?

    A. Increased phenobarbital level
    B. Increased phenytoin level
    C. Increased carbamazepine level
    D. Increased valproate level
    E. Toxicity related to carbamazepine epoxide

13. A 4-month-old infant is diagnosed with infantile spasms. He did not respond to 2-week course of ACTH at 150 units/m^2. Which of the following antiepileptic medications would you use next?

    A. Vigabatrin
    B. Levetiracetam
    C. Topiramate
    D. Clobazam
    E. Tiagabine

14. Irritability is most common with the following AEDs:

    A. Lamotrigine and oxcarbazepine
    B. Perampanel and levetiracetam
    C. Felbamate and zonisamide
    D. Phenobarbital and primidone
    E. Valproate and ethosuximide

15. Insomnia is most likely with which of the following?

    A. Gabapentin
    B. Pregabalin
    C. Ezogabine
    D. Perampanel

E. Felbamate

16. The mechanism of action of levetiracetam is as follows:

A. Binding to the synaptic vesicle protein
B. Binding to the GABA A receptor
C. Antagonism of NMDA receptors
D. Blocking of sodium channels
E. Opening of potassium channels

17. Which AED is an NMDA receptor antagonist?

A. Perampanel
B. Topiramate
C. Phenobarbital
D. Zonisamide
E. Felbamate

18. Q-T interval prolongation is a potential adverse effect of:

A. Levetiracetam
B. Ezogabine
C. Lacosamide
D. Vigabatrin
E. Tiagabine

19. All is true about perampanel except:

A. Weight gain
B. Short half-life
C. Selective AMPA antagonist
D. Black box warning on behavioral abnormalities
E. High protein bounding

20. In general, antiepileptic drug levels in pregnancy:

A. Increase
B. Decrease
C. No changes
D. Antiepileptic drugs should not be used during pregnancy
E. None of the above

21. The optimal dosage of folic acid in high-risk pregnant patients with the history of major congenital malformations is as follows:

A. 0.4 mg/day
B. 1 mg/day
C. 2 mg/day
D. 5 mg/day
E. No need for folic acid

22. Following are all risk factors for the development of epilepsy in elderly patients except:

A. REM behavior disorder
B. Hypertension
C. Depression
D. Cardiovascular disease
E. Obstructive sleep apnea

23. A 19-year-old neurologically challenged male had ongoing complex partial seizures in spite of a therapeutic dose of depakote. The addition of topiramate reduced his seizures significantly. However, his caregiver reports progressive somnolence and decreased responsiveness. The next most appropriate step is as follows:

A. Urgent EEG to rule out subclinical status
B. Lumbar puncture
C. Urgent brain imaging
D. Ammonia level
E. Topiramate blood level

24. All of these AEDs are highly protein-bound except

A. Carbamazepine
B. Valproate
C. Tiagabine
D. Phenytoin
E. Lamotrigine

25. Which antiepileptic drug has an FDA indication for myoclonic seizures?

A. Pregabalin
B. Valproate

C. Ethosuximide
D. Levetiracetam
E. Lamotrigine

26. Physiologic changes with advanced age include all of the following except:

A. Decreased renal clearance
B. Decreased hepatic clearance
C. Decreased and erratic drug absorption
D. Increased protein binding
E. Increased blood levels

27. Progesterone therapy was effective in the following patient subgroup:

A. Patients with catamenial epilepsy with seizure exacerbation at ovulation
B. Postmenopausal women
C. Women with catamenial epilepsy and seizure exacerbation around menstruation
D. Women with anovulatory cycles
E. All women with catamenial epilepsy

28. Which of the following is an animal model of drug-resistant epilepsy?

A. 6-Hz psychomotor seizures
B. PTZ (pentylenetetrazole)
C. Maximal electroshock (MES)
D. Penicillin
E. All of the above

29. Which of the following is true about catamenial epilepsy?

A. Seizure cluster around ovulation in C1 pattern
B. Seizure cluster before and during menses in C2 pattern
C. Seizure cluster in anovulatory cycles in C3 pattern
D. Estrogen is anticonvulsant
E. Progesterone is proconvulsant

30. Which of the following is not true about brivaracetam?

A. Analog of levetiracetam
B. Less potent than levetiracetam
C. Binds to SV2A
D. Blocks sodium channels
E. All of the above is true about brivaracetam

31. A 77-year-old man with newly diagnosed epilepsy started having tremors suspicious for Parkinson's disease. The likely cause:

A. Carbamazepine
B. Valproate
C. Phenytoin
D. Clonazepam
E. Ethosuximide

32. All of the following are animal models of partial epilepsy except?

A. Pentylenetetrazole
B. Kindling
C. Pilocarpine
D. 6-Hz psychomotor seizures
E. Poststatus epilepticus model in rats

33. The visual field changes with vigabatrin:

A. Are reversible
B. Represent an optic neuropathy
C. Are related to dose and duration of treatment
D. Typically occur within 2 months of treatment
E. Are less likely when vigabatrin is combined with a sodium channel blocking drug

34. Which of the following is true about tiagabine?

A. Can be given once daily at bedtime
B. Is effective against absence seizures

C. Is approved as initial monotherapy
D. Increases GABA levels at the synapse
E. Is associated with retinal toxicity

35. Which is not true of felbamate idiosyncratic toxicity?

A. Aplastic anemia has not been reported below age 13
B. Aplastic anemia and hepatic failure are most likely within one month of initiating therapy
C. Underlying autoimmune disease increases the risk of aplastic anemia
D. Aplastic anemia is highly unlikely to occur after one year of therapy
E. The risk of aplastic anemia is estimated at one in 5000 exposures

36. Which of the following is unlikely to exacerbate absence seizures?

A. Carbamazepine
B. Oxcarbazepine
C. Valproate
D. Tiagabine
E. Vigabatrin

37. Which of the following antiepileptic drug is not known to modulate GABA?

A. Phenobarbital
B. Tiagabine
C. Clonazepam
D. Pregabalin
E. Topiramate

38. For which of the following conditions is the ketogenic diet indicated?

A. Primary carnitine deficiency
B. Pyruvate carboxylase deficiency
C. Pyruvate dehydrogenase deficiency
D. Porphyria
E. None of the above

39. Incidence of epilepsy in institutionalized patients with intellectual developmental disability is as follows:

A. 5%
B. 9%
C. 21%
D. 32%
E. 80%

40. Which antiepileptic requires monitoring of visual fields during treatment?

A. Clobazam
B. Vigabatrin
C. Tiagabine
D. Primidone
E. Clorazepate

41. Screening for potential psychosocial barriers to the safety and success of the ketogenic diet should take place before initiation of therapy. Which of the following features makes the ketogenic diet a better/easier treatment option?

A. Presence of a gastrostomy tube
B. Severe failure to thrive/inability to maintain adequate nutrition
C. Potential surgically resectable seizure focus
D. Multiple siblings in an unstructured home environment
E. Available premanufactured formulas

42. Prolonged episodes of altered responsiveness are most likely with:

A. Tiagabine
B. Perampanel
C. Vigabatrin
D. Clobazam
E. Pregabalin

43. Screening for disorders of fatty acid metabolism should be performed prior to initiation of the ketogenic diet. Specifically, this testing could include which of the following?

    A. Complete blood count and complete metabolic panel including liver function tests and BUN and creatinine
    B. Acylcarnitine profile, urine organic acids, and carnitine
    C. CSF glucose, lactate, folate metabolites, amino acids, and neurotransmitters
    D. Kidney ultrasound and nephrology consult

44. A 23-year-old man with idiopathic generalized epilepsy was initially maintained on lamotrigine. Valproate was added as adjunct therapy. Which of the following effects may result from interaction between these drugs?

    A. Lamotrigine toxicity because of glucuronidation inhibition
    B. Decreased lamotrigine efficacy due to inhibition of cytochrome 2C9 and 2C19
    C. Decreased valproate efficacy due to induction of CYP2C9
    D. Increased risk of liver disease
    E. Valproate toxicity due to inhibition of its β-oxidation

45. With rare exceptions, the ketogenic diet is initiated during an inpatient hospitalization. Complications during the initiation period could include all of the below, except:

    A. Vomiting due to hypoglycemia, dehydration, excessive acidosis, constipation, or exacerbation of gastroesophageal reflux
    B. Precipitation of deterioration in a patient with an undiagnosed disorder of fat metabolism
    C. Excessive metabolic acidosis in a patient also treated with a carbonic anhydrase inhibitor
    D. Deficiency of calcium and vitamin D, leading to bone mineralization loss
    E. Encephalopathy due to hypoglycemia, dehydration, and excessive acidosis

46. Epilepsy is most commonly associated with:

    A. Dementia
    B. Stroke
    C. Birth defect
    D. Bipolar disorder
    E. Psychosis

47. There is a need for more research and data regarding the incidence and prevention of long-term complications in patients who have been on the ketogenic diet for long durations, for instance greater than 5 years. Which of the following tests would be reasonable to perform in such a patient, who is otherwise asymptomatic?

    A. Blood draw for amylase, lipase
    B. Renal ultrasound looking for renal stone
    C. Abdominal X-ray for stool
    D. Blood draw for 25-hydroxy-vitamin D and consideration of bone density scan
    E. CRP

48. The literature supports the probable benefit of the ketogenic diet in which of the following conditions?

    A. Benign myoclonus of infancy
    B. Juvenile myoclonic epilepsy
    C. Glucose transporter protein 1 deficiency
    D. Pyruvate carboxylase deficiency

49. A 36-year-old male from Nepal is evaluated for a generalized tonic seizure. Few weeks ago, he started taking rifampin and isoniazid for a positive tuberculin test. His neurological examination, EEG, and brain MRI are all normal. What is the likely mechanism responsible for his seizure?

    A. Reversible inhibition of GABA reuptake
    B. Impaired pyridoxine synthesis

C. Activation of glutamate
D. Hypermagnesemia
E. Prolactin surge

50. A trial comparing valproate, ethosuximide, and lamotrigine for absence demonstrated

A. All three AEDs were equally effective
B. Valproate and ethosuximide were more effective than lamotrigine
C. Valproate was better tolerated than lamotrigine
D. Valproate had less neuropsychological adverse effects than ethosuximide
E. Ethosuximide was more effective than valproate

51. Which of the following statements accurately conveys the typical recommendations (by consensus) for discontinuation of the ketogenic diet?

A. Discontinue the ketogenic diet if it seems ineffective by 1 month following initiation
B. Wait for 3 months following initiation before deciding to discontinue the diet
C. Abrupt discontinuation is preferred over gradual weaning over 2–3 months
D. Wean after 1 year of seizure freedom

52. A 23-year-old male from El Salvador is seen for new onset–partial seizures. His brain MRI shows multiple ring-enhancing lesions. The best treatment is as follows:

A. Ceftriaxone
B. Acyclovir
C. Albendazole and steroids
D. Natalizumab
E. Aspirin

53. Which is not true of valproate teratogenicity?

A. Valproate exposure during gestation is associated with decreased verbal IQ
B. Valproate exposure during gestation is associated with autism
C. Valproate teratogenicity is dose-dependent
D. Folate supplementation reduces valproate-associated teratogenicity rate to control value
E. Malformation rate with valproate exposure is elevated with both monotherapy and polytherapy

54. A 58-year-old man was started on phenytoin for weekly partial seizures. His seizure frequency dramatically decreased but has not reached seizure freedom. He developed postherpetic neuralgia in the left abdominal dermatome 6 months ago with persistent pain. He also had a history of diabetes and a history of a previous lacunar infarct. Attempts to increase the dose of phenytoin resulted in intolerable drowsiness. Which of the following would be the most appropriate adjunct therapy in this patient?

A. Carbamazepine
B. Lamotrigine
C. Pregabalin
D. Levetiracetam
E. Lacosamide

55. Which is incorrect of valproate and phenytoin protein binding?

A. Both phenytoin and valproate are highly protein-bound
B. When used together, phenytoin free fraction is increased
C. Valproate protein binding is increased at higher concentration
D. Phenytoin free fraction is increased in low protein states
E. Intravenous valproate may displace warfarin from protein binding

56. The potential benefit of the ketogenic diet has been suggested for and is being investigated in all of the following except:

A. Amyotrophic lateral sclerosis
B. Traumatic brain injury
C. Alzheimer's disease
D. Brain tumors
E. Epileptologists studying for the epilepsy boards

57. Which of the following antiepileptic drugs does not affect bone health in women with epilepsy?

A. Topiramate
B. Lamotrigine
C. Phenytoin
D. Phenobarbital
E. All of the above

58. All of the following AEDs are appropriate to use in elderly with epilepsy except:

A. Lamotrigine
B. Gabapentin
C. Levetiracetam
D. Topiramate
E. Pregabalin

59. Faciobrachial dystonic seizures are an early manifestation of:

A. Anti-NMDA antibody limbic encephalitis
B. Anti-LGI1 antibody limbic encephalitis
C. Anti-GAD antibody limbic encephalitis
D. Hashimoto's encephalitis
E. Landau–Kleffner syndrome

60. Which of the following does not cause phenytoin accumulation?

A. Amiodarone
B. Carbamazepine
C. Cimetidine
D. Fluconazole
E. Felbamate

61. Which of the following does not cause carbamazepine accumulation?

A. Erythromycin
B. Ceftriaxone
C. Grapefruit juice
D. Fluoxetine
E. Propoxyphene

62. Estrogen affects seizure control by:

A. Enhancing inhibition at GABA A receptor
B. Increasing GABA synthesis
C. Accentuating the action of glutamate
D. Inhibiting synthesis of GABA
E. Estrogen in protective against seizures

63. In patients with epilepsy, the yield of first routine EEG is as follows:

A. 25%
B. 50%
C. 75%
D. 100%
E. EEG is not needed for diagnosis

64. Autism has been associated with the intrauterine exposure to:

A. Phenobarbital
B. Lamotrigine
C. Phenytoin
D. Carbamazepine
E. Valproate

65. Which has the shortest half-life for parent drug and active metabolite?

A. Diazepam
B. Lorazepam
C. Clorazepate
D. Clonazepam
E. Clobazam

66. The half-life of the following AED is prolonged when the serum concentration is above the recommended therapeutic range:

A. Phenobarbital
B. Carbamazepine
C. Phenytoin

D. Valproate
E. Oxcarbazepine

67. The half-life of the following AED becomes shorter after two weeks of treatment:

A. Phenobarbital
B. Carbamazepine
C. Phenytoin
D. Valproate
E. Oxcarbazepine

68. A 42-year-old man is brought to the ED because of a generalized tonic–clonic seizures. He has no previous history of seizures, and his MRI is normal. His EEG reveals left temporal sharp waves. His seizure recurrence rate is as follows:

A. 10%
B. 20%
C. 50%
D. 80%
E. 100%

69. Which of the following is incorrect about primidone?

A. Same acute adverse effects as phenobarbital
B. Similar chronic adverse effects as phenobarbital
C. The primidone dose needed to produce a certain phenobarbital level is about 5 times that of phenobarbital
D. Similar interactions to phenobarbital
E. Produces two active metabolites

70. Which of the following antiepileptic drugs requires dose adjustment in a patient with newly diagnosed creatinine of 4 mg/dl?

A. Phenytoin
B. Carbamazepine
C. Phenobarbital
D. Gabapentin
E. Perampanel

71. All of the following features are associated with higher seizure recurrence except:

A. Focal onset
B. Cluster seizures
C. Status epilepticus
D. Intermittent temporal slow activity
E. Abnormal brain imaging

72. Oral contraceptive medications can be affected by all except:

A. Oxcarbazepine
B. Phenytoin
C. Primidone
D. Topiramate
E. Levetiracetam

73. Ophthalmological adverse effects can be seen with:

A. Rufinamide, ezogabine, and vigabatrin
B. Ezogabine, vigabatrin, and topiramate
C. Zonisamide, topiramate, and felbamate
D. Vigabatrin, perampanel, and zonisamide
E. Clobazam, rufinamide, and pregabalin

74. An adolescent boy treated for seizures suffers from a heatstroke during a soccer game. The boy is most likely taking:

A. Ezogabine
B. Pregabalin
C. Zonisamide
D. Valproate
E. Carbamazepine

75. Risk of seizure recurrence after first symptomatic seizure is highest in:

A. Acute Stroke
B. Remote stroke
C. Acute head trauma
D. Remote head trauma
E. All of the above carry the same seizure recurrence rate

76. Which is not true about vigabatrin's visual defect?

A. Most visual field defects are irreversible
B. Central vision is most affected
C. Risk of visual defect increases with the treatment duration
D. Periodic eye examination may detect early damage
E. May occur in up to one-third of patients

77. All of the following antiepileptic drugs are considered to be broad spectrum except:

A. Valproate
B. Zonisamide
C. Pregabalin
D. Lamotrigine
E. Felbamate

78. Clinical trials have been completed or are underway for all but one of the following treatments for acute repetitive seizures:

A. Intramuscular diazepam by autoinjector
B. Intranasal diazepam
C. Intranasal lorazepam
D. Intranasal midazolam
E. Buccal midazolam

79. All but one of the following has an extended release preparation:

A. Topiramate
B. Zonisamide
C. Levetiracetam
D. Oxcarbazepine
E. Lamotrigine

80. As compared to older AEDs, newer AEDs tend to have:

A. Similar safety
B. Better efficacy
C. Lower drug–drug interaction
D. Lower cost
E. Higher protein binding

81. Which antiepileptic drug blocks T-type calcium channel:

A. Ethosuximide and valproate
B. Carbamazepine and valproate
C. Felbamate and pregabalin
D. Valproate and felbamate
E. Lamotrigine and valproate

82. Before starting a Taiwanese man on carbamazepine for trigeminal neuralgia, which genetic testing is recommended:

A. HLA-B 23
B. HLA-A 322
C. HLA-B 1502
D. HLA-A 150
E. No need for genetic testing

83. Which of the following is known to be an inducer of the cytochrome P450 (CYP):

A. Aspartame
B. White chocolate
C. Aloe Vera
D. Yohimbine
E. St John's wort

84. In seizure-free patients, seizure recurrence after antiepileptic drug withdrawal is lower in:

A. Children
B. Adults
C. Men
D. Women
E. Same in all of the above

85. In December 2006, at the American Epilepsy Society meeting, the Charlie Foundation commissioned a panel of 26 pediatric epileptologists and dietitians from 9 countries with expertise in the ketogenic diet, in order to create a consensus statement regarding the clinical management of the ketogenic diet. Which of the following statements accurately conveys the

International Ketogenic Diet Study Group's recommendation?

A. The ketogenic diet should be considered in a patient whose epilepsy is controlled by a single medication, but whose family prefers "natural" therapies
B. The ketogenic diet should be considered only as a last resort, since it is hard to administer, is unpalatable, and there is no data from randomized controlled trials to support it
C. The ketogenic diet should be considered in a child who has failed 2–3 anticonvulsant therapies, as long as he/she is older than 1 year and younger than 12 years of age
D. The ketogenic diet should be considered in a child who has failed 2–3 anticonvulsant therapies, regardless of age or gender

86. Brivaracetam has the following mechanism of action:

A. Potassium channel opening
B. Blocking of sodium channels
C. Binding to the synaptic vesicle protein
D. Binding to the GABAA receptor
E. Binding to the synaptic vesicle protein and blocking of sodium channels

87. There has been growing interest and confidence in the use of the ketogenic diet and subsequently a growing body of literature. Which of the following statements is true?

A. Four randomized controlled trials showed that at least 38% of patients had a 50% reduction in seizures compared to controls at 3 months, with this response maintained for up to a year
B. A meta-analysis has shown that a third of all patients on the ketogenic diet may become seizure-free
C. A recent retrospective, multicenter study assessing the ketogenic diet for various epilepsy syndromes showed that only 20% had a greater than 75% decrease in seizures
D. There are currently no randomized controlled trials published on the efficacy of dietary therapies in epilepsy treatment

88. Which antiepileptic drug should be avoided in a patient with known sulfa drug allergy?

A. Pregabalin
B. Zonisamide
C. Carbamazepine
D. Vigabatrin
E. Lamotrigine

89. The following statement is false:

A. A common ratio of the ketogenic diet is 4 g of fat to 1 g of protein plus carbohydrate (4:1)
B. In a 4:1 ratio ketogenic diet, approximately 90% of energy comes from fat
C. A fasting period during initiation of the ketogenic diet is necessary to achieve ketosis
D. The modified Atkins diet is approximately a 1:1 ratio
E. In the low glycemic index treatment, foods are chosen which produce slower/steadier changes in blood glucose

90. A 72-year-old man is seen in clinic for a new diagnosis of epilepsy, with recurrent partial seizures secondary to a right MCA ischemic infarct. His medical history includes chronic afib (for which he takes warfarin), osteoporosis, and a history of kidney stones. Which of the following is the most appropriate antiepileptic medication for this patient?

A. Carbamazepine
B. Levetiracetam
C. Primidone
D. Ethosuximide
E. Zonisamide

91. In addition to the traditional ketogenic diet, alternative dietary therapies have been developed for epilepsy treatment. Which of the following is an alternative dietary therapy for epilepsy treatment?

    A. The low glycemic index treatment
    B. The Atkins diet
    C. The Paleo diet
    D. The short-chain triglyceride diet

92. The blood levels of which antiepileptic will not be altered after the addition of phenytoin?

    A. Felbamate
    B. Topiramate
    C. Zonisamide
    D. Tiagabine
    E. Pregabalin

Answers

1. (E). In this case, levetiracetam is the most appropriate choice for treating juvenile myoclonic epilepsy in a woman of childbearing age. Pregabalin and carbamazepine are typically efficacious against partial–onset seizures and may potentially exacerbate generalized seizures, notably absence and myoclonic seizures. Lacosamide lacks evidence to support its use in this condition, while valproate should be avoided in women of childbearing age due to significant risk of teratogenicity.
2. (A). The clinical scenario describes partial seizures with secondarily generalization. Oxcarbazepine is an appropriate drug for treating this condition. Lamotrigine and topiramate would not be a good choice due to the slow titration schedule. Phenobarbital and valproate must be avoided in women of childbearing age.
3. (A). The pentylenetetrazole (PTZ) model is predictive of efficacy against absence seizures, although some effective drugs may be missed by this model. The kindling model does not typically have spontaneous seizures. The audiogenic seizure model is predictive of efficacy against generalized tonic–clonic seizures. Levetiracetam efficacy was missed by the maximal electroshock model (MES) and PTZ models. The 6 Hz model is a model of pharmacoresistant epilepsy.
4. (B). In the first VA cooperate, all four antiepileptic drugs compared had equal efficacy, but phenobarbital and primidone were less well tolerated.
5. (D). In contrast to the listed benzodiazepines, Clobazam is a 1,5 benzodiazepine; the brand name "On-fi" is derived from "One-five."
6. (D). Diazepam and clobazam have important active metabolites (desmethyldiazepam and desmethylclobazam). Clonazepam is converted to an inactive metabolite.
7. (B). Connective tissue diseases in particular Dupuytren's contractures and plantar fibromatosis may be seen with long-term phenobarbital use.
8. (B). Enzyme-inducing antiepileptic medications can induce the metabolism of other concomitant medications such as carbamazepine and phenytoin and can lower the serum concentration of simvastatin by about 50%.
9. (C). Both zonisamide and topiramate are mild carbonic anhydrase inhibitors. The resulting decreased sweat may lead to overheating and possible heatstrokes especially in children.
10. (A). While some of the other antiepileptic drugs have a long half-life (such as zonisamide, clobazam, and ethosuximide), they do not have FDA approval for once-daily dosing. The main reasons are the potential sedation and cognitive or gastrointestinal side effects that may incur from high doses given once daily.
11. (C). Ezogabine may be associated with urinary retention in about 2% of patients. It is generally reported within the first six months of treatment, but can also be observed later.
12. (C). Felbamate reduces carbamazepine level through induction of CYP3A4, but may

cause accumulation of carbamazepine epoxide leading to carbamazepine toxicity.

13. (A). Treatment of infantile spasms should be started as soon as the diagnosis is confirmed. The first-line recommended therapy includes high-dose ACTH or vigabatrin. If the cause is tuberous sclerosis, vigabatrin tends to be more effective than ACTH.
14. (B). Among the listed antiepileptic drugs, both levetiracetam and perampanel are more associated with irritability, which may limit their use.
15. (E). In contrast to most antiepileptic drugs which are sedating, felbamate and lamotrigine are stimulating drugs and may be associated with insomnia.
16. (A). Levetiracetam was first approved in USA in 1999. Its mechanism of action is binding to the synaptic vesicle protein SV2A. This seems to result in nonspecific decrease in neurotransmitter release. There is a functional correlation between SV2A binding affinity and anticonvulsant potency of levetiracetam analogues.
17. (E). Felbamate is anti-NMDA receptor antagonist. Topiramate and perampanel are AMPA antagonists.
18. (B). Q-T prolongation may occur with the use of ezogabine, while P-R prolongation may occur with the use of lacosamide.
19. (B). All of the listed properties are true about perampanel except for a short half-life. Perampanel's half-life is long, about 105 h on average.
20. (B). Changes in AED pharmacokinetics are common during pregnancy due to increased clearance most prominent for lamotrigine, but other AEDs show substantially more modest increases in clearance. Seizures worsen when AED levels fall >35% from preconception levels. Regular monthly monitoring of AED levels during pregnancy is recommended to adjust the dose to prevent seizure recurrence.
21. (D). For high-risk pregnant patients with previous history of major teratogenicity, higher folic acid dose of 4–5 mg/day is recommended. It is also recommended to start folic acid 3–6 months before conception.
22. (A). REM behavior disorder is a risk factor for degenerative neurologic disease but not for epilepsy while all the other choices are established risk factors for developing epilepsy in the elderly.
23. (D). The addition of topiramate to valproate may cause accumulation of ammonia, which could explain the increased responsiveness and somnolence.
24. (E). Lamotrigine protein binding is low (55%) compared to the other choices that have higher protein binding (>70%) causing high potential for drug–drug interactions.
25. (D). Levetiracetam is indicated as adjunctive treatment for myoclonic seizures.
26. (D). With advancing age, several physiological changes have a direct effect on drug pharmacokinetics. These include decreased renal and hepatic clearance, reduced and erratic absorption, and decreased protein binding. All these changes can result in higher antiepileptic blood levels with higher risks of adverse effects and toxicity.
27. (C). Progesterone can be effective in the subgroup of women with catamenial epilepsy who have the C1 pattern, with seizure exacerbations around menstrual periods.
28. (A). The 6-Hz psychomotor seizure model in mice and the methylazoxymethanol acetate (MAM) rat model of cortical dysplasia serve as a model of pharmacoresistant epilepsy.
29. (C). In catamenial epilepsy, seizures tend to follow a cyclical pattern related to the menstrual cycle. There are three cyclical patterns of catamenial epilepsy: C1 pattern where seizures increase in frequency just before and during menses, C2 pattern where seizures increase around the time of ovulation, and C3 pattern where seizures occur with anovulatory cycles. Catamenial epilepsy is thought to be related to progesterone and estrogen fluctuations. Estrogen appears to be proconvulsant, and progesterone appears to be anticonvulsant.
30. (B). Brivaracetam is an analog drug of levetiracetam which has a sodium blocking

mechanism in addition to its SV2A binding. In general, it exhibits a similar profile to levetiracetam general but with a higher potency (about 10 times higher).

31. (B). Valproate can produce tremors and Parkinsonism that is usually dose-dependent and more common in the elderly. It is usually reversible with reduction or elimination of the drug.
32. (A). Pentylenetetrazole (PTZ) is an animal model of absence seizures, while the other listed animal models are specific for partial seizures.
33. (C). Vigabatrin visual toxicity is a slowly progressive, usually irreversible retinopathy that is related to dose and duration of treatment.
34. (D). Tiagabine has a short half-life; it is a narrow-spectrum agent for partial (focal) seizures, approved only as adjunctive therapy; it increases GABA levels by inhibiting its reuptake in the synapse.
35. (A). Aplastic anemia and hepatic failure are unlikely within one month of initiating felbamate therapy. Known risk factors include prior cytopenia, allergy to or significant toxicity with other antiepileptic drugs, and underlying autoimmune disease.
36. (C). Valproate is a wide-spectrum antiepileptic drug effective against absence seizures; the other listed AEDs may exacerbate absence seizures.
37. (D). Unlike other listed antiepileptic drugs, pregabalin does not interact with GABA receptors.
38. (C). In pyruvate dehydrogenase deficiency, pyruvate cannot be metabolized into acetyl-coA. The ketogenic diet bypasses this step and provides ketones as an alternative fuel for the brain. All of the other choices are contraindications to the ketogenic diet. Long-chain fatty acids are transported across the mitochondrial membrane by carnitine (helped by CPT I and II and carnitine translocase); once in the mitochondrion, fatty acids are beta-oxidized to 2 carbon units of acetyl-CoA that can then enter the tricarboxylic acid cycle, to be used for energy production or ketone body production. A shift to use of fats as the primary energy source in disorders of fat metabolism would precipitate deterioration. Lack of carbohydrates would exacerbate acute intermittent porphyria.
39. (D). Incidence of epilepsy increases with the severity of mental retardation (MR), but it varies depending on epidemiological methodologies as well. In population-based studies, 21% of those with mild MR had epilepsy. Another study reported epilepsy in 11% of subjects with mild MR and in 23% in those with severe MR. On the other hand, in institution-based studies including patients with severe MR, the prevalence of epilepsy varies from 32 to 34%.
40. (B). Vigabatrin use is associated with visual field constriction in about one-third of patients. Periodic visual field monitoring is required for the prescription of vigabatrin.
41. (E). Premanufactured ketogenic formulas are available, ensuring more accuracy of measurements and minimizing barriers such as food refusal or aversions.
42. (A). Prolonged encephalopathy or nonconvulsive status epilepticus may be seen as a dose-related adverse effect of tiagabine.
43. (B). This should adequately screen for disorders of fatty acid metabolism including carnitine deficiency, CPT I or II deficiency, carnitine translocase deficiency, and the beta-oxidation defects. The other choices are also reasonable considerations for preinitiation screening, but for other conditions.
44. (A). Valproate inhibits uridine glucosyl transferase, the enzyme that metabolizes lamotrigine. Initiation of valproate therapy will result in lamotrigine toxicity. This addition usually requires immediate reduction of the dose of lamotrigine by about 50%.
45. (D). This would be a longer-term complication. Osteoporosis in the ketogenic diet is contributed to by calcium/vitamin D deficiency as well as acidosis.

46. (B). Most common known etiology for epilepsy is cerebrovascular disease at 11%, followed by neurologic deficits from birth, mental retardation, or cerebral palsy at 8%.
47. (D). Long-term complications in children on the ketogenic diet for >2 years have not been systematically reviewed. There may be increased fractures and kidney stones. Symptoms, however, would be expected in the setting of pancreatitis, renal calculi, or severe constipation. Specific guidelines for monitoring of bone health, however, still need to be delineated.
48. (C). In GLUT1 deficiency syndrome, glucose transport across the blood-brain barrier is impaired. Since the ketogenic diet provides ketones that bypass the metabolic defect, serving as an alternative fuel to the brain, the ketogenic diet is the treatment of choice for this syndrome. Such epilepsy treatment is not necessary for benign myoclonus of infancy. Although the ketogenic diet may be particularly helpful for generalized epilepsies, there has not been data supporting its use in JME as of yet. The ketogenic diet is contraindicated for pyruvate carboxylase deficiency, which would impair tricarboxylic acid cycle function and energy production in the ketogenic diet.
49. (B). Isoniazid is an antibiotic commonly used in treating tuberculosis. It may trigger de novo seizures by competing with the mechanism of pyridoxine and its metabolites. Pyridoxine is an essential cofactor for many enzymatic reactions, including GABA an inhibitory neurotransmitter.
50. (B). A large, multicenter, double-blind, randomized, controlled trial to compare the efficacy, tolerability, and neuropsychological effects of ethosuximide, valproic acid, and lamotrigine favored ethosuximide. After 16 weeks of therapy, the freedom-from-failure rates for ethosuximide and valproic acid were similar and higher than the rate for lamotrigine. However, attentional dysfunction was more common with valproic acid than with ethosuximide. As a result, ethosuximide became the drug of choice for pure generalized absence seizures.
51. (B). Although the benefit on seizure control can be seen within 2 weeks after initiation (in 75% of children in one study), it is recommended that the ketogenic diet be continued for 3 months before deciding to continue or discontinue. Gradual weaning rather than abrupt discontinuation is preferred and may assist with determining whether there has been benefit of the ketogenic diet on seizure control. The recommendation is to discontinue after 2 years of seizure freedom, similar to the time period used for anticonvulsant medications.
52. (C). The likely diagnosis of this patient is neurocysticercosis. Epilepsy is the most common presentation (70% of patients) followed by headache, stroke, and psychiatric manifestations. It is more common in Southern America due to ingestion of uncooked egg-infected pork meat. Brain imaging often reveals several ring-enhancing lesions. Treatment consists of anthelminthic medication (such as albendazole) and steroids (e.g., dexamethasone) to suppress the inflammatory response induced by destruction of live cysticerci.
53. (D). Valproate exposure during pregnancy is associated with decreased verbal IQ and autism in offsprings. The teratogenic effect is dose-dependent and is irrespective of monotherapy or polytherapy use. Supplementation with folic acid is not sufficient to reverse the teratogenic effect.
54. (C). This patient is suffering from partial–onset seizures and postherpetic neuralgia for which pregabalin is FDA indicated for. Topiramate, lamotrigine, and levetiracetam have not yet been proven effective in this setting. Carbamazepine could be helpful but has the risk of drug interactions at the level of hepatic metabolism.
55. (C). Both valproate and phenytoin are highly protein-bound antiepileptic drugs. When used together or added to a highly protein-bound medication (such as warfarin), they can compete on protein binding,

increasing the free fraction of either drugs. Valproate free fraction decreases at higher concentrations due to protein saturation.

56. (E). The use of the KD is being investigated in several neurologic conditions beyond epilepsy and in traumatic brain injury, Alzheimer's disease, amyotrophic lateral sclerosis, autism, glial tumors, diabetic nephropathy, and Parkinson's disease. In addition, in development is 2-deoxy-(D)-glucose (2-DG), an agent which is a nonmetabolizable glucose analog that inhibits glycolysis.
57. (B). Lamotrigine does not affect bone health while phenytoin, phenobarbital, and topiramate can, because of their enzyme induction properties.
58. (D). Topiramate should be avoided in elderly because it has significant cognitive effects. These can significantly limit or compromise their intellectual reserves.
59. (B). Faciobrachial dystonic seizures are frequent brief dystonic seizures, typically affecting the ipsilateral arm and face found in association with LGI1 antibodies. Faciobrachial dystonic seizures often precede LGI1-antibody encephalitis. Recognition may lead to early diagnosis and early institution of immunotherapy, with improved outcome.
60. (A). Excluding carbamazepine, all the other four medications (amiodarone, cimetidine, fluconazole, and felbamate) may inhibit phenytoin metabolism and may cause phenytoin accumulation.
61. (B). Excluding ceftriaxone, all the other three medications (erythromycin, fluoxetine, and propoxyphene) and grapefruit juice may inhibit carbamazepine metabolism and may cause carbamazepine accumulation.
62. (D). Estrogen may be proconvulsant as it may reduce inhibition at the GABAA receptor and also inhibits the synthesis of GABA. On the other hand, progesterone may be anticonvulsant as it enhances inhibition at the GABAA receptor and increases GABA synthesis.
63. (B). In one pooled analysis of 1766 subjects, 51% of patients (pooled analysis) had an abnormal initial routine EEG. An additional 35% were identified to have abnormalities on the second sleep-deprived EEG. An abnormal EEG predicts a higher recurrence rate, and a normal EEG predicts a lower recurrence rate but does not rule out epilepsy.
64. (E). Maternal use of valproate during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring.
65. (B). Lorazepam and clonazepam do not have active metabolites; lorazepam has the shortest half-life.
66. (C). Phenytoin has nonlinear (saturable) kinetics; its half-life becomes longer after the saturation point which is usually within the recommended therapeutic range.
67. (B). Carbamazepine induces its own metabolism so that its half-life becomes shorter with continued use. The process of autoinduction is completed over 2–4 weeks.
68. (C). Recurrence rate after the first seizure averages around 30–40% by two years. The risk is higher (approaching 50–60%) when the EEG or brain MRI is positive.
69. (A). Primidone is converted into phenobarbital and phenylethylmalonamide (PEMA), which is also an active metabolite. Primidone has acute toxic reactions that are different from phenobarbital. It can produce transient drowsiness, dizziness, ataxia, nausea, and vomiting that can be debilitating. These reactions are present even before phenobarbital has appeared as a metabolite.
70. (D). Among the listed antiepileptic drugs, gabapentin is mostly excreted in urine; hence, its dose should be reduced according to the renal function.
71. (D). Overall, risk factors that carry higher seizure recurrence rate include focal-onset seizures, status epilepticus or cluster seizures at first seizure, abnormal EEG with epileptiform activity (sharp waves or spikes), and abnormal brain MRI or neurological examination.
72. (E). Levetiracetam does not interact with oral contraceptive medications, while all the

other choices can lower oral contraceptive medication levels.

73. (B). Antiepileptic drugs with potential ophthalmological adverse effects include topiramate (acute open-angle glaucoma), vigabatrin (peripheral visual constriction), and ezogabine (photoreceptor damage).
74. (C). Zonisamide and topiramate are mild carbonic anhydrase inhibitors and are known to decrease sweat production (causing anhydrosis or hypohydrosis). This may particularly be dangerous in patients with high physical activity, without compensatory hydration.
75. (B). Risk of seizure recurrence after first symptomatic seizure is about 33% in an acute (less than 7 days) stroke setting and 70% in a remote setting (more than 7 days). Risk of seizure recurrence after first symptomatic seizure is about 13% in the setting of acute TBI and 45% in the setting of remote TBI.
76. (B). Vigabatrin's visual field defect may affect about one-third of patients with variable severity. It primarily consists of peripheral visual field constriction. Risk factors include longer duration of treatment and higher dosage.
77. (C). All of the listed antiepileptic drugs are considered to be broad-spectrum except pregabalin which targets focal-onset seizures and may alternatively worsen generalized seizures especially myoclonic seizures.
78. (C). Several clinical trials were concluded or underway for (up to the current writing) the treatment of acute repetitive seizures. This includes intranasal diazepam and midazolam, intramuscular diazepam (by autoinjector), and buccal midazolam.
79. (B). Zonisamide does not have an extended release preparation, but has a prolonged half-life, obviating the need for such a preparation.
80. (C). Overall, when compared to older AEDs, newer AEDs tend to have better safety profile and tolerability (except for felbamate, vigabatrin) but comparable efficacy. They also tend to offer pharmacological advantages in regard to lower protein binding, minimal drug–drug interaction, and absence or minimal liver inhibition/induction. They are, however, more expensive than older AEDs.
81. (A). Ethosuximide and valproate are both known to block T-type calcium channels, which conveys efficacy against absence seizures.
82. (C). HLA allele B*1502 is a marker for carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis, particularly in Han Chinese. The FDA recommends genotyping all Asians for the allele before treatment initiation.
83. (E). St John's wort (or *Hypericum perforatum*) is a popular medicinal herb used for the treatment of depression. It is known to induce cytochrome P450 affecting the pharmacokinetics of several AEDs such as phenobarbital, carbamazepine, and phenytoin, resulting in adverse events.
84. (A). Overall, 11–41% of patients will relapse after antiepileptic drug discontinuation. The relapse rate tends to be lower in children ($\sim$20%) and higher in adults ($\sim$40).
85. (D). This is the consensus statement made by the International Ketogenic Diet Study Group.
86. (E). Brivaracetam binds to the synaptic vesicle protein as well as blocks sodium channels.
87. (A). Compared to the Cochrane Review performed in 2003, in which no RCTs were available, the Cochrane Review in 2012 reviewed 4 RCTs, which showed that at least 38% of patients had a 50% decrease in seizures at 3 months, with this positive response maintained for a year. Henderson CB et al's meta-analysis in 2006 showed 1/3 of patients having a >90% decrease in seizures. Caraballo R et al's multicenter retrospective study in 2011 showed 22% with seizure freedom and 56% with greater than 75% decrease.
88. (B). Zonisamide's chemical structure includes a sulfa moiety and thus should be

avoided in patients with known history of sulfa allergy.

89. (C). Traditionally, the patient would fast for 24–48 h. Once urine ketones appeared, the ketogenic diet would then be initiated gradually. Data support the fact that ketosis occurs without this initial fasting period and that tolerance of the diet may be higher without this fasting period.
90. (B). In this case, levetiracetam is the most appropriate choice for treating partial seizures. Ethosuximide is efficacious exclusively against absence seizures. Carbamazepine and primidone are liver enzyme inducers that can decrease warfarin efficacy and worsen osteoporosis. Zonisamide can precipitate kidney stones.
91. (A). The *Modified* Atkins diet, the *medium*-chain triglyceride diet, and the low glycemic index treatment are alternative dietary therapies developed for epilepsy treatment.
92. (E). Pregabalin is not metabolized and is not affected by phenytoin and other enzyme inducers.

Part V

Presurgical Evaluation and Epilepsy Surgery

Neuroimaging in Epilepsy

21

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Computed Axial Tomography

Computed tomography (CT) is widely available and used in emergency rooms. With multiple detector helical CT, high spatial resolution can be obtained in all dimensions allowing 3D reconstructions and operator selected multiplanar reformats in any plane. CT may be the only option in patients who cannot obtain MRI due to contraindications such as patients with pacemakers, defibrillators, specific metal prostheses (e.g., cochlear implants), ferromagnetic aneurysm clips, metallic foreign bodies within eyes, and shrapnel or bullets located near vascular structures. There may be other barriers in obtaining a conventional MRI in unstable or uncooperative patients, or patients with significant claustrophobia or morbid obesity. CT scans provide better details about bony structures and can easily detect hemorrhages, calcifications, strokes after 24 h, and large tumors. However, CT may fail to recognize commonly encountered lesions in patients with epilepsy such as hippocampal atrophy, hippocampal sclerosis, cortical dysplasias, or low-grade gliomas (LGG).

Magnetic Resonance Imaging (MRI)

MRI is a noninvasive test, which does not cause exposure to ionizing radiations and is considered safe across all age groups. It possesses excellent spatial resolution down to millimeters. MRI scanners with higher magnetic strengths (3-, 4-, or 7-Tesla) have proliferated over the past decade. The typical MRI epilepsy protocol includes multiplanar diffusion, T2-weighted, FLAIR, gradient echo, or susceptibility-weighted images of the brain. This protocol is supplemented with a 3D volumetric T1-weighted acquisition and oblique coronal plane FLAIR and T2-weighted images orthogonal to the long axis of the temporal lobes. Gadolinium administration may have utility in certain patient populations with seizures or when there is clinical suspicion for infectious, inflammatory, or neoplastic etiologies.

The presence or absence of lesion(s) and their location on brain MRI helps identify patients who may be good surgical candidates for lesionectomy, corticectomy, topectomy, corpus callosotomy, or hemispherectomy. For example, patients with medically refractory seizures and hippocampal sclerosis should be evaluated for

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either standard anterior temporal lobe resection or selective amygdalohippocampectomy. A lesionectomy of a cavernoma with or without corticectomy is a reasonable option if anti-seizure medications are not effective in controlling seizures. A more aggressive surgical approach, such as a functional hemispherectomy, may be warranted in patients with Sturge Weber syndrome, Rasmussen's encephalitis, large porencephalic cyst due to previous traumatic or ischemic insult, hemimegalencephaly, or Dyke–Davidoff–Masson syndrome (congenital or acquired). Neuroimaging may have a direct influence on therapeutic options that neurologists offer to their patients; e.g., a scan supporting a diagnosis of Tuberous Sclerosis (TS) in an infant with infantile spasms may justify the use of vigabatrin or m-TOR inhibitors over adrenocorticotrophic hormone (ACTH). Not all structural lesions are epileptogenic; therefore, it is prudent to correlate incidental findings on MRI with clinical history, seizure semiology, and EEG data. Some of the commonly encountered lesions in patients with epilepsy are described below.

Mesial temporal sclerosis: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy. Mesial TLE is more prevalent than neocortical epilepsy and often intractable to anti-seizure medications. The most common identifiable lesion on MRI brain is mesial temporal sclerosis (MTS; Fig. 21.1). In patients with TLE, subtle anatomic features of the medial temporal lobes and pathologies such as MTS or incomplete hippocampal inversion (Fig. 21.2) are best appreciated in an oblique coronal plane. This orientation is orthogonal to the long axis of the temporal lobe and reduces volume averaging problems for the thin laminar appearance of the hippocampus. Oblique coronal temporal high-resolution T2-weighted and FLAIR are the best sequences to diagnose MTS. This entity is characterized by (1) hippocampal atrophy, (2) increased T2 signal, and (3) abnormal morphology or loss of internal architecture of hippocampus. In 10% of the cases, MTS can be bilateral (Fig. 21.3). Secondary findings may include dilatation of the temporal horn of the lateral ventricle, loss of gray–white matter differentiation in the temporal lobe or decreased white matter in the adjacent temporal lobe (e.g., collateral eminence and temporal stem). There can be atrophy of the ipsilateral fornix and mammillary body (Fig. 21.4). High-resolution 3D T1WI are also useful when performing hippocampal volumetric analyses. However, paracentral lesions are more evident on axial sequences. Figure 21.5 shows a less common case of temporal lobe seizures from a temporal lobe encephalocele involving the subjacent sphenoid wing.

Neuronal migrational disorders: Heterotopias are neuronal migrational disorders (NMDs) where gray matter gets arrested as neurons migrate from periventricular regions toward pia during embryonic stages. High-resolution 3D T1-weighted volumetric imaging provides superior gray–white contrast that is critical to identify subtle cortical malformations in patients with epilepsy (Fig. 21.6). Higher magnetic strengths (3- or 7-Tesla) can detect very subtle cortical dysplasias.

Heterotopias can either be focal, nodular, or multifocal (as in TS) or preferentially involve one hemisphere as in hemimegalencephaly. Subcortical band heterotopias (SBH) are typically periventricular, bilateral nodular collections of gray matter with relatively smooth margins, which gives the appearance of a double cortex. Pachygyria is abnormal tissue in the right location with abnormal sulcation and gyration of the mantle which is typically > 8 mm thick (Fig. 21.7a). Polymicrogyria (PMG) is either two- or four-layered cortex, which is less than 5–7 mm (Fig. 21.7b). PMG is commonly associated with hypoxic-ischemic injury, or prenatal cytomegalovirus (CMV) infection.

FCDs are classified into three categories (Type I, II, and III) and further divided into various subtypes (Table 21.1). In a fully myelinated brain, FCD type I may be characterized by subtle blurring of the gray–white junction with typically normal cortical thickness, moderately increased white matter signal hyperintensities on T2/FLAIR images and decreased signal intensity on T1-weighted images. FCD Type IIA cortical dysplasias are characterized by marked blurring of

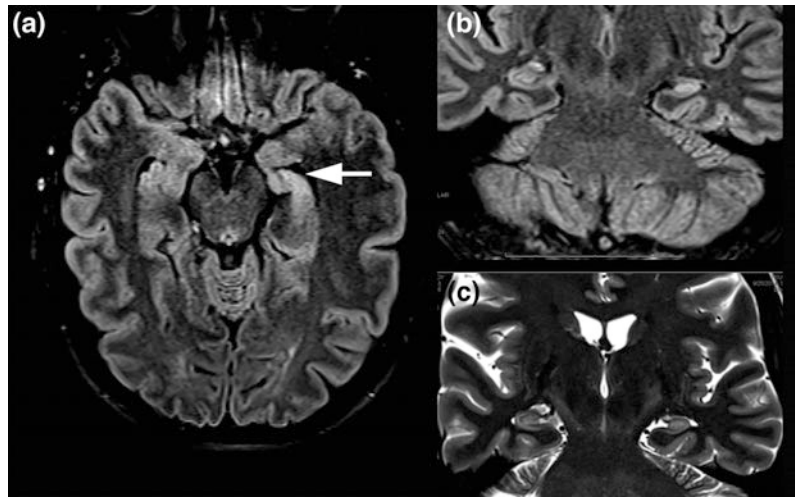

Fig. 21.1 Axial FLAIR (**a**) demonstrates enlargement of the left lateral ventricle temporal horn and the left hippocampus is relatively smaller and hyperintense compared to the contralateral side. Note that the lateral aspect of the left hippocampal body is abnormally smooth, and hippocampal head digitations are reduced (*arrow*). Companion coronal FLAIR (**b**) and T2-weighted MRI (**c**) demonstrate volume loss, hyperintensity, and subtle laminar blurring. These are classic MRI findings for left hippocampal sclerosis. If the amygdala also is involved, this can be classified as left mesial temporal sclerosis

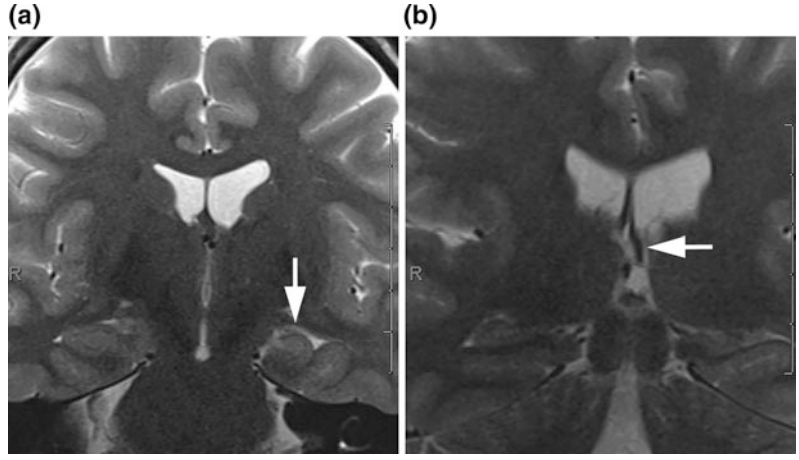

Fig. 21.2 Coronal T2-weighted images demonstrating globular left hippocampus (*arrow*, panel **a**) more vertical left collateral sulcus and low-lying left body of the fornix (*arrow*, panel **b**) consistent with incomplete hippocampal inversion (IHI). This patient also had left hippocampal sclerosis, but it remains controversial whether IHI predisposes to sclerosis or is just an incidental association

the gray–white junction on T1 and T2-FLAIR images due to hypomyelination or dysmyelination of the subcortical white matter with or without cortical thickening. Here, the increased white matter signal changes on T2, WI, and FLAIR images frequently tapers toward the ventricles (aka the "*transmantle sign*") which marks the involvement of radial glial neuronal bands. This radiological feature differentiates FCD from low-grade tumors. Type II lesions are more commonly seen outside the temporal lobe with predilection for the frontal lobes. Type III FCD is

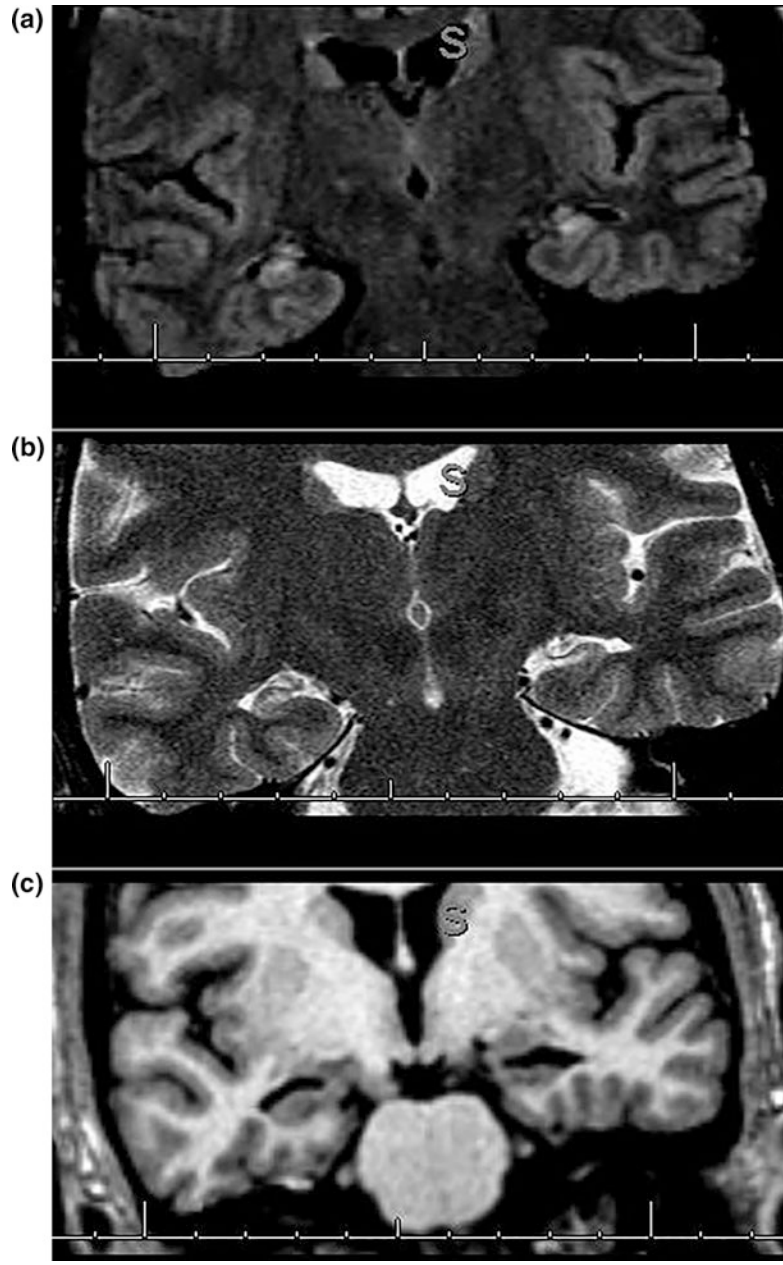

Fig. 21.3 Coronal FLAIR (**a**), T2-weighted (**b**) and 3D T1-weighted demonstrate bilateral hippocampal body hyperintensity, laminar blurring, and volume loss, respectively. Findings are consistent with bilateral hippocampal sclerosis

typically associated with another principal lesion such as hippocampal sclerosis, tumor, a vascular malformation, or other acquired pathology during early life.

Other important NMDs include lissencephaly, which is characterized by smooth brain surface and abnormal gyration, which varies between agyria and pachygyria. Lissencephaly with posteriorly predominantly gyral abnormalities is caused by mutation in LIS1 gene (Fig. 21.8). Anteriorly predominant lissencephaly in heterozygous males and subcortical band heterotopia (SBH) in heterozygous females are caused by mutations of the XLIS (double cortex gene on chromosome X). Schizencephaly is another rare form of MCD which is characterized by the presence of a

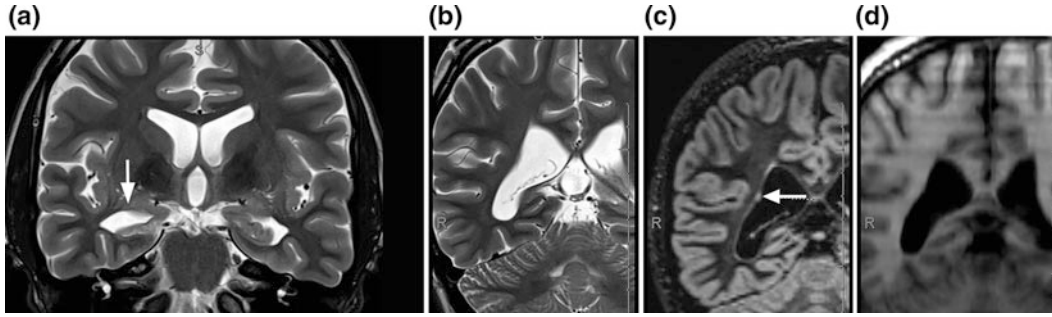

Fig. 21.4 Oblique coronal T2 demonstrates obvious volume loss and laminar blurring of the right hippocampal head (*arrow*, panel **a**) consistent with right hippocampal sclerosis and right fornix atrophy (**b**). There is a small gray matter heterotopia in the lateral wall of the right lateral ventricle, best seen on the coronal double-inversion recovery image (*arrow*, panel **c**) compared to companion T2 and T1-weighted MRI (**b** and **d**)

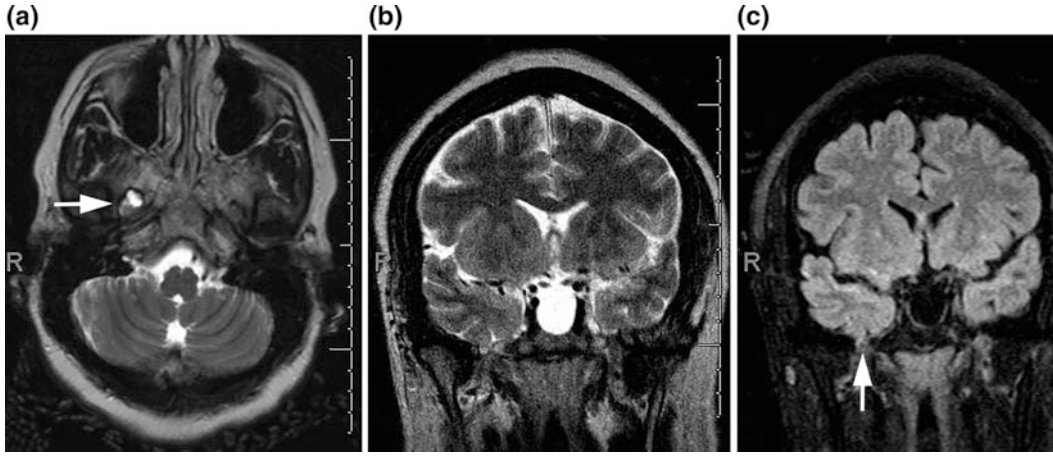

Fig. 21.5 Axial and coronal T2-weighted MRI, and coronal FLAIR demonstrate a small encephalocele that involves a focal portion of the fusiform gyrus cortex extending into the right foramen ovale (*arrows*). The MRI abnormality is not always associated with seizures, but should be considered suspicious. In this case, the finding was concordant with semiology and EEG

transcortical cleft that can extend from ventricles to the pia with open or fused lips, and often polymicrogyria is seen on the lips of the schizencephaly (Fig. 21.9). Hemimegalencephaly is the unilateral hamartomatous excessive growth of all or part of one cerebral hemisphere at different phases of embryologic development. MRI in these cases reveals an enlarged hemisphere with increased white matter volume, cortical thickening, agyria, pachygyria, polymicrogyria or lissencephaly, and blurring of the gray–white matter junction. Often, a large, ipsilateral irregularly shaped ventricle may be seen.

Brain tumors: Approximately 20–40% of the adults with primary brain tumors experience one seizure prior to the tumor diagnosis, and another 20–45% will suffer from seizures during the course of the illness [1]. This incidence rate varies depending on the tumor type, the grade of the tumor, and its location. Seizures are more common in slow growing tumors such as meningiomas, gangliogliomas (GGs), dysembryoplastic neuroepithelial tumors (DNETs), or diffuse low-grade tumors such as Grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas (Table 21.2). Typically, the low-grade

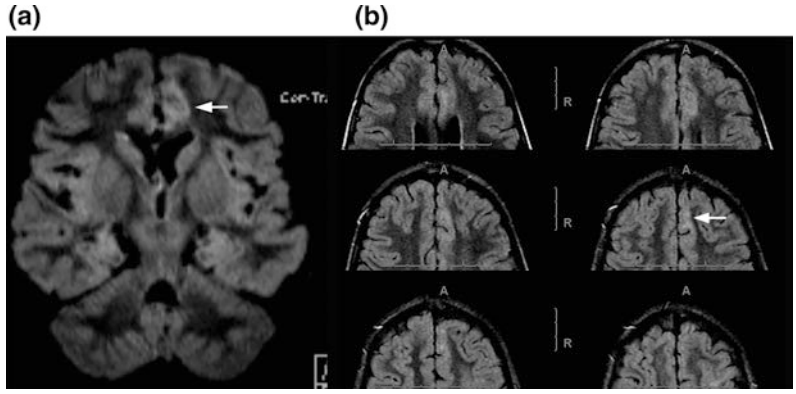

Fig. 21.6 Coronal FLAIR MRI (**a**) and serial axial FLAIR MRI of the frontal lobes (**b**) demonstrating subtle *gray–white* blurring and FLAIR hyperintensity in the left anterior cingulate gyrus and adjacent left medial frontal gyrus (*arrows*) from a pathologically proven cortical dysplasia

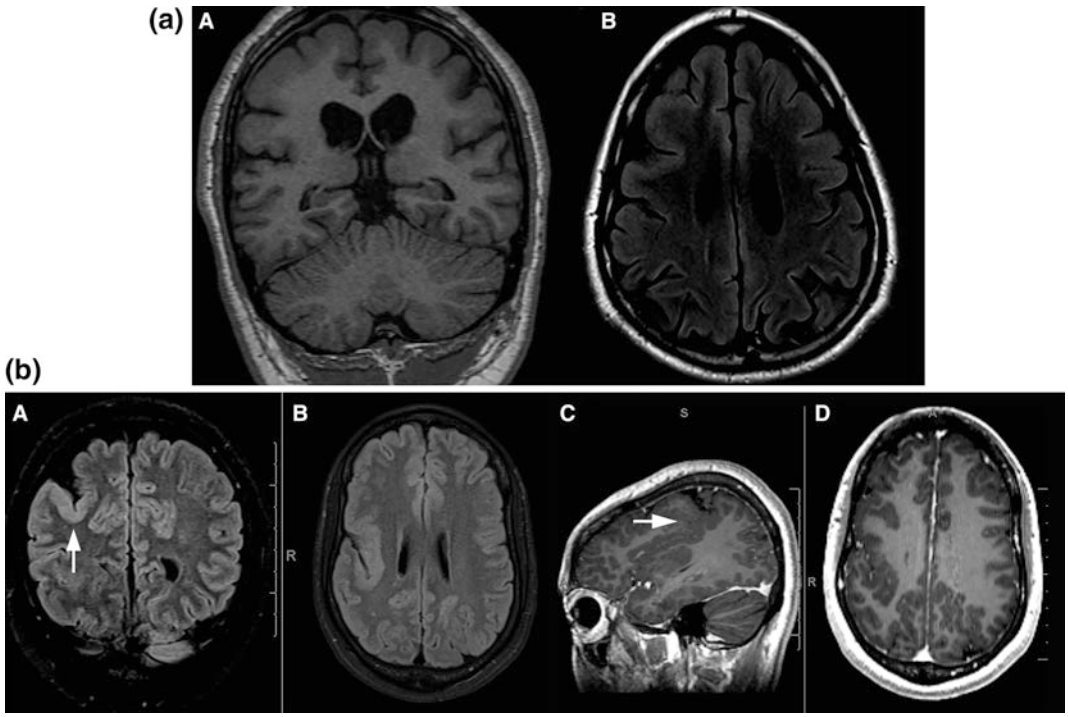

Fig. 21.7 **a** Coronal 3D T1-weighted (**A**) and axial FLAIR MRI (**B**) demonstrate broad, simplified gyri with relatively shallow sulci in the bifrontal regions compared to the temporal and parietal regions consistent with pachygyria. **b** Coronal and axial FLAIR (**A** and **B**), sagittal, and axial post-contrast 3D T1 (**C** and **D**) MRI show abnormal cortex that appears thickened extending from the posterior right Sylvian fissure (*arrow*). The fissure is lengthened with a vertical orientation toward the vertex (*arrow*, panel **C**). Findings consistent with unilateral polymicrogyria

tumors do not enhance on Gd-administration. The most common location is temporal lobe, followed by the parietal, frontal, and occipital lobes. Gangliogliomas typically present with temporal lobe epilepsy, presumably due to the temporal lobes being a favored location (Fig. 21.10).

Table 21.1 Classification of focal cortical dysplasias

Types	Features
Type I	Ia: abnormal vertical alignment of neurons Ib: abnormal horizontal alignment Ic: horizontal and vertical malalignment
Type II	IIa: dysmorphic neurons without balloon cells IIb: dysmorphic neurons with balloon cells
Type III	IIIa: mesial temporal sclerosis IIIb: glioneural tumors e.g., ganglioglioma, DNET IIIc: vascular malformations (CCMs, AVMs, telangiectasias, and meningoangiomatosis) IIId: prenatal or perinatal ischemic injury, TBI, and scars due to inflammatory or infectious lesions

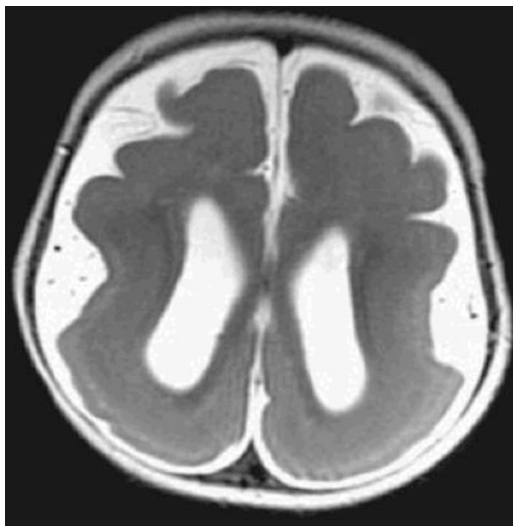

Fig. 21.8 MRI brain axial T2-weighted image shows lissencephaly agyria and smooth brain. Especially posteriorly in a patient with LIS1 mutation

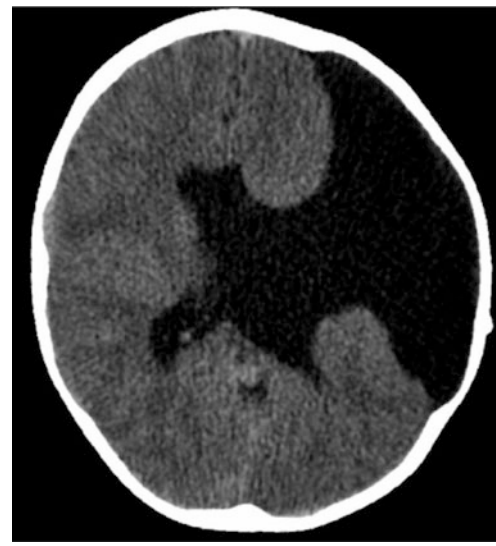

Fig. 21.9 CT brain axial image shows a cleft in the left hemisphere consistent with schizencephaly

Gangliogliomas are closely related to gangliocytomas, which contain essentially only mature neural ganglion cells, and ganglioneurocytoma, which in addition have small mature neoplastic neurons. On MRI, these tumors may show cystic changes or calcifications.

DNETs are cortically based benign neoplastic cortical malformations, which may show subcortical extension in approximately 30% of tumors giving them a triangular appearance (Fig. 21.11). These tumors appear as well-defined lobulated, and solid tumors that are hyperintense on T2WI and may erode the overlying calvarial bone or show microcystic changes. The most common location is temporal (60%) followed by temporal lobes (30%). Meningiomas are the most common extra-axial tumors of the central nervous system. They are nonglial neoplasms that originate from the arachnoid cap cells of the meninges and have characteristic imaging findings, although there are many variants (Fig. 21.12). GBMs are aggressive malignant tumors that are associated with significant vasogenic edema and heterogeneous enhancement. The overall incidence of seizures in Grade IV glioblastoma multiforme (GBM) patients, without considering the location, has been reported between 25 and 50% at presentation and another 20–30% during the course of the disease [2]. Metastatic lesions tend

Table 21.2 Common epilepsy associated tumors

Tumors	Radiological features
Meningioma	Isointense on T1 and T2; homogeneous enhancement with Gd, extra-axial, dural tail, and CSF cleft sign
Ganglioglioma	Cyst with enhancing mural nodule/solid; calcifications in ~50%
Dysembryoplastic neuroepithelial tumors (DNET)	Bubbly cystic appearance with small cysts within the tumor that are hyperintense on T2WI, wedge shaped mass which expands the affected gyri and point toward the ventricle, swollen gyrus, may be associated with focal cortical dysplasia
Pleiomorphic xanthoastrocytoma (PXA)	Supratentorial cyst with enhancing mural nodule which abuts the peripheral meninges, peritumoral edema, mild meningeal enhancement
Oligodendroglioma	Hypointense on T1, hyperintense on T2, calcification seen as areas of blooming, 50% enhance heterogeneously, minimal peritumoral edema
Hypothalamic hamartomas	Nonenhancing non-neoplastic congenital gray matter heterotopia in the region of tuber cinereum of the hypothalamus which can be sessile or pedunculated
Subependymal giant cell astrocytomas (SEGA)	Heterogeneous mass near the Foramen of Monro, usually >1 cm; hypo or isointense on T1 and hyperintense on T2, marked enhancement; other findings of Tuberous Sclerosis such as cortical tubers and subependymal nodules, "transmantle sign" in some tubers; nodular, ill-defined, cystic and band-like lesions seen in the white matter and radial bands
Glioblastoma multiforme (GBM)	Hypo or isointense on T1, hyperintense on T2, vasogenic edema, susceptibility artifact on T2 from intratumoral lesions due to hemorrhage or rarely calcification, "butterfly glioma" when bilateral and cross the corpus callosum, necrosis may be present, peripheral or irregular nodular enhancement; no diffusion restriction but lower ADC than low-grade tumors
Metastases	Hypointense on T1 (except melanomas can be hyperintense), hyperintense on T2 and FLAIR, intense enhancement (ring-enhancing, punctate or uniform), often multiple lesions present at diagnosis, vasogenic edema out of proportion to the size of the lesion, hemorrhage, and necrosis may be seen

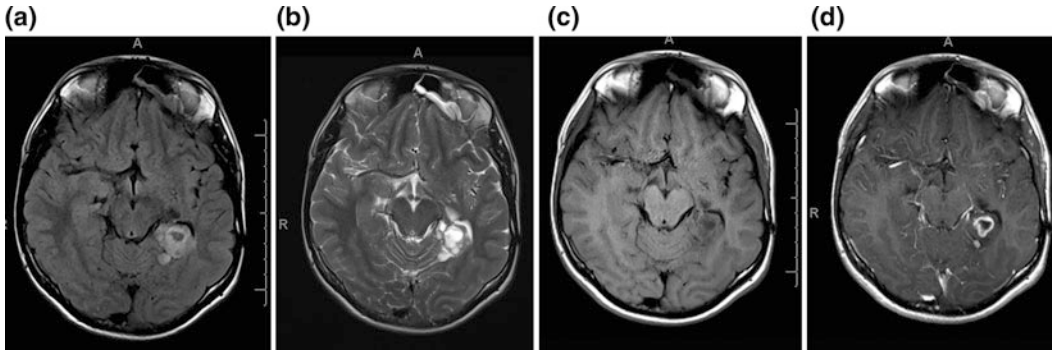

Fig. 21.10 Axial FLAIR (**a**), T2-weighted (**b**), pre-contrast (**c**), and post-contrast T1-weighted MRI (**d**) demonstrating solid and cystic mass in the left posteromedial temporal lobe with focal areas of contrast enhancement most consistent with ganglioglioma. CT also often demonstrates focal calcification

to have a smaller risk for seizures, one exception being metastatic melanoma.

Perfusion-weighted imaging is a useful tool, which involves several image acquisitions during the first pass of a bolus of contrast agent. This method allows the radiologist to determine the relative cerebral blood volume (rCBV). In general, the underlying principle is the greater the

rCBV, the higher the grade of tumor. Lack of notable flow indicates a nonneoplastic etiology with abnormal signal intensity, such as demyelination. Of note, mixed oligodendrogliomas can have low rCBV. Besides the prognostic information it provides, perfusion-weighted imaging can increase the yield of brain biopsy and help in differentiating recurrent neoplasm from radiation necrosis. On perfusion MRI, GBMs typically show increased regional blood flow (Fig. 21.13).

Another interesting but rare kind of focal congenital tumor is hypothalamic hamartoma (HH). These tumors are typically associated with ictal spells of laughter without mirth or gelastic seizures (Fig. 21.14). HH are composed of cytologically normal, small, and large neurons, which are organized in poorly demarcated clusters of variable size and density. These tumors are categorized by the Delalande classifications I–IV. Type I has a horizontal orientation and may be lateralized on one side; Type II has a vertical orientation and an intraventricular location; Type III is a combination of types I and II; Type IV is a giant hamartoma.

Vascular malformations: Vascular malformations can be either high flow or low flow. High flow malformations include arteriovenous malformations (AVMs), which can be parenchymal, dural, or mixed. In contrast, low flow vascular malformations are cerebral cavernous malformations (CCMs), developmental venous anomaly (DVA), or mixed vascular malformations (Fig. 21.15). CCMs have a unique "popcorn" appearance with hemorrhages of different ages. They may be bright on CT due to pooling of blood within the cavernoma. The most characteristic feature is blood products of different ages with an area of hyperintensity representing methemoglobin surrounded by a hypointense ring of hemosiderin on T2W MRI. Gradient echo (GRE) sequences are useful to detect CCMs and may show low or minimal enhancement on Gd. MRI brain is superior to CT scan to look for the nidus of an AVM which is hyperdense compared to adjacent brain (Fig. 21.16). It is easier to appreciate fast flow voids on T2WI due to fast flow and enlarged draining veins may be seen. Phase contrast MR angiography can help subtract the hematoma components in patients who present with acute hemorrhage into an AVM. CTA can demonstrate feeding arteries, nidus, and draining veins visible, which resembles a "bag of worm" appearance. The exact anatomy of feeding vessels and draining veins is often difficult to delineate, and

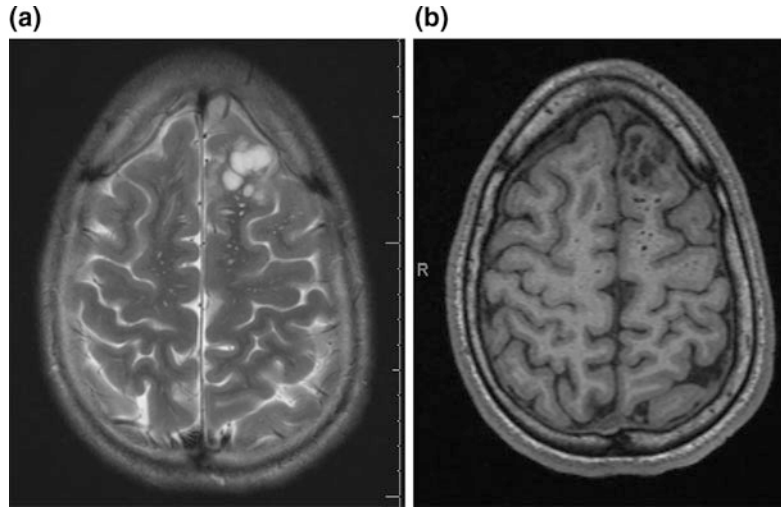

Fig. 21.11 Axial T2- and T1-weighted MRI (**a** and **b**) demonstrate bubbly T2 bright lesion in the left superior frontal gyrus with minimal mass effect that does not enhance (contrast not shown). In a patient with seizures, these findings are most consistent with dysembyroblastic neuroepithelial tumor (DNET)

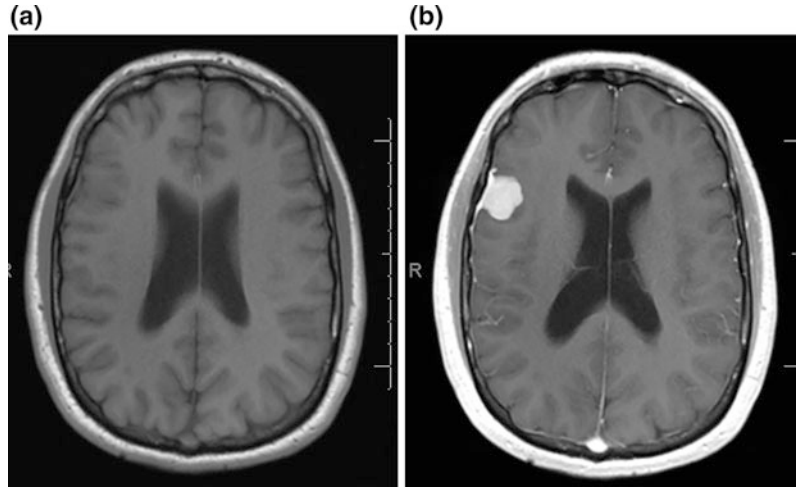

Fig. 21.12 Axial pre-contrast (**a**) and post-contrast T1-weighted MRI (**b**) demonstrate an extra-axial mass overlying the right frontal operculum that is isointense to *gray* matter and shows homogeneous enhancement with dural tail consistent with meningioma

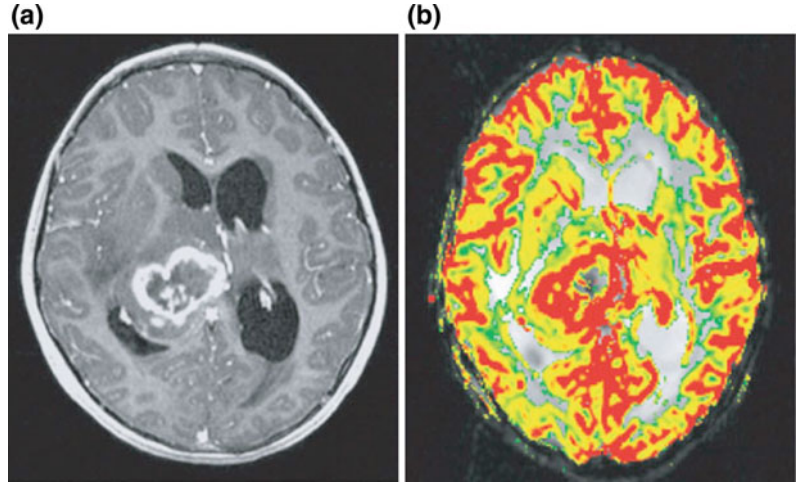

Fig. 21.13 MRI brain post-Gd T1-weighted image (**a**) showing ring enhancement in the right thalamus and *deep gray* structures with associated mass effect, midline shift, and obstructive hydrocephalus. Pathology was consistent with glioblastoma multiforme. Perfusion MRI (**b**) shows increased regional cerebral blood flow at the tumor margins

thus angiography remains necessary. Digital subtraction angiography (DSA) remains the gold standard in delineating the location and number of feeding vessels supplying the central nidus and the pattern of venous drainage (superficial or deep). The susceptibility-weighted images (SWI) are particularly sensitive to iron content in the brain, both in cortical layers and in blood vessels and identify hemosiderin in CCMs, old infarcts or old contusions.

Infectious/Inflammatory disorders: A common etiology for seizures in all age groups, both in the developing and developed world, includes infections of the nervous system. A wide variety of

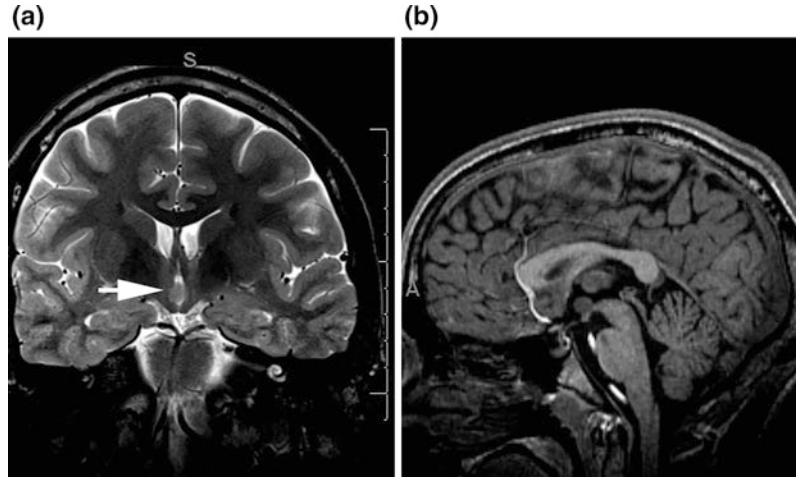

Fig. 21.14 Coronal T2-weighted (**a**) and sagittal T1-weighted MRI (**b**) demonstrating ectopic gray matter along the wall of the 3rd ventricle (*arrow*) in adolescent patient with gelastic seizures. Findings support diagnosis of hypothalamic hamartoma

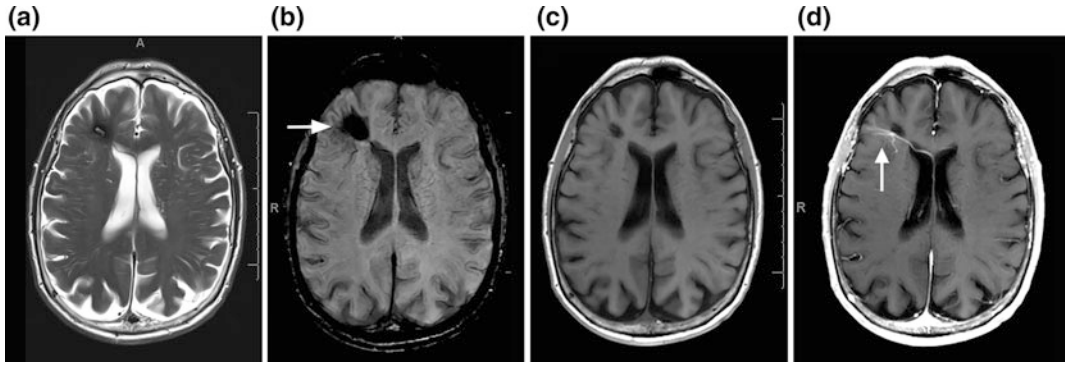

Fig. 21.15 Axial T2-weighted and axial susceptibility-weighted MRI (**a** and **b**) demonstrate a popcorn-like T2 bright lesion with surrounding hypointense susceptibility (*arrow*). Pre- and post-contrast axial MRI (**c** and **d**) demonstrate associated developmental venous anomaly (*arrow*) strongly supporting diagnosis of cavernoma

pathogens including viral, bacterial, fungal, parasitic, and other opportunistic pathogens can cause CNS disease in humans. Though gold standard of diagnosis remains either biopsy or CSF analysis, neuroimaging can aid in rapid diagnosis by helping identify typical lesion patterns. While it is outside the scope of his chapter to comprehensively discuss CNS infections, we have attempted to list typical radiology findings with common CNS infections associated with epilepsy in Table 21.3. More recent MRI techniques, such as DWI and MRS also aid in diagnosis by providing additional information, which is discussed in relevant sections in this chapter. Briefly, restricted diffusion helps in differentiation of progenitor abscesses from ring-enhancing lesions of other etiology. Also, the presence of lactate and cytosolic amino acids and the absence of choline on MRS are seen in the cases of pyogenic abscesses. Autominnune encephalitides can also be associated with seizures. Figure 21.17 illustrates an example of progressive volume loss and denudation of the overlying cortex Rasmussen's syndrome is one kind of autoimmune encephalitis

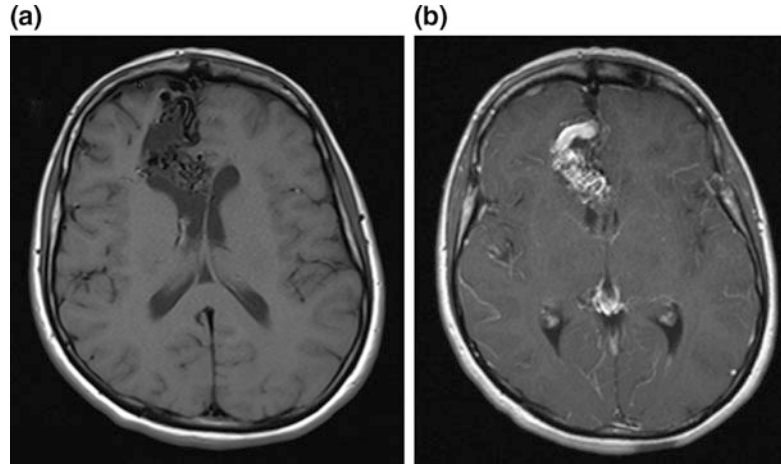

Fig. 21.16 MRI brain axial T1-weighted image (**a**) shows right mesial frontal arteriovenous malformation. Post-Gd T1-weighted (**b**) reveals enlarged draining vein

associated with intractable unilateral seizures, progressive hemiparesis or weakness on one side, and intellectual dysfunction.

Neurocutaneous Syndromes (Phacomatoses): These are a group of inherited disorders characterized by hamartomas and neoplasms throughout the body along with involvement of the nervous system and skin. The neuroradiological features of common phacomatoses, namely, Tuberous sclerosis (TS), Neurofibromatosis (NF1 and NF2), and Sturge Weber syndrome (SWS) are summarized in Table 21.4.

Figure 21.18 illustrates a few salient neuroradiological features of TS and SWS in patients with medically refractory seizures.

Trauma: Traumatic brain injury (TBI), especially severe closed skull injury and penetrating dural injury have been well documented to cause post-traumatic epilepsy [3]. Patients with prolonged loss of consciousness, post-traumatic amnesia, or hemorrhage in the brain (subarachnoid hemorrhage, subdural, epidural, intraparenchymal, and intraventricular) are at a higher risk of developing immediate (onset within 24 h), early (onset within a week), or late-onset epilepsy. The findings on imaging vary from contusions, with or without diffuse axonal injury (DAI), or hemorrhages in different locations (Table 21.5). T2WI and the FLAIR images are sensitive to edema in the brain, while GRE and SWI are very sensitive to microhemorrhages. Figure 21.19 shows temporal encephalomalcia as a result of TBI. SWI and DWI are the best sequences to detect DAI. Tong et al. group showed that number of hemorrhagic DAI lesions seen on SWI was six times greater than that on conventional T2-weighted 2D GRE imaging and the volume of hemorrhage was approximately twofold greater.

Positron Emission Tomography (PET)

PET is a noninvasive, diagnostic imaging technique for measuring the metabolic activity of cells in the human body. PET studies characterize genotype–phenotype interactions because this technique directly measures neurometabolic changes and receptor binding. PET produces images of the body by detecting the radiation emitted from radioactive substances. These substances are injected into the body and are usually tagged with a radioactive atom (^{11}C, ^{18}Fl, ^{15}O or ^{13}N) that has short decay time (Table 21.6). The radioactivity localizes in the appropriate areas of the body and is detected by the PET scanner.

Different colors and/or degrees of brightness on a PET image represent different levels of tissue or organ function. For example, as healthy tissue uses glucose for energy, it accumulates some of the tagged glucose, which shows up on PET images. However, epileptogenic tissue during interictal phases utilizes less glucose than healthy normal tissue, and thus, it appears less bright than normal tissue on the PET images

Table 21.3 Radiological features of common infections

Infections	Radiological features
Brain abscess	Ring of isodense or hyperdense tissue with central hypoattenuation on CT. MRI classically shows T1 hypointense, T2/FLAIR hyperintense, Diffusion restricted lesion. The four stages of an abscess with imaging findings are listed below. * Early cerebritis—Poorly marginated cortical or subcortical hypodensity with mass effect with little or no enhancement * Late cerebritis—irregular rim enhancing lesion with hypodense center, better defined than early cerebritis * Early capsule—well-defined rim enhancing mass; an outer hypodense and inner hyperdense rim (double rim sign) classically * Late capsule—rim enhancing lesion with thickened capsule and diminished hypodense central cavity
CNS tuberculosis	Can be leptomeningeal, pachymeningeal, or intracranial (tuberculomas) * Leptomeningeal—intense heterogenous basal enhancement. * Pachymeningeal—intense enhancement of thickened meninges. * Intracranial: T1 isointense with central hyperintensity (possible caseation), T2 isointense with central hyperintensity (possible gliosis), ring-enhancing.
Herpes simplex encephalitis	Preferential involvement of mesial temporal lobes. If hemorrhagic, blooming on GRE/SWI
Japanese encephalitis	Predominant involvement of deep gray matter, especially bilateral thalami (though may be asymmetric) with sparing of cortices
Rabies encephalitis	In classic cases, increased T2 signal in affected parts with predilection for the gray matter especially basal ganglia, thalami, hypothalami, brainstem, limbic system, and spinal cord as well as the frontal and parietal lobes
Neurocysticercosis	Findings are based on location (parenchymal or in sub-arachnoid-intraventricular space; which appears grape-like (racemose) cystic, often associated with ventriculitis) or stage of infection (as below). * Vesicular—T1 hyperintense scolex ±, Cyst with dot sign (parasitic cyst with eccentric scolex), no or faint enhancement * Colloidal vesicular—T1 hyperintense with surrounding edema, scolex with eccentric focus of enhancement * Granular nodular—Edema decreases, cyst retracts, enhancement persists but less marked from prior stage * Nodular calcified—end-stage quiescent, no edema, no enhancement
Toxoplasmosis	Multiple lesions, T1 isointense or hypointense and T2 isointense to hyperintense, with predilection for basal ganglia and corticomedullary junction that often show ring or nodular enhancement. Increased lipid lactate peak on MRS is characteristic.
Schistosomiasis	Rare, seen either as intracerebral and intracerebellar hematomas or nonspecific granulomatous lesions (hypodense on CT and T1-hypointense and T2-isointense on MRI) due to a response of the host to the ova
Toxocariasis	Multiple cortical, sub-cortical, or white matter lesions that are hypodense on CT, hyperintense on T2-weighted MRI images, and homogeneously enhancing
Cryptococcosis	Leptomeningeal involvement, "soap bubble" appearance with pseudocysts—common in mid brain and basal ganglia with parenchymal cryptococcomas. Also, tendency to spread along peri-vascular spaces with dilated perivascular spaces

(Fig. 21.20). ^{18}F FDG-PET is particularly helpful in identifying subtle FCDs. FDG is useful for tumor grading because most high-grade tumors, such as high-grade gliomas, medulloblastoma, and primary central nervous system lymphoma, have high concentrations and activity of glucose transporters (GLUTs). Most low-grade tumors have lower concentrations of GLUTs and can usually be distinguished from high-grade gliomas by the lower FDG uptake on PET [4]. FDG-PET is a useful tool in distinguishing post-radiation necrosis from tumor progression,

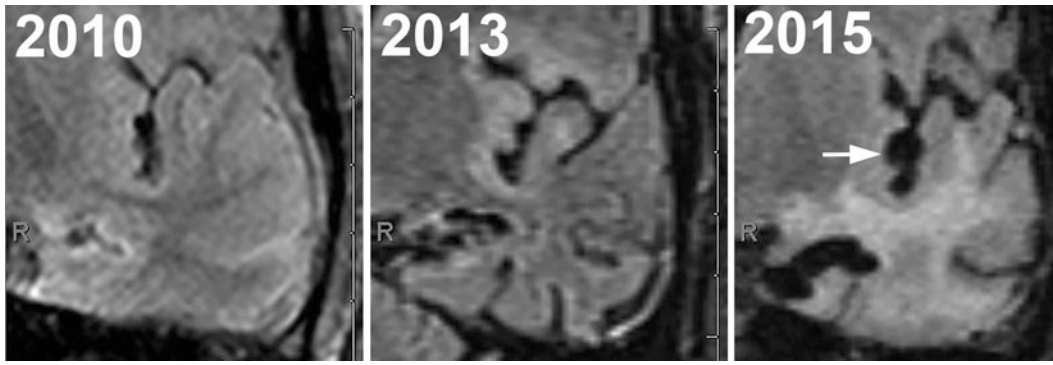

Fig. 21.17 Serial coronal FLAIR images of the left temporal lobe in an adult patient with autoimmune encephalitis. Between 2010 and 2015, there was progressive volume loss and denudation of the overlying cortex (*arrow*). Similar focal lobar volume loss can happen in Rasmussen encephalitis

Table 21.4 Neuroradiological findings in common phacomatoses

Phacomatoses	Neuroradiological findings
NF1 (peripheral)	Optic glioma, peripheral or cranial nerve sheath tumors, macrocephaly, sphenoid wing dysplasia, scoliosis, astrocytomas
NF2 (Central)	Vestibular schwannomas, meningiomas, schwannomas/neurilemmomas of the dorsal roots of the spinal cord
TS	Cortical tubers (calcifications, cysts, or fibrosis may be seen in tubers), subependymal nodules (SENs), SENs near the foramen may enhance on Gd and transform into a SEGA → serial MRIs may show progressive growth, papilledema, and obstructive hydrocephalus; white matter heterotopias, arachnoid cyst, aneurysms
SWS	Leptomingeal angiomatoses, calcification of gyri in form of rail-road shape, cerebral atrophy, venous, or arterial infarcts

both in high-grade gliomas and brain metastases. In general, recurrent tumor is FDG avid, and radiation necrosis is not FDG avid.

Subtraction Ictal SPECT Co-registered to MRI (SISCOM)

SISCOM is a novel neuroimaging technique that couples MR images with nuclear medicine SPECT (Single-Photon Emission Computed Tomography) scans to identify areas of increased perfusion with respect to regional cerebral flow (rCBF). It is commonly used as a tool in pre-surgical evaluation to localize the seizure focus in both pediatric and adult patients with refractory epilepsy [5]. Technically, radio tracer injections (typically Tc-99 m) are administered during an ictal event that allows computation of variations in rCBF between ictal and inter-ictal states. Studies by multiple groups have validated SISCOM as a valuable tool that offers improved localization of seizure focus by visualization of the region of hyperperfusion and thus higher neuronal activity (40–86%). Further, SISCOM findings serve as a guide for further intracranial monitoring, electrode placement, and in determining the extent of surgical resection, which in turn offers a higher probability of post-surgical seizure freedom [6–8]. Occasionally, incongruous findings have been reported between intracranial vEEG and SISCOM in post-surgical patients [5]. These likely reflect an altered blood flow pattern in

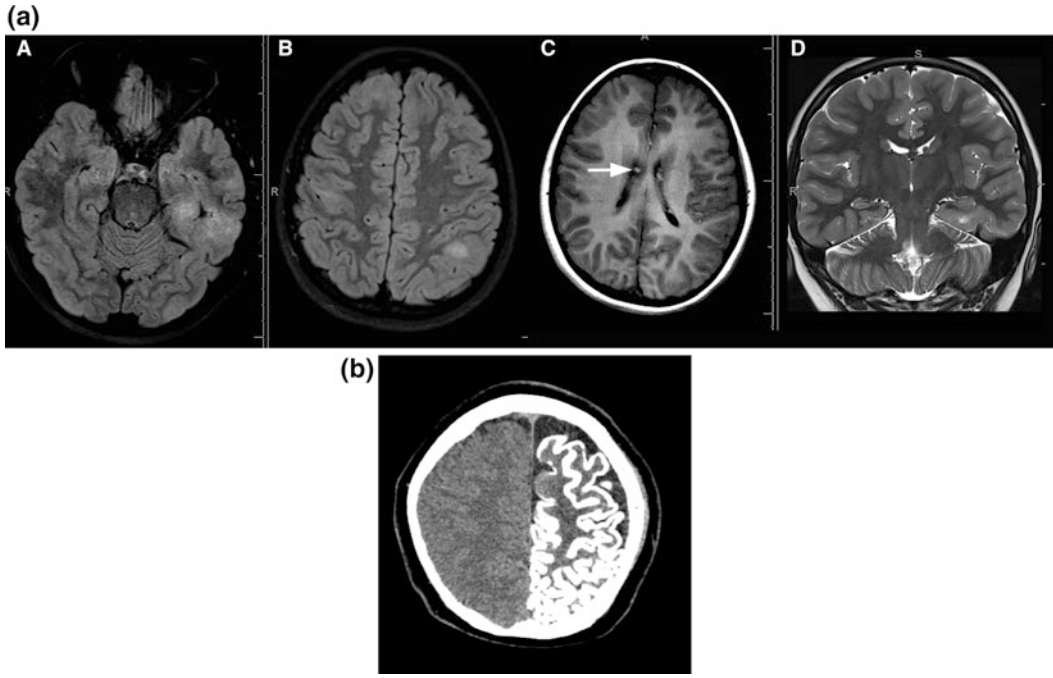

Fig. 21.18 Axial FLAIR (**a**, **b**) demonstrates focal T2 hyperintense masses in the cortex and subcortical white matter of the basal left temporal lobe and left inferior parietal lobule consistent with tubers. Axial pre-contrast T1 and coronal T2-weighted MRI demonstrate multiple ependymal nodules along the bilateral caudo-thalamic grooves. These lesions demonstrate subtle T1 hyperintensity (*arrow*) attributed to calcification that can be seen on CT (not shown). Video EEG suggested the adjacent tubers in the posterior basal left temporal lobe were responsible for the majority of seizures in this patient with tuberous sclerosis. Axial CT slice (**c**) demonstrating cortical tram-track calcification throughout most of the left cerebral hemisphere consistent with pial angiomatosis. There is a volume loss, but with relative sparing of the left frontal operculum. Findings are consistent with Sturge Weber syndrome

Table 21.5 Radiographic findings in patients with TBI

Pathology	Comments
Gliding contusions	Due to sagittal angular acceleration with stretching and tearing of parasagittal veins
Hemorrhages	Scalp hematoma, subdural, epidural, subarachnoid, intraparenchymal, ventricular with or without mass effect
Diffuse axonal injury (DAI)	Areas affected are parasagittal regions of the frontal lobes, periventricular areas in temporal lobes, near internal and external capsules, gray–white matter junctions, dorsolateral quadrants of the rostral brainstem, and cerebellum. GRE and SWI show small regions of susceptibility artifacts

these patients rather than the actual seizure onset zone. However, SISCOM still exists as a valuable tool in pre-surgical planning in both identification of the ictal zone and guiding surgical resection. For the clinician, though, it is essential to remember that the complete workup must be tailored to each individual patient.

Magnetoencephalogram (MEG)

A separate chapter is devoted to MEG but is mentioned briefly here. MEG measures small electrical currents arising inside the neurons of the brain, which produce very weak magnetic

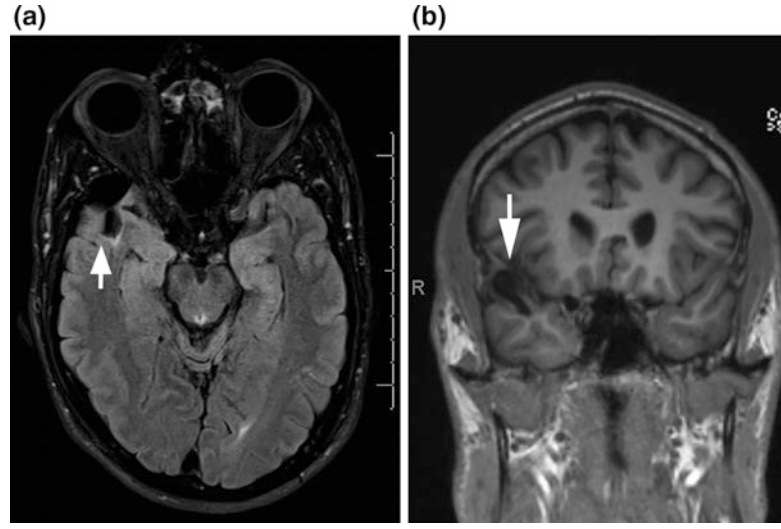

Fig. 21.19 Axial FLAIR (**a**) and coronal 3D T1-weighted MRI (**b**) demonstrating subtle encephalomalacia in the anterior right superior temporal gyrus (*arrows*) attributed to remote trauma in a patient with seizures and history of high-speed motor vehicle accident

Table 21.6 Common ligands used during PET scans

Types of PET	Techniques used
FDG	Glucose metabolism
H_2O	Cerebral blood flow
[^{11}C] Carfentanil	Binds to mu-opiate receptors
[^{11}C] Doxepine	Binds to histamine H1 receptors
α [^{11}C] methyl-L-Tryptophan	Measures tryptophan metabolism by serotonin and kynurenine pathways
[^{11}C] Flumazenil	Measures tryptophan metabolism by serotonin and kynurenine pathways

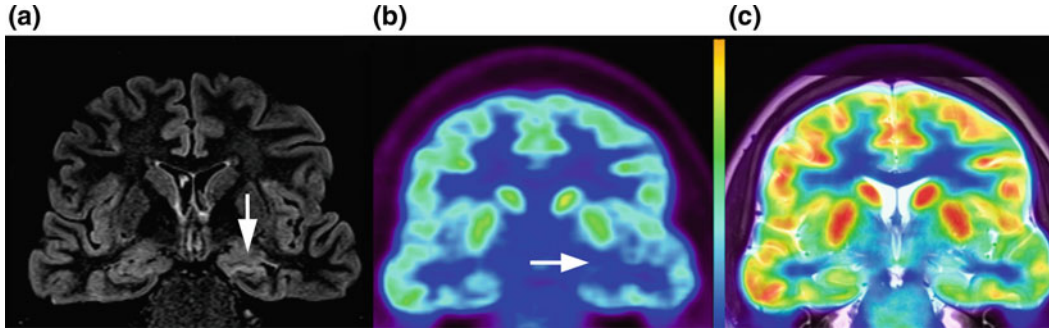

Fig. 21.20 Simultaneous PET-MRI technology in a temporal lobe epilepsy patient. Coronal FLAIR demonstrates volume loss and hyperintensity in the left hippocampal head (*arrow*, panel **a**). Coronal FDG demonstrates hypometabolism that involves both medial and lateral left temporal lobe (*arrow*, panel **b**). Blended images combining MRI and FDG data can also be obtained to assist visual detection of abnormalities (here, FLAIR with color FDG map superimposed)

fields in the range of femto and pica Tesla. Patient wears a helmet containing an array of 100+ sensitive magnetic field measurement devices. The measurement devices are called **S**uperconducting **Q**uantum **I**nterference **D**evices (SQUIDS). MEG has a high resolution in both space (2–3 mm) and time (<1 ms). The skull and the tissue surrounding the brain affect the

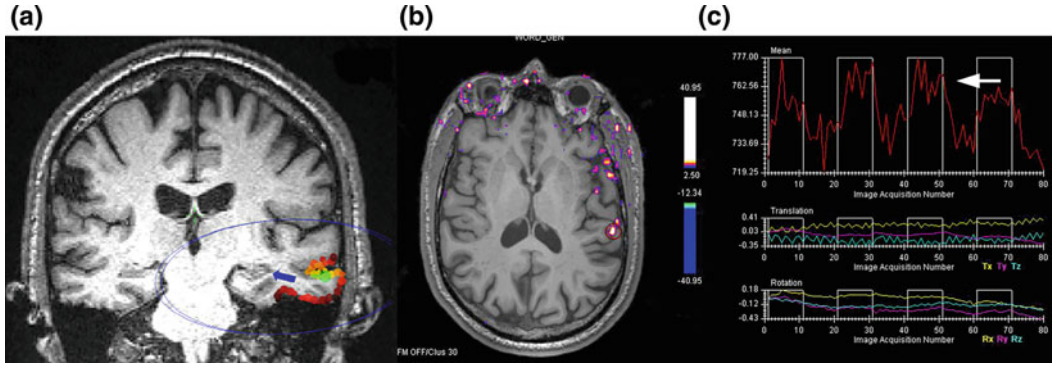

Fig. 21.21 Advanced imaging workup in patient with MRI-negative left temporal lobe epilepsy. Coronal MPRAGE with interictal MEG dipole cluster in the left middle temporal gyrus (*blue arrow*, panel **a**) was concordant with semiology and EEG. Task-based functional MRI of the patient performing word generation task demonstrates left language dominance (**b**). A region-of-interest of BOLD signal in the planum temporale (presumably Wernicke's area) demonstrated a strong correlation with performance of the task (*arrow*, panel **c**)

magnetic fields measured by MEG much less than they affect the electrical impulses measured by electroencephalogram. MEG is usually performed with simultaneous EEG. For Magnet Source Imaging (MSI), information from MEG and MRI is coregistered to form magnetic source localization images that provide detailed structural–unctional information of the brain. MSI helps in characterization and localization of epileptiform activity and pre-operative mapping of brain areas supporting sensory, motor, and language function (Fig. 21.21). MSI is complimentary to PET, fMRI, and EEG as it provides unique information on the spatiotemporal dynamics of brain activity.

Diffusion-Weighted Imaging (DWI)

DWI adds spatially encoding magnetic gradients to the standard MRI sequence to make the image sensitive to the translational motion of water molecules. In the absence of T2 weighting, the "bright regions" represent decreased water diffusion, and "dark regions" represent increased water diffusion. Hence an acute stroke with cytotoxic edema and slow water diffusion will appear very bright. However, a T2-bright tissue, such as edema or gliosis from a late subacute or chronic infarct, also can appear bright on a diffusion trace image (this is called "T2 shine through"). In apparent diffusion coefficient (ADC) maps calculated from the diffusion-weighted images, the intensity of pixels is more directly proportional to extent diffusion, and the T2 weighting is removed from the data. A bright signal on DWI and dark signal on ADC supports the evidence of cytotoxic edema seen with infarctions (Table 21.7). A focus of increased signal intensity on DWI with a normal ADC signal suggests vasogenic edema and referred to as "T2 shine through."

Diffusion Tensor Imaging (DTI)

DTI is based on the basic principle that the diffusion of water molecules in the brain is restricted by intracellular and extracellular membranes, particularly myelin. The image intensities are inversely related to the relative mobility of water molecules in tissue and the direction of motion. Anisotropy is a measure of the orientation dependent water diffusion within an image voxel, e.g., CSF has a fractional anisotropy of near zero, whereas highly coherent white matter has a fractional anisotropy near 1. The diffusion data can also be given color codes based on principal direction of diffusion, and the intensity of color is proportional to the fractional anisotropy. The transverse axis (*x*-axis) is represented by red color; the green color depicts anterior posterior (*y* axis), and blue is designated

Table 21.7 DWI and ADC characteristics in different disorders

Pathology	DWI	ADC	Cause
Stroke	High	Low	Cytotoxic edema
Solid tumor	Variable	Variable	Depends on the cellularity
Arachnoid cyst	Low	High	CSF signal intensity
Herpes encephalitis	High	Low	Cytotoxic edema
Abscess	High in the center	Low	Dense pus
Acute diffuse axonal injury	High	Low	White matter shearing

to superior inferior (z-axis). DTI tractography then uses fractional anisotropy and the principal orientation of diffusion with the voxel to characterize the coherent white matter bundle 3D orientations with the brain and spinal cord. Thus, tractography allows accurate diagnosis of even subtle congenital and acquired lesions that might disrupt the axonal organization.

Practical applications of DTI and tractography in epilepsy include precise delineation of white matter tracts in the brain, especially in identification of eloquent white matter tracts, such as the arcuate fasciculus adjacent to neoplasms or epileptogenic regions [9, 10]. Another area where tractography has significant implications is in mapping of optic radiations during pre-surgical planning of anterior temporal lobe resection procedures. Here, pre-operative tractography can demonstrate the anterior extent of Meyer's loop, which is variable between people and cannot be visualized on traditional MRI studies. Thus, one can predict the extent of visual field defects that might happen post-surgery. DTI has relatively poor spatial resolution and is less sensitive to injury at crossing fibers and close to gray–white matter junction [11, 12].

MR Spectroscopy (MRS)

In the field of epilepsy, MRS acts as a valuable tool by complementing MRI. While conventional MRI is very helpful in studying anatomy, MRS offers a noninvasive means to determine the biochemical and metabolic characteristics of the tissue of interest. Though both are based on similar principles, MRS uses signal from protons to estimate the concentration of metabolites, chiefly N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), and lactate in brain tissue. ^{1}H spectroscopy, most widely used, is useful for assessment of markers of neuronal loss such as NAA, products of anaerobic metabolism such as lactic acid, and direct measures of primary excitatory and inhibitory neurotransmitters. ^{31}P spectroscopy is directed toward the characterization of the bio energetic status of the tissue of interest phosphocreatine (PCr), adenosine triphosphate (ATP), and phosphoinositol (Pi).

Applications of MRS in epilepsy imaging are widespread. In patients with hippocampal sclerosis, the MRS shows evidence of neuronal dysfunction such as decreased NAA and decreased NAA/Cho and NAA/Cr ratios and decreased myoinositol (MI) in ipsilateral temporal lobe and increased lipid and lactate soon after a seizure [13]. Conventionally, MRS has been used in characterization and differentiation of masses that appear equivocal on MRI. MRS can help differentiate between dysplastic versus neoplastic masses, recurrent brain neoplasm versus radiation injury, or between an abscess versus a tumor [14]. Further, MRS has also been used to screen for inborn errors of metabolism such as Canavan's disease and creatine deficiency. There is a typically decreased NAA/Cr ratio in patients with dysplastic cortex as in hemimegalencephaly. Interestingly, multiple studies have now validated MRS as a tool in identifying the seizure focus, thus making it useful in the evaluation of both

focal and generalized epilepsy. Work by numerous groups has shown specific metabolic abnormalities that are confined to the seizure zone [15, 16]. Inter-ictal changes include increased inorganic phosphate (Pi), increased pH, and decreased phosphomonoesters, a decreased PCr/Pi ratio together with a decrease in NAA (reduction of 22% ipsilateral to seizure focus). Also, an increase in lactic acid is usually seen post-ictally. While MRS has been reported to have localizing value by numerous groups (65–96% chances of lateralization in TLE by proton MRS and 65–75% value in TLE by phosphorus MRS), research is still ongoing to determine the value of MRS in localization of the epileptogenic focus.

Functional MRI (F-MRI)

Functional MRI is a noninvasive imaging technique that has grown in popularity over the past two decades. Its role has been increasingly recognized in clinical practice to lateralize language and motor functions. The intracarotid sodium amobarbital angiographic procedure (the "Wada") and intraoperative cortical stimulation mapping procedures are still the clinical gold standards to localize the epileptogenic zone and map the functional areas of the brain. However, these mapping techniques have their own limitations due to afterdischarges and seizures produced by stimulation. The spatial resolution of fMRI is great, but the temporal resolution is suboptimal for dissecting out the different functional areas of the brain that are related to a particular task.

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Neuropsychological Evaluation in Epilepsy

22

Madison M. Berl and Leigh Sepeta

Neuropsychology Principles

Neuropsychology is the study of learning and behavior in relationship to the brain. It is a framework that draws from neurology, neuroanatomy, cognitive sciences, and clinical, social, developmental, and biological psychology. It is critical that with pediatric evaluation, the brain is understood in the context of developmental change. A neuropsychologist has earned a PhD in clinical psychology and completed 2 years of specialized postdoctoral training.

Purpose of a Neuropsychological Evaluation

There are several appropriate reasons for referral to people with epilepsy to undergo neuropsychological evaluation:

- Obtain profile of strengths and weaknesses
  - Measure the presence and degree of behavioral and cognitive difficulties
  - Identify strengths to inform treatment planning
- Profile provides evidence for the localization of dysfunction/function
- Measure the cognitive or behavioral impact/risk of rehabilitation, pharmacological, surgical, or therapeutic interventions
  - Establish the baseline of functioning for systematic comparisons across time
- Increase patient preparedness and inform items selection/protocol adjustments on an individual basis for cognitive mapping procedures: Intracarotid Amytal Test (IAT)/WADA, functional MRI (fMRI), Electrocortical Stimulation (ECS)
- Help formulate appropriate treatment plans (educational/vocational and medical)
- Predict individual's ability to achieve success in particular settings

Different from general psychological practice, a neuropsychologist:

- Does not necessarily diagnose psychiatric conditions or provide therapy/treatment
- May not assess specific vocational skills (driving, interest inventory, etc.).

Components of a Neuropsychological Evaluation

Through history, testing, and behavioral observations, there is an examination of external

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behavior to make inferences about brain function and structure. The history is similar to other providers where information is systematically gathered through interview with the patient and their caregivers/spouses, and record review. Formal testing of abilities and behavioral observations are conducted over the course of one or more office visits or, less ideally, on an inpatient basis. There are numerous neuropsychological measures available. Table 22.1 is not an exhaustive list; however, the measures listed are commonly used both clinically and in research in epilepsy populations. Formal testing refers to a standardized method of administration and scoring of responses. A profile of strengths and weaknesses is derived by comparing a person's test scores to a normative population of a similar age across domains. Domains of functioning include the following:

- General Cognitive Functioning/Intelligence Quotient (IQ)
- Language
- Memory and Learning
- Attention
- Executive-Regulatory Function
- Visual/Spatial/Nonverbal processing
- Motor
- Academic Achievement
- Adaptive Functioning
- Social/Emotional
- Personality

Neuropsychological Findings by Domain in Epilepsy

Overview

It is long recognized that persons with epilepsy have greater incidence of cognitive and psychiatric comorbidities (Gowers 1881). Consistent with the heterogeneity of seizure disorders, but even often within a single type of epilepsy, *no* single cognitive profile exists for epilepsy. Other general considerations are as follows:

- Although there are some findings that focal epilepsy is associated with focal deficits, this is true for adults more than children likely due to the plasticity of children's brains. Therefore, children do not follow adult profiles. Moreover, even though focal epilepsy may result in a deficit related to the location of the epilepsy, this is not the *only* deficit that the person is contending with. For example, a person with left temporal lob epilepsy may have verbal memory difficulties, but also has inattention and slow processing speed.
- Seizures (focal or generalized) may impact functioning across any or all domains.
- Cognitive difficulties may predate and/or persist beyond onset, which may indicate that cognitive difficulties may share a common underlying neuroanatomic substrate with what is generating the seizures.
- Progressive deterioration of cognitive skills is observed in a minority of individuals. As such, a plateau and/or regression of skills is a strong impetus for surgery, in particular for hemispherectomy, but any other resection as well. Please see below within specific domain areas for further discussion.

There are multiple factors that combine to determine neuropsychological outcome:

- Age of onset
- Seizure type
- Underlying pathology
- Neuronal discharges (ictal and interictal)
- Episodes of status
- Antiseizure medications (ASMs)
- Psychosocial
- Public attitudes/stigma
- Individual attitude (e.g., self-worth; depression)

The challenge has been to unravel this complex picture due to a lack of quality studies and challenges (e.g., suitable controls, complex interactions; sensitivity of neuropsychological test; small sample sizes/lots of tests; validity). With that caveat, some general cognitive outcomes include the following:

Table 22.1 Neuropsychological measures by domain

Domain	Common measures—but not exhaustive list	
Skill	All (most) ages	
	Adult version	Pediatric version
Intellectual functioning		
	Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)	
	Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)	Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)
Language		
Verbal fluency	Delis–Kaplan Executive Function System (DKEFS)—Verbal Fluency; Controlled Oral Word Association Test (COWA or COWAT); FAS	
		NEPSY-Second Edition (NEPSY-II): Word Generation
Naming	Boston Naming Test (BNT); Expressive One-Word Picture Vocabulary Test-Fourth Edition (EOWPVT-4)	
Receptive vocabulary	Peabody Picture Vocabulary Test-Fourth Edition (PPVT-IV); Receptive One-Word Picture Vocabulary Test-Fourth Edition (ROWPVT-4)	
Comprehension	Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-IV): Concepts and Following Directions; Token Test	
		NEPSY-II: Comprehension of Instructions subtest
Phonological skills	Comprehensive Test of Phonological Processing-Second Edition (CTOPP-2) (to age 24)	Comprehensive Test of Phonological Processing-Second Edition (CTOPP-2)
Memory		
Visual	Rey–Osterrieth complex figure test—immediate, delayed, recognition trials	
	Wechsler Memory Scale-Fourth Edition (WMS-IV): Visual Reproduction, Design Memory; Brief Visual Spatial Memory Test—Revised (BVMT-R)	Children's Memory Scale (CMS): Dot Locations, Faces; NEPSY-II:Memory for Designs
Verbal	Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2):Story Memory; Rey Auditory Verbal Learning Test (RAVLT)	
	WMS-IV: Logical Memory, Verbal Paired Associates; California Verbal Learning Test-Second Edition (CVLT-II); Hopkins Verbal Learning Test–Revised (HVLT-R)	CMS: Stories, Word Pairs; California Verbal Learning Test-Children's Version (CVLT-C)
Attention and executive functioning		
Attention	Test of Variables of Attention (TOVA); Conners' Continuous Performance Tests-Second Edition (CPT-II);	
	Test of Everyday Attention (TEA)	Test of Everyday Attention for Children (TEA-Ch)
Working memory	Digit Span Backwards (Wechsler measures); Auditory Consonant Trigrams (ACT); WRAML-2 Finger Windows, Sentence Memory	
Set-shifting	Trail Making (Trail Making Test (TMT)) Parts A and B; DKEFS: Trail Making); 20 Questions; Wisconsin Card Sorting Test (WCST)	
Inhibition	Stroop Color Word Test (Kaplan); DKEFS Color Word Interference	
Planning	Tower of London-DX-Second Edition; DKEFS Tower Test; Rey–Osterrieth Complex Figure Test	

(continued)

Table 22.1 (continued)

Domain	Common measures—but not exhaustive list	
Skill	All (most) ages	
	Adult version	Pediatric version
Overall	Behavior Rating Inventory of Executive Function (BRIEF)	
Visual-spatial skills/visual-motor integration		
	Beery-Buktenica Developmental Test of Visual-Motor Integration-Sixth Edition (VMI): Visual-Motor Integration, Visual Perception; Hooper Test of Visual Organization (VOT); Judgment of Line Orientation Test (JLO); Rey–Osterrieth Complex Figure Test—Copy Trial	
Fine motor		
	Grooved Pegboard Test or Purdue Pegboard Test; Beery-Buktenica Developmental Test of Visual-Motor Integration-Sixth Edition (VMI): Motor Coordination subtest	
Academic achievement		
	Woodcock Johnson III Tests of Achievement (WJ-III); Wechsler Individual Achievement Test–Third Edition (WIAT–III); The Wide Range Achievement Test 4 (WRAT4)	
Social/Emotional-Personality-Adaptive (Rating scales)		
	Vineland Adaptive Behavior Scales, Second Edition (VABS-II); Adaptive Behavior Assessment System-Second Edition (ABAS); The Scales of Independent Behavior-Revised (SIB-R)	
	Achenbach Adult Self-Report (ASR); Beck Depression Inventory-Second Edition (BDI-II); Beck Anxiety Inventory (BAI); ADHD Rating Scale-IV	Achenbach Child Behavior Checklist (CBCL)/Youth Self-Report (YSR)/Teacher Report Form (TRF); Children's Depression Inventory-Second Edition (CDI-2); Revised Children's Manifest Anxiety Scale-Second Edition (RCMAS-2)
	The Minnesota Multiphasic Personality Inventory-2 (MMPI-2); NEO Personality Inventory-Revised (NEO PI-R)	The Minnesota Multiphasic Personality Inventory-Adolescent (MMPI-A)

- Generalized seizures are worse than focal, and tonic–clonic seizures are worse than absence
- Earlier onset is associated with more difficulties
- Interictal subclinical discharges are associated with transient cognitive impairment (TCI). This has mixed evidence, but fewer studies.

Intelligence

Approximately one-third of people with epilepsy have IQ scores below 70, which falls in the Intellectually Deficient (ID—formally MR) range. The majority (≈ 2/3) of people with epilepsy have average range (or higher) intelligence. Nonetheless, even taking this cohort—excluding the one-third with IQ < 70)—there is a downward shift of IQ with a Mean IQ (≈ 90) which falls in the low average range compared to the normal population where Mean IQ = 100.

Risk factors for ID in epilepsy:

- Primary generalized epilepsy, West syndrome, Lennox–Gastaut syndrome, localization-related epilepsy, but seizure focus difficult to isolate
- Severe volumetric abnormalities
- Early onset of epilepsy
- Frequent seizures, more episodes of status epilepticus
- Polytherapy
- Comorbid diagnoses (e.g., autism)

As such, IQ is considered a proxy for outcome, disease severity, and extent of underlying pathology.

Language

Along with memory, language is probably one of the most studied domains in people with epilepsy given that focal epilepsy is most often in the temporal, followed by frontal lobes.

- Language representation: There is a higher incidence (25–30%) of atypical dominance (right or bilateral) than the normal right-handed population (5%).
  - Atypical language dominance is more likely with large, early in development insults (e.g., perinatal stroke), with earlier onset and with left-handedness.
  - If language remains ipsilateral to focus, a left hemispheric focus may have impact on language functions (speeded naming).
- Appropriate simple, single-word knowledge, untimed language skills.
- Adults with TLE frequently have word-finding problems, which is found by confrontation naming tasks (e.g., Boston Naming Test), which may be related to the hippocampal role in word retrieval.
- Progressive language impairment is associated with Rasmussen's encephalitis and Landau–Kleffner syndrome, both of which have a period of normal language development.

Memory

Similar to language findings, memory difficulties are commonly associated with TLE.

- The presence of mesial temporal pathology and degree of hippocampal atrophy is associated with greater impairment.
- "Material specificity" of memory problems is true more so in adults such that left TLE is associated with verbal memory problems. Similarly, right TLE is associated (but not as strongly) with visual memory problems. This finding is the basis of the utility of presurgical evaluation by providing evidence for location of seizure focus and determining the risk of postsurgical cognitive deficits. List learning measures tend to be the most predictive of hippocampal dysfunction.
- Unlike for other areas of functioning, there is evidence for progressive loss with continued seizures which is consistent with the changes seen on MRI.
- One hypothesis of why memory deficits are not specific to TLE is that memory performance may also be disrupted due to other skills such as poor organization or attention that rely on frontal lobe functions.

Attention/Executive Functions

Beyond the effects of IQ, attention problems are commonly observed.

- Prevalence of ADHD is 20–40%.
- ADHD Inattentive Presentation is more common, and the boys and girls are equally represented, which is different from developmental ADHD with no seizures.
- There may be higher rates of attention problems with FLE and CAE.
- Associated issues such as nocturnal seizures or medication side effects may be the primary cause of inattention.
- Myth that stimulants used for ADHD symptoms would lower seizure threshold; however, many studies have shown this to be untrue.

Executive functioning (EF), a set of skills that is necessary for efficient and goal-directed behavior is less well studied, but is a common difficulty. Aspects of EF that are shown to be impaired in people with epilepsy include shifting, cognitive flexibility, working memory, and organization.

- Parent questionnaire of EF was a significant predictor of performance and helpful in identifying an "at-risk" group of children with new-onset epilepsy.

Visual/Spatial

Findings are less consistent for visuospatial skills such as object recognition, drawing objects, and visual closure. While some studies have found these to be lower in right-hemispheric seizure foci, others have noted that language dominance may be an important factor. If language function has reorganized to the right related to a left hemispheric focus, a deficit in visuospatial processing may develop because the transfer of language to the right hemisphere is displacing visuospatial function to preserve language. This is referred to as the "crowding hypothesis."

Psychomotor/Reaction Time

Slow processing speed is a common finding in people with epilepsy and may be due to neuroanatomic anomalies or treatment effects.

- Processing speed deficits are the most common side effect of ASMs. Slower speed is associated with polytherapy (defined by load or toxicity as well as number) and type of ASM (topiramate; phenobarbital; GABA-ergic inhibition).
- Seizure type has been implicated, particularly FLE and benign rolandic epilepsy.

Academic Functioning

Poor academic achievement is associated with all epilepsy types. Outcome is moderated by psychosocial variables. As with other cognitive skills, problems may predate seizure onset; however, should seizure control disrupts school attendance, there may be a larger gap following seizure onset.

Psychosocial

There are increased rates of mood disorders (anxiety/depression) with a lifetime prevalence risk of 35%.

- Limbic/temporal seizures have greater risk, which may be an evidence of shared neurophysiology
- Less clear evidence of increased rates of aggression or psychosis
- Evidence for both environmental causes (stigma, missed school/work, unpredictability/lifestyle changes) and shared neurophysiology (higher rates than other medical disorders)

Quality of life is markedly lower in people with epilepsy and is not necessarily improved with seizure control. About 50% of persons with epilepsy feel stigmatized.

Mapping Cognition

Mapping cognition is a role that may be undertaken primarily by either the neuropsychologist or neurologist or as a shared venture.

- Purpose is that the information is needed to avoid morbidity of surgical procedure.
- Techniques used to map language, memory, and motor functions are changing with available technology.
- Prior gold standard method was to pharmacologically inactivate ipsilateral anterior and middle cerebral arteries for several minutes. This procedure is referred to many ways, including the intracarotid amobarbital test (IAT)/Wada or etomidate speech and memory test (eSAM), and has no standard protocol. The aims are to 1) lateralize function (language and memory) and 2) demonstrate the

capacity of contralateral hemisphere to sustain function.
  - Use of IAT/Wada is on the decline due to drug availability and clinical validity of fMRI
  - Consists of presenting language and memory items during a brief window (1–2 min) of drug effect; eSAM protocol allows for continuous infusion which is a distinct advantage but not widely used
  - Based on each hemisphere and in context of baseline functioning, count errors or aphasia to get an asymmetric index of functioning for language and memory
  - Disadvantages are that it is invasive, site-specific method, and feasibility relies on institution
  - Advantage is that it is still the best established method for memory functioning (at this point) and is probably more widely used in adult centers for that reason
- Functional MRI (fMRI) involves having the patient do language or motor tasks while in an MRI. The blood oxygen level-dependent (BOLD) signal is extracted and analyzed. There is increasing availability of fMRI packages on standard clinical systems. There is an advantage of localization and lateralization of function noninvasively; however, mapping of memory functioning is still fraught with practical and technical challenges. Disadvantage is that movement may render a study uninterpretable; however, technological advances may combat this in the near future.
- Electrocortical stimulation (ECS) mapping is either intraoperative or bedside mapping (grids) of function for motor or language functions. Grids for seizure localization purposes are discussed elsewhere. Again no standardized protocol exists; however, in general, language responses must be brief enough to occur during the stimulation time frame, so they may be limited to single words. The patient must also be able to answer questions immediately (without long pauses) at baseline to ensure accurate interpretation of pauses in responding related to stimulation.

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Magnetoencephalography and Magnetic Source Modeling

23

Manoj Raghavan

Introduction

The generators of neuromagnetic signals are essentially the same as those of EEG signals. Summation of synchronous postsynaptic potentials occurs to a greater degree when there are regular arrays of similarly oriented cells, as for instance in the pyramidal cell layer in the cortex. Magnetic fields generated by electrical currents in the cortex are oriented perpendicular to the direction of neuronal currents. This, together with the folded geometry of the cortex, results in some differences in the cortical surfaces that contribute to EEG and magnetoencephalography (MEG) signals. MEG sensors are sensitive to magnetic fields that are orthogonal to the head surface. This corresponds to electrical fields that are parallel to the scalp surface, such as those generated by cortical surfaces in the sulcal banks. EEG, on the other hand, is preferentially sensitive to radially oriented electrical fields generated at the crests of gyri.

Magnetic fields generated by the brain are of the order of 100 femtotesla ($\sim 10^{-13}$ T). For comparison, the electrical activity of the heart generates magnetic fields that are greater by many orders of magnitude. The ambient electromagnetic noise in an urban environment is even greater. The detection of weak magnetic fields generated by the brain, therefore, requires not only highly sensitive instruments, but also a magnetically quiet environment that is usually provided by a magnetically shielded room (MSR).

MEG History

The key enabling technology that allows the recording of very weak magnetic fields is the superconducting quantum interference device (SQUID). This device is based on a quantum phenomenon called the Josephson effect which describes the current flow through a very thin insulator that separates two superconductors. Before the era of SQUIDs, David Cohen at MIT had demonstrated in 1968 that it is possible to record cortically generated magnetic fields in a magnetically shielded environment. The recordings used coils wound around ferrite cores and employed signal averaging based on simultaneous recorded EEG signals. The earliest commercially available SQUIDs were used by David Cohen and others at MIT to record the first magnetocardiogram—a signal that is several orders of magnitude larger than magnetic fields generated by the brain. By 1971, the first MEG records of the alpha rhythm were demonstrated [1].

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MEG Equipment and Recording

From early devices with a single magnetometer, MEG recording technology has evolved over the years to multichannel systems with several hundred sensors.

MEG recording systems are housed in a magnetically shielded room, which isolates the recording system from ambient magnetic interference from various sources in the environment. In order to achieve sufficient attenuation of ambient magnetic interference, the walls of the MSR may have several layers of different types of metal that attenuate magnetic interference in different frequency bands. In addition to passive shielding, some MSRs may also have active coils in the walls which generate their own magnetic fields to cancel ambient fields.

Magnetic fields generated by the brain are picked up by *flux transformers* which are inductively coupled to the SQUIDs. The flux transformers can be configured as *magnetometers* or *gradiometers*. Magnetometers—a simple example being a conducting loop—produce output currents with magnitudes that are determined by the magnetic flux through the loop. Gradiometers, on the other hand, are configured by coupling two conducting loops either side by side (in the same plane), or along an axis, in such a fashion that the net output is proportional to the difference in magnetic fluxes through the two loops. These planar or axial gradiometers detect magnetic field gradients rather than absolute magnetic flux at a location. In typical MEG recording systems, an array of flux transformers are arranged in the shape of a helmet at the bottom of a container called a *dewar*. The *dewar* also houses the SQUIDs and is filled with liquid helium to maintain the temperatures low enough to permit superconductivity. The outputs of these sensors are amplified, then digitized, and recorded using digital recording systems.

In addition to localizing spontaneous epileptic activity, MEG studies are often performed to localize functional cortices. Localization of primary sensory areas is performed by source modeling of evoked responses to simple stimuli (visual, auditory, or somatosensory). For the lateralization of language functions, a language task such as a word listening task or word reading task may be employed. Localization of motor areas requires the patient to perform simple motor tasks such as tapping a finger. For evoked responses to be sufficiently well defined and stand out above the resting background oscillations, many trials of the task (typically >100) are usually repeated. The responses recorded at each sensor are averaged across trials in order to obtain satisfactory signal-to-noise ratios prior to modeling the sources of these evoked responses.

Magnetic Source Modeling

In tandem with the development of the recording hardware, the rapid evolution of computing technology has made it possible to take the recorded activity from the MEG sensors and model the cortical generators of the activity. This step is referred to as magnetic source modeling or magnetic source imaging (MSI).

The objective of magnetic source modeling is to account for the topography of the magnetic fields measured at a given point in time in the MEG sensors using a hypothetical generator within the brain. The problem of determining brain sources from a set of measurements at the sensors is an example of an *inverse problem*. In this case, the inverse problem is highly underdetermined; i.e., there are far too many unknown variables and not enough constraints for there to be a unique solution to the problem. Such inverse problems are often referred to as "ill-posed" inverse problems. There are an infinite number of configurations of model sources within the brain which could all produce the same observed sensor level recordings. In order to make this problem tractable, we first need to model how magnetic fields associated with any given electrical generator within the head propagate to the sensors. This is called the

forward model. The forward model requires an anatomical model of the head and the structures from which the electrical activity arises. This is referred to as the *head model*. Once a forward model is defined, it is possible to generate many hypotheses about possible generators of the observed sensor measurements and identify the hypothesis that best explains the measurements. Different source modeling techniques differ in the nature of the forward modeling and the types of generators permitted.

Of the various source modeling methods that have been developed over the years, *equivalent current dipole* (ECD) modeling has found wide use in clinical applications. ECD modeling assumes that the electrical generators of activity measured at MEG sensors are point dipoles: a source and sink (positive and negative ends) separated by an infinitesimally small distance. Although real generators of electrical activity in the brain are not point sources, ECD modeling has proven to be clinically useful in localizing the sources of epileptic spike activity and evoked potentials. Dipolar models are defined by their locations (x-, y-, and z-coordinates in a frame of reference to which the patients' head model has been co-registered) and orientation (defined by 2 parameters). Additional "goodness-of-fit" parameters quantify how well a model dipole accounts for the observed neuromagnetic fields.

Several alternative techniques for source modeling currently exist, for instance techniques that model the generators as a distributed field of point dipolar sources. These distributed source modeling approaches have predominantly been used in research applications thus far. Source modeling methods can also be applied to the electrical signals recorded by EEG. However, because magnetic fields are not affected by CSF, meninges, skull and scalp, or skull breaches, the head modeling requirements for magnetic source modeling are much simpler. This translates into higher spatial resolution for an equivalent number of recording locations around the head for magnetic source modeling compared to electrical source modeling [2].

Source Modeling of Epileptic Activity and Evoked Responses

When modeling the sources of epileptic activity, the recorded MEG data are first reviewed visually by an experienced electroencephalographer to identify epileptic spike events or ictal activity which can then be subjected to source modeling.

Epileptic spikes seen in MEG may not always be seen in the simultaneous EEG recording, and likewise, not all EEG spikes are represented in MEG. Since MEG sees the magnetic component of an electrical event in the cortex, it is in theory more sensitive to electrical currents that are tangential to the head surface—as for instance from the banks of sulci. EEG, on the other hand, is more sensitive to radial sources, such as those generated at the crests of gyri. In most instances, however, epileptic spikes have generators that are several square centimeters in area and have both radial and tangential components. However, the spike may lead in one or the other modality depending on whether the tangential or radial sources dominate at the onset of the spike.

Once epileptic spikes are identified in the MEG sensors, dipolar models are typically employed to localize the sources in clinical applications. Figure 23.1 shows an example of interictal epileptic spike events whose sources localize to the right medial temporal regions. Due to the relatively short duration of MEG recordings compared to long-term EEG monitoring studies, ictal events during MEG are uncommon. However, when ictal activity is recorded, early ictal rhythms that precede any head movements can be subjected to source modeling to localize seizure onset zones. An example of dipolar source modeling applied to ictal rhythms is shown in Fig. 23.2.

There is ample evidence that magnetic source modeling of evoked responses can reliably localize primary sensory cortices (visual, auditory, and somatosensory). Figure 23.3 shows an example of source modeling of somatosensory evoked response to median nerve stimulation using dipolar modeling and dSPM [3]. Localization of primary motor cortex using dipolar

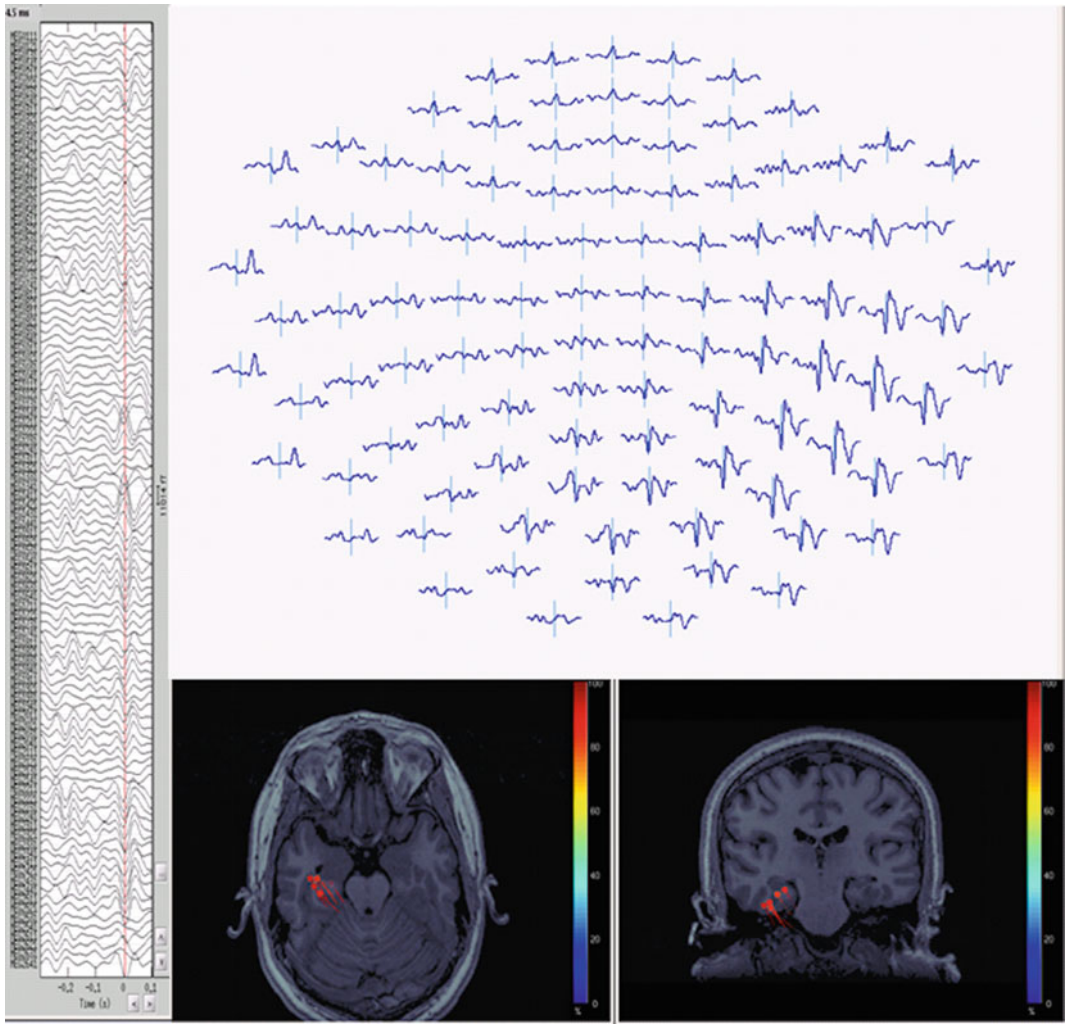

Fig. 23.1 Dipolar sources of epileptic spikes. The panels above show an example of dipolar source models of epileptic spike activity. The panel on the *far left* shows MEG traces from a subset of magnetometers with the cursor marking an epileptic spike event. A sensor level topographic representation of the event is shown in the *top right panel*, along with dipolar sources of a collection of such events on axial and coronal planes through the dipole cluster in the *bottom right panel*

modeling of motor preparation potentials is, however, less reliable [4]. Alternative methods to localize changes in beta band oscillatory activity in the motor cortex have been explored with greater success [5], although yet to be widely adopted.

For lateralizing language, neuromagnetic responses to auditory language stimuli have been found to be concordant with the Wada test in 87% of patients [6]. Using the same methods, Doss et al. [7] found language representation in the hemisphere to be treated with a concordance rate of 86% with the Wada test in 35 patients, with a sensitivity of 80% and specificity of 100%. Several smaller studies have reported MEG–Wada concordance rates between 69 and 100% using a variety of paradigms and analysis methods.

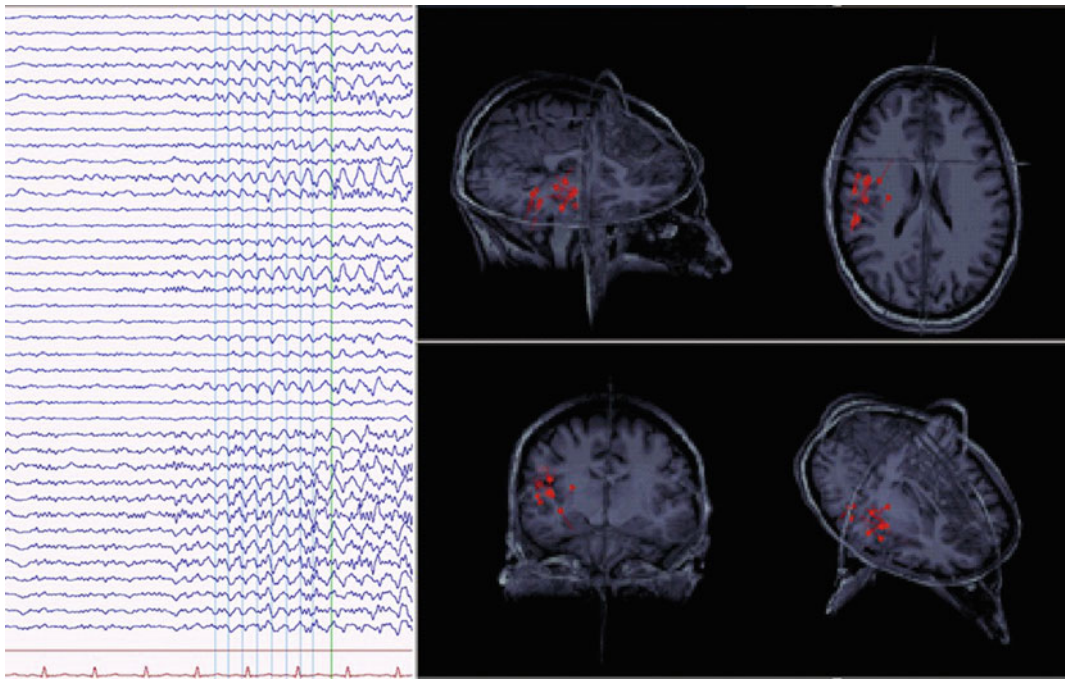

Fig. 23.2 Dipolar sources of ictal sharp rhythms. The *panels above* show an example of ictal source modeling using MEG. The traces on the *left panel* show seizure onset as recorded in a subset of MEG sensors. Dipolar sources of successive peaks of the ictal waveform are shown on planar views in the panels on the *right*

The Role of MEG in Presurgical Evaluations

Unlike EEG, MEG is not indicated for the initial evaluation of new-onset seizures but can provide valuable localization of epileptic pathology in patients with medically refractory epilepsy who are undergoing evaluations for epilepsy surgery. MEG primarily localizes interictal epileptic abnormalities which help identify "irritative zones" in the brain. Source modeling of interictal spikes using MEG may be particularly useful in patients with normal MR imaging, large or cystic lesions, lesions of indeterminate significance to the patient's epilepsy, or with multifocal or rapidly propagated spikes.

MEG is also clinically indicated for localizing primary motor or sensory cortices (somatosensory, visual, or auditory) to guide surgical planning for epilepsy, tumors, or vascular lesions, and can also be used to determine hemispheric language dominance.

The spatial accuracy of MEG and magnetic source modeling for localizing "irritative zones" is second only to invasive EEG [8]. MEG-guided review of MRI data has also been reported to identify subtle abnormalities that were previously missed, especially focal cortical dysplasia [9–11]. However, MEG should not be viewed as a tool that replaces invasive EEG or other noninvasive tests such as PET or SPECT. There is now sufficient evidence that MEG can provide significant non-duplicative information to improve surgical outcomes or preempt expensive invasive intracranial EEG studies [12–15]. While MEG may not eliminate the need for intracranial EEG studies, it can help generate better hypotheses about seizure onset zones, and thereby guide electrode placement for invasive EEG studies [16, 17].

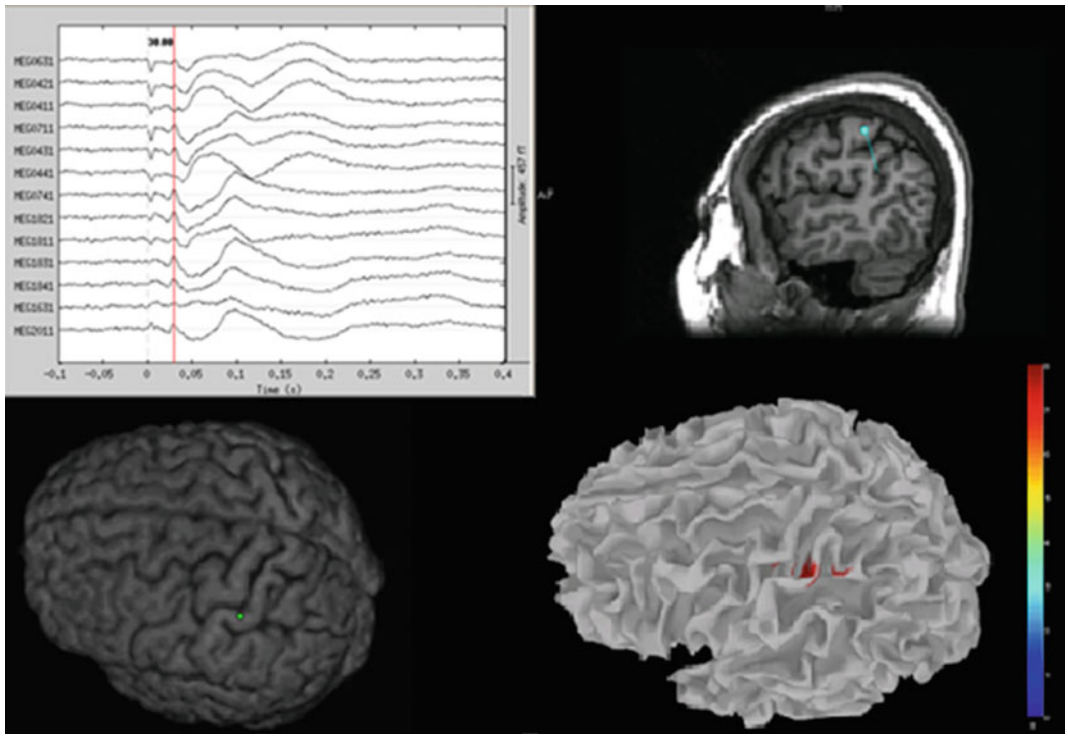

Fig. 23.3 Dipolar and distributed source models (dSPM) for somatosensory evoked responses. The *left upper panel* shows the evoked responses to somatosensory stimulation of the right median nerve in a subset of MEG sensors in the left central region. Dipolar sources at the peak of the response are shown in the *top right* and *bottom left panels*. A distributed source model for the same point in time is shown in the *bottom right panel* (dSPM with a threshold of $p < 0.001$). Both the dipole model and maxima of the dSPM activation localize to the post-central gyrus in an area consistent with anatomically predicted hand somatosensory representation

Some Limitations of Current Clinical MEG Methodologies

Localizing "irritative zones" is often insufficient to predict seizure onset zones, especially when they are multifocal. Unfortunately, ictal MEG studies are not the norm since it is impractical to monitor patients in a MEG scanner for an extended period of time in order to capture seizures. In about 20% of MEG studies, no epileptic spikes may be observed during the recording. In these cases, MEG is unable to provide useful localizing information about epileptic pathology. Alternative interictal biomarkers of epilepsy such as focal slow waves or pathological high-frequency oscillations are therefore of interest.

While most clinical applications of MEG employ dipolar source modeling techniques, dipolar models are unsuitable for studying network phenomena such as functional connectivity, causal interactions, or network dynamics which may have relevance to localizing and modeling epileptic networks.

For localizing function, although source modeling of evoked responses provides good localization of primary sensory cortices, these techniques remain to be validated for mapping language networks in the anterior temporal or frontal neocortices to guide surgical resection boundaries.

Summary

MEG and magnetic source modeling provide a noninvasive technique for localizing spontaneous and evoked brain activity with high spatiotemporal resolution. Single *equivalent current dipoles* remain the most widely used source modeling method in clinical applications, although imaging methods are increasingly being explored. MEG and source modeling of epileptic activity can provide significant non-redundant information to help improve outcomes of epilepsy surgeries or preempt expensive invasive EEG studies. MEG also provides an alternative to fMRI for noninvasively localizing eloquent cortices for neurosurgical planning.

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Vagus Nerve Stimulation and Other Neuromodulation

24

Gholam K. Motamedi

History of VNS Therapy in epilepsy

1985	First animal studies
1988	First human implant
1992	First randomized active control study (E03) completed
1994	European community approval
1996	Second randomized active control study (E05) completed
1997	US Food and Drug Administration commercial approval in patients $\geq$12 years with refractory partial epilepsy
2005	US Food and Drug Administration commercial approval in patients $\geq$18 years with chronic major depression refractory to adequate treatment with $\geq$4 antidepressants
Feb. 2009	50,000 + implants worldwide for both epilepsy and depression (currently >65,000)

Wheless JW, Wyllie's Treatment of Epilepsy: Principles and Practice, 2011
http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s050a.pdf

Approved Indications of VNS Therapy

The VNS has been approved by the food and drug administration (FDA) for:

1. Adjunctive therapy in patients $\geq$12 years with refractory (drug-resistant) partial onset epilepsy, and
2. Adjunctive therapy in *patients* $\geq$*18 years with* chronic or *recurrent* major depressive episodes refractory to adequate response to $\geq$4 adequate *antidepressants.*

Refractory Epilepsy—Definition

More than 50% of patients with epilepsy have partial epilepsy. The AED success rate in patients with partial epilepsy is about 50% compared to more than 80% rate in primary generalized epilepsy [1–3]. The current definition of refractory epilepsy requires failure of adequate trials of two appropriate and tolerated AEDs at maximum possible doses, whether as monotherapy or in combination, for enough time (a follow-up period 3 times the longest inter-seizure interval or 1 year, whichever longer) [4]. However, only about 20% of these patients will be eligible for

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resective brain surgery. Therefore, in these patients, VNS Therapy is a viable palliative treatment option.

Clinical Indications of VNS

Patients with documented refractory partial epilepsy who are not eligible for brain surgery, e.g., having multifocal epilepsy, unclear seizure focus, overlapping eloquent cortex, or those who are opposed to are considered potential candidates for the VNS Therapy. VNS may have a limited role in patients with previous unsuccessful resective epilepsy surgery. In a recent series, 18.75% of such patients had $\geq 50\%$ reduction in seizure frequency with one case of worsening seizures, but it may be an option given its potential antipsychotic and mood-stabilizing effects [5].

Vagus Nerve Anatomy and Lead Placement

The lead electrodes must be placed below where the superior and inferior cervical cardiac branches separate from the vagus nerve. Stimulation of either of these two branches during the system diagnostics (lead test) may cause bradycardia and/or asystole. In most patients, the main vagus nerve is the largest of the three nerves (Figure 24.1).

Electrode Polarity and Pulse Stimulus

A bipolar lead transmits stimulation from the generator to the left vagus nerve. The lead consists of a pin that connects to the generator on one end, and the helices that contain the stimulation electrodes and anchor tether on the other end.

Initial Clinical Trials—Overview

Adjunctive use of left VNS Therapy in patients with refractory epilepsy was tried in five acute-phase landmark clinical studies in 45 centers (40 US, 1 Canada, 4 EU). A total of 454 patients were implanted with VNS with a total patient exposure of 901 device-years. Individual mean patient exposure was 24 months (8 days–7.4 years).

Eligible patients were implanted (baseline period 12 weeks) and the generator was activated 2 weeks later. In the two randomized, blinded, active control trials (E03 and E05), patients were randomized to: (1) HIGH group (higher frequency, pulse width, higher duty cycle) and

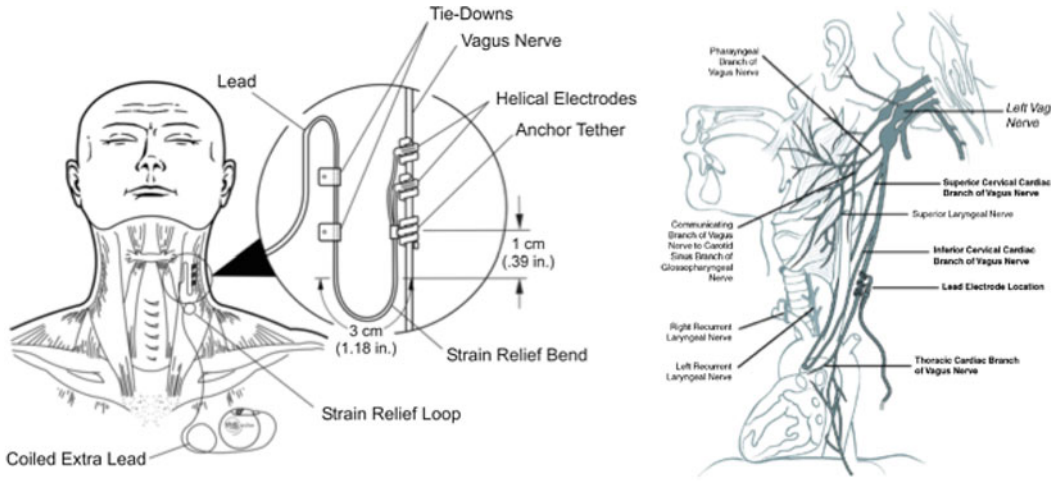

Fig. 24.1 Cyberonics.com, Implantation procedure, 2010

(2) LOW group (active control) and were followed for a 14-week treatment period (E05: [6]).

Clinical Trials: Efficacy and Safety

The HIGH group showed significant seizure frequency reduction compared with the baseline and the LOW group (24.5% vs. 6.1%, $p = 0.01$). In the HIGH group, 31% experienced $\geq 50\%$ seizure reduction as opposed to 13% in the LOW group ($p = 0.02$). The most common adverse events were voice alteration and dyspnea. The treatment was well tolerated and 97% patients (306 of 314) continued into the long-term follow-up phase of the study (Fig. 24.2).

Stimulation Parameters and Safety

VNS Therapy is based on:

- output current,
- signal frequency,
- pulse width, and
- ON/OFF time.

Therefore, each parameter can be programmed in a variety of combinations to achieve optimal stimulation setting. However, based on animal studies stimulation at high frequency (≥ 50 Hz) + ON time $\geq$ OFF time may result in degenerative nerve damage. The ON time OFF time can be induced by continuous or very frequent magnet activation (> 8 h) and therefore should be avoided.

Suggested Initial Dosing Settings

The VNS is activated ≥ 2 weeks after implantation and when the healing process is completed. The initial recommended parameters are as follows:

- Output current of 0.25 mA,
- ON time 30 s/OFF time 5 min,
- Signal frequencies of 20–30 Hz, and
- Pulse width 250–500 μs.

It is recommended to keep all AEDs stable for the first 3 months of VNS before any changes are attempted. The current intensity can be increased by 0.25 mA every 2–4 weeks, to reach a minimum of 1 mA over a 6–8 week period, or as tolerated. It is also recommended to give the patient enough time to adapt before leaving the office, and before the next increment.

Adverse Effects

The most common side effects associated with VNS Therapy include:

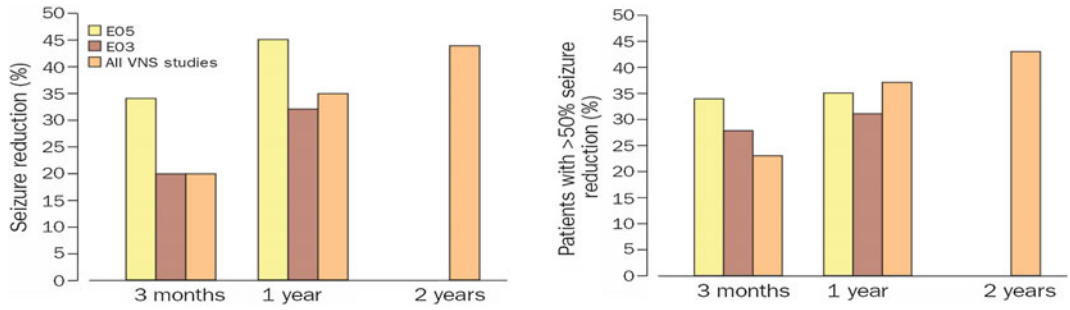

Fig. 24.2 *Left* median seizure reduction (%) of patients participating in E03 ($n = 114$) and E05 ($n = 105$) randomized placebo-controlled trials, and all VNS studies combined (E01–E05, $N = 440$) at 3 months, 1 year, and 2 years of follow-up (intent-to-treat analysis). *Right* proportion of patients with $\geq 50\%$ seizure reduction in the same groups (Ben-Menachem, Lancet Neurol. 2002)

- Hoarseness: up to 60% and may indicate device malfunction, nerve constriction (apparent within a few days), nerve fatigue with intense stimulation parameters (turn off for several days until hoarseness subsides), and persistent hoarseness not associated with stimulation suggests nerve irritation (requires immediate investigation).
- Dysphagia and aspiration: there is higher risk with preexisting swallowing difficulties.
- Dyspnea: higher risk with underlying COPD or asthma.
- Obstructive sleep apnea (OSA): higher risk of apneic events during the stimulation with OSA (lower stimulus frequency of 2 Hz or longer "OFF" time recommended). Since new onset cases of OSA have been reported, prior evaluation in high-risk patients should be considered.
- Nerve damage with device malfunction: may cause painful stimulation (tape magnet over the generator to stop stimulation if suspect a malfunction; evaluate for possible surgical intervention).
- Laryngeal irritation: more common in smokers.
- Lead break: may prevent patients from receiving efficient therapy. If diagnostics suggest a fracture, turn the pulse to 0 mA output current (to prevent possible dissolution of the conductor material hence pain, inflammation, and vocal cord dysfunction).
- Trauma to the vagus nerve: can occur during surgery and can result in permanent vagal nerve dysfunction.
- Sudden unexplained death in epilepsy (SUDEP): through August 1996, 10 (definite/probable and possible) cases were recorded among 1000 VNS patients (2017 patient-years of exposure) indicating an incidence rate of 5/1000 patient-years. However, estimates for non-VNS epilepsy patients range from 1.3 to 3.5 in the epilepsy population and 9.3 in surgical candidate population. Therefore, the recorded rates of SUDEP did not seem to have been increased significantly by VNS Therapy.
- Manipulation of pulse generator and lead by patients through the skin (Twiddler's syndrome): may damage or disconnect the lead from the generator (Cyberonics.com, Physician's manual).

Precautions

Cardiac evaluation: in case of family history, past medical history, or EKG indications of dysfunctional cardiac conduction systems (reentry pathway).

Serum electrolytes: Mg^{2+}, Ca^{2+} levels to be checked before implantation.

Postoperative bradycardia: can occur in patients with cardiac arrhythmias; consider postimplant EKG and Holter monitoring.

Bradycardia (<40 bpm) and/or asystole: may occur during intraoperative system diagnostics (lead test). In such patients cardiac monitoring at the time of device activation is recommended.

Optimizing Parameters and Alleviating Side Effects

Optimizing Results

This can be achieved by increasing output current and/or modifying ON/OFF times (duty cycle).

Managing Side Effects

The following steps may be taken as needed to alleviate side effects: decreasing signal frequency (from 30 to 20 Hz) or decreasing output current

(by 0.25 mA). If decreasing the output current does not achieve tolerability, lowering the pulse width (from 500 to 250 μs) may be considered.

VNS Warning with MRI

The VNS is MRI compatible including 1.5T and 3T scanners. Head and extremity scans are allowed using a transmit and receive type of RF coil. Before patient enters into the MR system room, both output current and magnet current should be set to 0 mA since MRI-induced magnetic field may cause magnet-mode activation and stimulation. After the MRI is done, reprogramming is needed to restore the setting parameters.

MRI should not be performed on patients with lead breaks, see product labeling for all conditions. Diathermy (shortwave, microwave, therapeutic—not diagnostic—ultrasound) should not be used on VNS Therapy patients.

Mechanism(s) of Action of VNS

The precise mechanism of action of VNS remains unknown. In animal models (maximum electroshock, PTZ, alumina gel, strychnine, kindling), VNS prevented seizures or seizure spread (except for the alumina gel model). A series of facts have been considered to play a role in its function, e.g., VNS affects heart and respiratory rates, vagus-initiated activity in the brain has been localized through use of fos1 immunoreactivity, regional brain glucose metabolism (in animals), and via PET imaging in human. The newest version of VNS labeled Aspire adds the advantage of cardiac rhythm detection of seizures.

Investigational Neurostimulators

In recent years, two pivotal trials of neurostimulation in humans with drug-resistant epilepsy have been conducted: deep brain stimulation (DBS) via chronic programmed bilateral stimulation of anterior thalamus (SANTE trial) [7] and closed-loop responsive neurostimulation (RNS) of intracranial structures [8]. The DBS (thalamic stimulation) has not yet been approved by the FDA, but it has been recently approved in Europe [3]. The RNS system (NeuroPace device) has been FDA approved in late 2014. There are also early reports of potential benefits of stimulating other extracranial sites (e.g., trigeminal nerve) ([9–11]).

Responsive Cortical Stimulation

Besides VNS, the other FDA-approved neurostimulation intervention is the responsive neurostimulator (RNS), NeuroPace®. The idea of RNS is based on studies that showed short trains of electrical stimulation can stop afterdischarges [12, 13]. Eligible candidates are patients with focal epilepsy with a well-defined but non-resectable epileptogenic zone such as eloquent cortex or bilateral mesial temporal foci. A multicenter, double-blinded, randomized trial involving 191 patients with partial epilepsy was conducted (≥ 3 seizures/month, 1 or 2 seizure foci). Responsive neurostimulator detecting abnormal EEG connected to depth or subdural leads was placed at 1 or 2 seizure foci. The pulse generator connects with the electrodes and is placed in the skull. One month after implantation, the subjects were randomized to receive or not receive (sham) stimulation. After a 12-week blinded phase, all patients received unblinded stimulation for 84 weeks. By the end of the blinded phase, stimulated group had a 37.9% seizure reduction compared to the sham group at 17.3% ($p = 0.012$) [8].

At 5 months postimplantation, 41.5% seizure reduction was seen in the stimulation group compared to a 9.4% reduction in the sham group. The seizure reduction continued to improve during a subsequent open-label phase where both arms received stimulation. A 50% responder rate (those who achieved 50% or more reduction of seizure frequency) was seen in 55% after two years. The median percentage seizure reduction was seen in 44% (at 1 year), and 53% (at 2 years) of patients. Intracranial hemorrhages

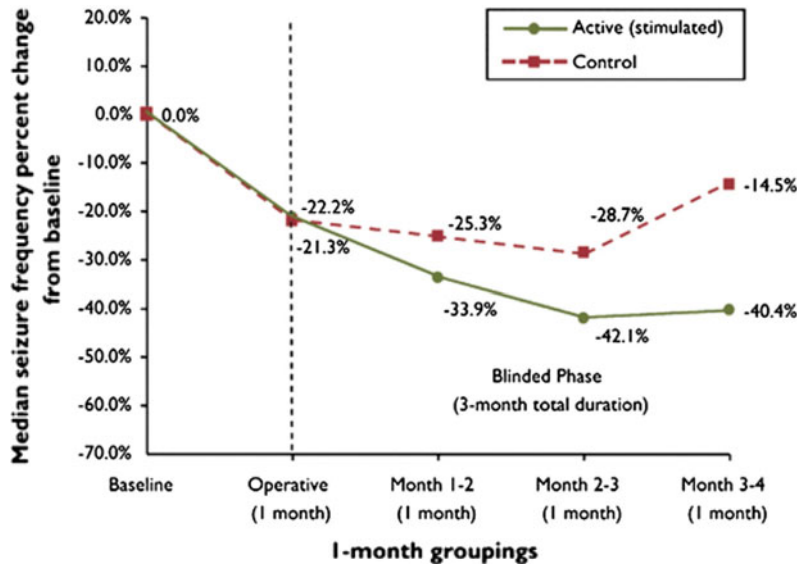

Fig. 24.3 Unadjusted median declines at the end of the blinded phase were 14.5% in the control group versus 40.4% in the stimulated group. By 2 years, there was 56% reduction in seizure frequency with $\geq 50\%$ reduction in 54% (14 seizure-free for at ≥ 6 months). There was no symptomatic hemorrhage or brain infection [7]

and infections each occurred in about 2% of implanted patients, but neither mood nor cognitive function worsened, and quality of life improved. Similar to the findings in VNS Therapy, seizure reduction appeared to further improve over time ($p < 0.0001$) and the RNS was well tolerated with acceptable safety [14].

Electrical Stimulation of the Anterior Nucleus of the Thalamus (SANTE Trial)

A multicenter, double-blind, randomized clinical trial including 110 patients with partial epilepsy (baseline seizure frequency 19.5/month) was conducted. After a 3-month blinded phase half of the patients received stimulation and the other half received no stimulation. Then, all patients received unblinded stimulation. In the last month of the blinded phase, the stimulated group had a 29% greater seizure reduction compared with the control group ($p = 0.002$) [7] (Fig. 24.3).

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Epilepsy Surgery Assessment and Testing

25

Gholam K. Motamedi

Refractory (Drug Resistant, Intractable, Pharmacoresistant) Epilepsy

The latest definition by the international league against epilepsy (ILAE) task force defines refractory epilepsy as failure of "adequate" trials of two antiseizure medications (ASMs) either as monotherapy or as combination (poly-) therapy, to control seizures [1]. In order to meet this criterion, it is critical to make sure that the ASMs have been given enough chance ("adequate trial")—i.e., they must have been used at the maximum tolerated dose (with no severe side effects)—and given enough time (determine seizure reduction after a follow-up period 3 times the longest interseizure interval, or one year, whichever longer). Therefore, with proper management, in most cases the diagnosis of refractory epilepsy should be possible to make within 1–2 years of the start of the seizures.

Treatment Options for Refractory Partial Epilepsy

Besides trying different combinations of ASMs, a variety of treatment options are available, including established methods of surgical resection of the seizure focus, or surgical "non-resection" options such as vagus nerve stimulation (VNS), responsive neurostimulation (RNS), or multiple subpial transections (MST). Currently there are also several investigational surgical treatments available such as deep brain stimulation (DBS, which has been approved as a treatment in Europe), transcranial magnetic stimulation (TMS), trigeminal nerve stimulation (TGNS), external VNS, or transcranial direct current stimulation (tDCS).

In particular circumstances, other non-surgical methods, e.g., ketogenic diet in young children, can be of therapeutic value. Currently, research for newer ASMs as well as novel potential therapies such as gene therapy, cell transplantation, or vaccination is underway.

Presurgical Evaluation

The purpose of presurgical evaluation is to characterize the seizure type and to lateralize and localize the seizure onset focus in patients with refractory partial epilepsy. Therefore, patients should be admitted to a properly equipped epilepsy monitoring unit (EMU) for continuous video-EEG monitoring. The ASMs are usually

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tapered down in order to record electrographic and clinical seizures for the above purposes. Patients also need appropriate neuroimaging studies including high-resolution epilepsy protocol MRI and other available imaging technologies as indicted or available such as MR spectroscopy (MRS), positron emission tomography (PET), single-photon emission computed tomography (SPECT), or magneto-encephalography (MEG).

In case the scalp recording is of limited value, patients who are considered potential candidates for surgical treatment may need invasive recordings using strips, grids, or depth electrodes and possibly cortical mapping before an appropriate surgical procedure could be planned. After lateralization and localization of the seizure onset focus, potential surgical candidates should undergo a series of tests for further evaluation to define their final candidacy for an appropriate surgical treatment including neuropsychological testing and functional MRI or intracarotid amobarbital procedure (IAP, Wada test).

Neuropsychology

The main questions that are addressed by a neuropsychological test include determining parts of the brain that are impaired. In particular, higher cognitive functions such as verbal and visual memory and language are studied. The test also helps establish a baseline for future comparison. This helps predict potential postsurgical deficits. Studies have shown that the best predictor of postoperative adequacy is the preoperative cognitive and psychosocial status; i.e., the lower the preoperative cognitive and psychosocial status, the lower the risk for further decline [2, 3].

Intracarotid Amobarbital Procedure (Wada Test)

This test "imitates" the prospective temporal lobectomy by temporarily inhibiting unilateral brain functions using a drug. Therefore, it helps lateralizing language dominance and memory function. The Wada test evaluates memory function of each temporal lobe separately to determine whether the nonepileptic side would be capable of handling memory function by itself after the affected temporal lobe is surgically removed. The test also can assist with seizure onset side since there is typically concordance between the seizure onset side and poor memory function on that side (upon contralateral injection).

Case Presentation #1

A 28-year-old woman with past medical history of seizures since age 9 years presented with the episodes of staring and left-hand clenching before convulsion (focal dyscognitive seizures with secondary generalization). These events occur twice a week on average. She had been on multiple ASMs in the past without much improvement. She has given up college and her previous jobs since she could not concentrate, drive a car, or work. Currently, she suffers from tremor, and memory and concentration problems. Her serum analysis shows high levels of phenytoin and valproate. A routine EEG and high-resolution brain MRI were obtained (Figs. 25.1 and 25.2).

Her presurgical evaluation indicated that she was a good candidate for a right anterior temporal lobectomy (Fig. 25.3). During the presurgical evaluation, she was started on levetiracetam, and her phenytoin and valproate were tapered off. Later, prior to her surgery, she responded better to combination therapy with levetiracetam and lamotrigine; i.e., her seizures were less frequent and her side effects improved significantly. The patient became seizure free after a right anterior temporal lobectomy and was kept on a lower dose of monotherapy with one of her ASMs (follow-up >4 years).

Is Epilepsy Surgery Warranted?

Randomized, controlled trials (RCT) to assess the efficacy and safety of epilepsy surgery were missing till 2001. In the first such study [4], 80 patients with temporal lobe epilepsy (TLE) were

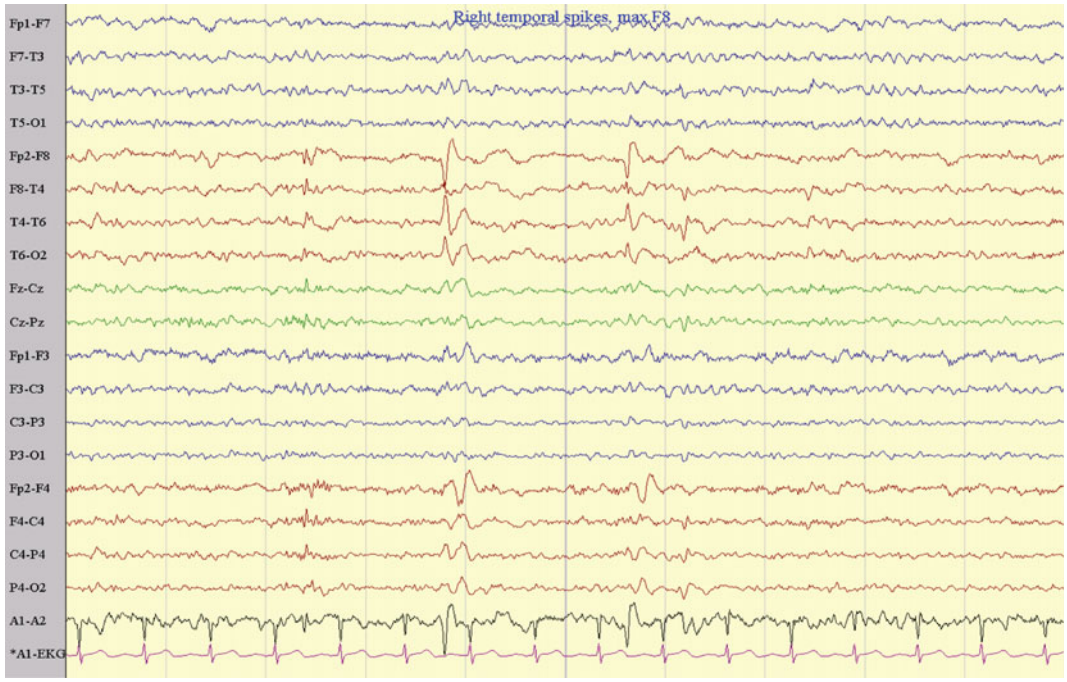

Fig. 25.1 Right anterior temporal spikes

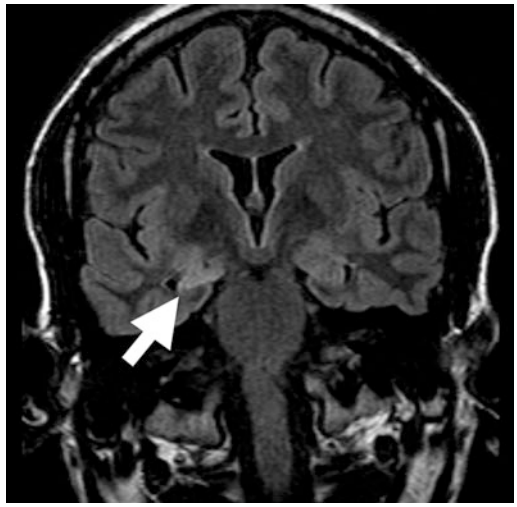

Fig. 25.2 High-resolution MRI detects mesial temporal sclerosis (MTS) in 80–90% of cases

randomly assigned to surgery ($n = 40$) or treatment with ASMs for one year ($n = 40$). The primary outcome was seizure freedom and secondary outcome included seizure frequency and severity, quality of life (QOL), disability, and death.

At 1 year, the cumulative proportion of patients who were seizure free was 58% in the surgical group versus 8% in the medical group ($P < 0.001$). Patients in the surgical group had fewer complex-partial seizures (CPS) and significantly better quality of life ($P < 0.001$ for both comparisons) than the patients in the medical group. Four patients (10%) had adverse effects of surgery (mainly the expected mild language and memory-related problems such as word finding and short-term memory difficulties) while one patient in the medical group died. This

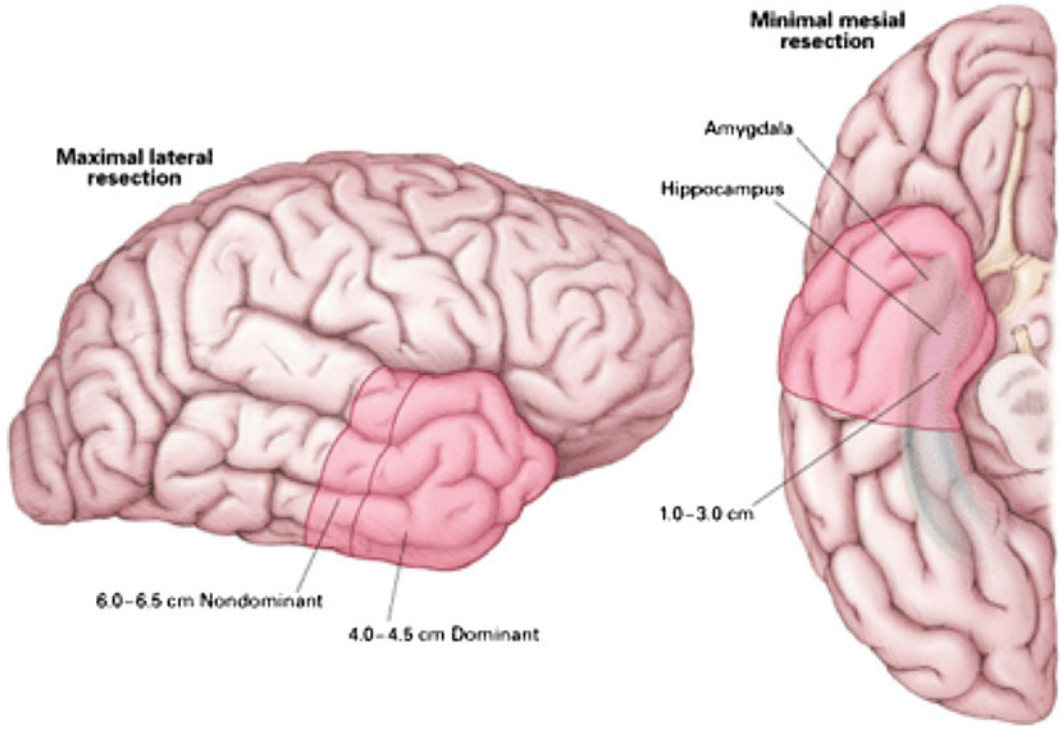

Fig. 25.3 Standard anterior temporal lobectomy [4]

study confirmed that in TLE, surgery is superior to prolonged medical therapy. This RCT also showed that randomized trials of surgery for epilepsy are feasible and appear to yield precise estimates of treatment effects.

Early Randomized Surgical Epilepsy Trial (ERSET)

It has been well established that years of active epilepsy predict cognitive impairment in children and adolescents [5, 6]. Therefore, in order to investigate the effects of early surgery, i.e., whether it would be superior to continued medical management, Engel et al., conducted a multicenter, parallel-group RCT soon after the failure of 2 ASM trials in patients with temporal lobe epilepsy [7]. Thirty-eight patients (18 M/20 F; age $\geq$ 12 years) with MTS and refractory MTLE who were within 2 consecutive years of adequate trials of 2 ASMs were randomized to (1) continued ASM (n = 23), or (2) anterior mesial temporal lobectomy (AMTR) plus ASM treatment (n = 15) and were followed for two years. The primary outcome was seizure freedom during the second year of follow-up, and the secondary outcome was health-related quality of life (QOL), cognitive function, and social adaptation.

Seizure freedom during the second year of follow-up was reported in 11 of 15 patients in the surgical group versus none of the 23 in the medical group ($P < 0.001$). Also, improvement of QOL was higher in the surgical group ($P = 0.01$). Memory decline occurred in 4 patients (36%) after surgery. Adverse events included one stroke in a surgical case versus 3 cases of status epilepticus in the medical group. It was concluded that resective surgery plus ASM in patients with new refractory MTLE results in lower probability of seizures during second year of follow-up than continued ASM treatment alone.

Surgical Methods

There are different surgical methods depending on the patient and seizure type and other characteristics including:

Temporal lobe surgery
Lobectomy
Resection of the epileptogenic zone
Lesionectomy
Corpus Callosotomy
Hemispherectomy
Multiple subpial transections (MST)

Temporal lobe surgery

Temporal lobectomy

There are different methods to remove the seizure focus in the temporal lobe. Anterior temporal lobectomy is the classic and most commonly used type of surgery, but it may be done using different approaches including:

- Standard (en bloc) anterior temporal lobectomy (ATL) including 3–6 cm of anterior temporal neocortex and 1–3 cm of mesial structures (amygdala and hippocampus)
- Modified (Yale group) and limited neocortical resection (3.5 cm from temporal pole) sparing superior temporal gyrus, to address language deficits
- Selective amygdalohippocampectomy
- Stereotactic radiosurgery [8, 9]

Selective Amygdalohippocampectomy (SAH)

This method was introduced by Niemeyer in 1958 in an attempt to preserve the lateral temporal cortex out of concern for language deficits. The technique includes accessing temporal horn to selectively resecting mesial temporal structures through a small incision in the middle temporal gyrus while preserving the neocortical area. Other approaches to selective amygdalohippocampectomy include:

- Transsylvian approach [10, 11].
- Subtemporal approach [12].
- Other variants of the transcortical approach [13].

Outcome Following Temporal Lobe Surgery

Long-term Surgery—MTLE and MTS

Temporal lobectomy provides continued long-term seizure control but risk of seizure recurrence ≥ 2 years after surgery is present. In one report, 50 consecutive post-temporal lobectomy patients with MTS (mean follow-up 5.8 years, range 2–9.2) seizure-free rates were 82% at 12 months, 76% at 24 months, and 64% at 63 months [14]. Complete, or better, seizure outcome was associated with significantly better long-term QOL, and risk factor for seizure recurrence was the reduction in ASM intake—or absorption—in 5 of 17 patients (29%), including 3 of 5 with a first seizure recurrence within 24 months.

Standard Anterior Temporal Lobectomy

In another study, 116 patients with MTS, MTLE, and post-anterior temporal lobectomy with amygdalohippocampectomy (ATL-AH) were studied (follow-up period: 6.7 years) [15]. Complete seizure freedom was seen in 103 patients (89%) and Engel Class I or II outcome in 109 patients (94%). The highest concordance (i.e., test consistent with the side of eventual surgery) was seen with video-EEG (100%), PET (100%), MRI (99.0%), and Wada test (90.4%). The lowest concordance was seen with SPECT (84.6%) and neuropsychological testing (82.5%). A strong Wada memory lateralization appeared

to be the predictor of excellent long-term seizure control, while less disparity in the memory score between the sides was the predictor of persistent seizures.

Temporal Lobectomy—Inferior Temporal Approach

Inferior temporal gyrus approach to mesial temporal lobe resection is safe and effective with low morbidity and mortality. One study reviewed 483 patients with AMTL resection via inferior temporal gyrus approach for TLE [16]. Thirteen complications (2.7%) (3 months post-op) were reported including eight delayed SDH (1.6%), two superficial wound infections (0.4%), one delayed ICH (0.2%), one small lacunar stroke (0.2%), and one transient frontalis nerve palsy (0.2%). There were no deaths or severe neurological impairments. Complications were more common among older patients.

Selective Amygdalohippocampectomy

SAH in TLE patients with MTS results in seizure-free outcomes comparable to procedures with more extensive temporal neocortical resections [17]. Although this method was introduced to minimize the neurocognitive side effects of temporal lobectomy, interestingly, at this point there is more controversy regarding postoperative neuropsychological outcomes, rather than seizure-free outcome, when compared to standard ATL. Some studies have suggested that SAH results in better cognitive function compared to ATL [10], while others have shown no evidence of a clear neurocognitive benefit and in fact SAH might cause significant verbal memory deficits in dominant temporal lobe resection [18, 19].

In another study, 76 adult patients with SAH for MTLE via the trans-middle temporal gyrus approach reported 92% Engel Class I or II with very low surgical morbidity and no mortality. Postoperative neuropsychological testing showed verbal memory decline in the left SAH group, but no memory decline in the right SAH group was seen while some even showed improvement [20].

Neurocognitive Deficits and Risk Factors Following ATL

Cognitive impairment is very common in epilepsy patients and may be negatively or positively affected by surgery. Larger temporal lobe resections are associated with better seizure control, but at the same time resecting more functional tissues carries higher risk of cognitive outcome [21].

Comparison of the changes in cognitive performance in relation to the extent of resection of mesial and lateral temporal structures (1–2 cm and >2 cm for mesial, and ≥ 4 or ≤ 4 cm for neocortical) in 47 right-handed patients with left temporal lobectomy for MTLE showed no difference in cognitive outcome between the groups. However, there was a negative correlation with patient age at seizure onset [22].

Standard Versus Selective Temporal Lobe Surgery

A meta-analysis of standard anterior temporal lobectomy (ATL) versus selective SAH for seizure control in TLE included 11 studies (1203 patients) and concluded that ATL is more likely to achieve an Engel Class I outcome compared with SAH ($p < 0.01$). Standard ATL confers better chance of achieving freedom from disabling seizures in patients with TLE [23].

Right Versus Left Temporal Lobectomy (RTL vs. LTL)

Comparison of neuropsychological outcome following RTL versus LTL shows postoperative decline in verbal memory after LTL, performance intelligence decline after LTL (depending on infero-lateral and basal region removal), and visuospatial memory outcome after RTL

(depending on basal and hippocampal region removal). More resection is associated with worse functioning and vice versa [24].

Case Presentation #2

A 43-year-old man developed seizures two years after surviving a left temporal aneurysm rupture. Following the surgery and aneurysm resection, he did well until the seizures started. Multiple ASMs were tried but he continued having partial seizures with secondary generalization about twice a month. His brain MRI findings were consistent with his history of prior surgery and an encephalomalacia involving the posterior temporal lobe. His video-EEG monitoring localized his seizure onset focus to the left temporal area including the posterior regions. His Wada test lateralized language to the left side and showed a significantly better memory function on the right. He was admitted for subdural grid placement in order to accurately localize the epileptogenic zone and perform language mapping prior to a prospective left temporal resective surgery (Figs. 25.4, 25.5, and 25.6).

Cortical mapping defined the language cortex next to the seizure focus. The patient underwent a left temporal lobectomy including the seizure foci while preserving the language and sensory cortex as depicted above. He had no language deficits after the resection. He has been completely seizure free since the surgery while continuing only one of his ASMs at minimal dose (he had one breakthrough seizure 5 years later after stopping his ASM but has remained seizure since resuming the ASM (follow-up since surgery >6 years)).

Case Presentation #3

A 35-year-old woman presented with seizures since age 5 years. She described her seizures as "day dreaming, head turning, lip smacking, right-hand posturing and at times convulsions." In the past, she had been on phenobarbital since childhood, as well as several other ASMs. Her current seizure frequency is about 3 times per week. She lives with her family, has never worked, and does not drive. Her mother reports behavioral problems (outbursts). After the first visit, while starting her presurgical evaluation, her ASM was changed to levetiracetam that resulted in some improvement in seizure frequency, but later she responded better to the combination therapy of levetiracetam and lamotrigine (i.e., her seizures decreased to 1–2 per

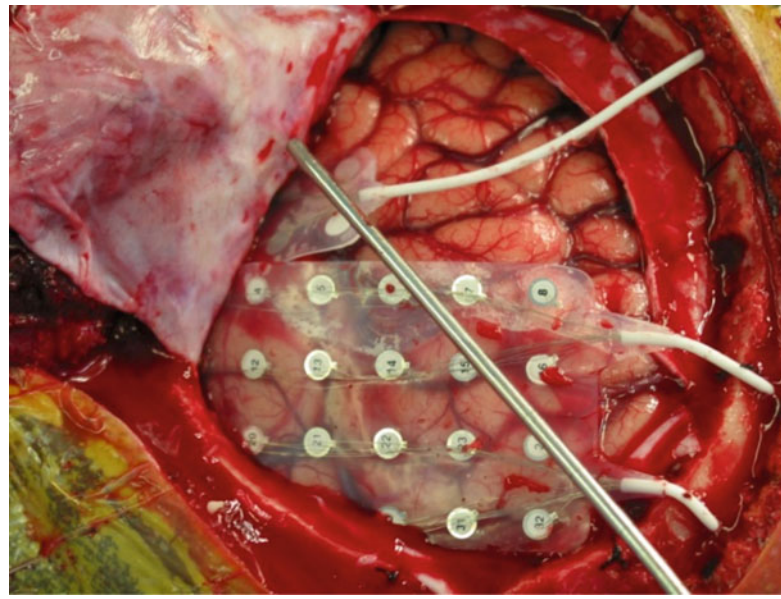

Fig. 25.4 Subdural grid and strip placement to cover the lateral and basal-medial areas of the left temporal lobe

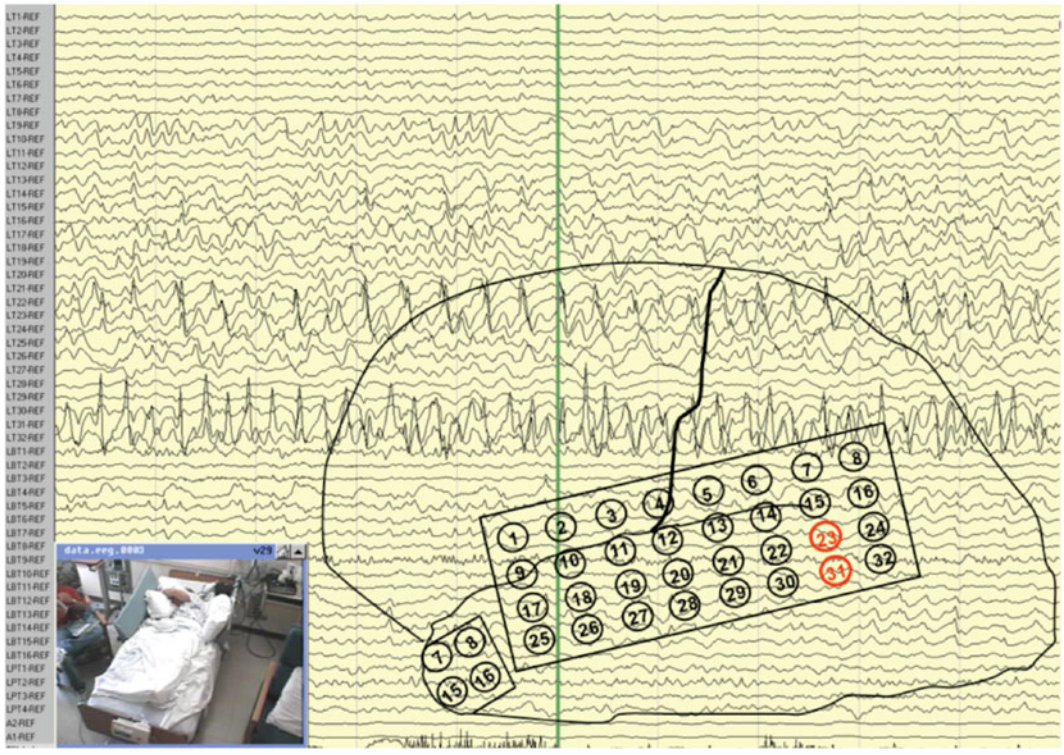

Fig. 25.5 Ictal discharges mainly limited to electrodes 23 and 31 (red), before spreading and secondary generalization; patient aware

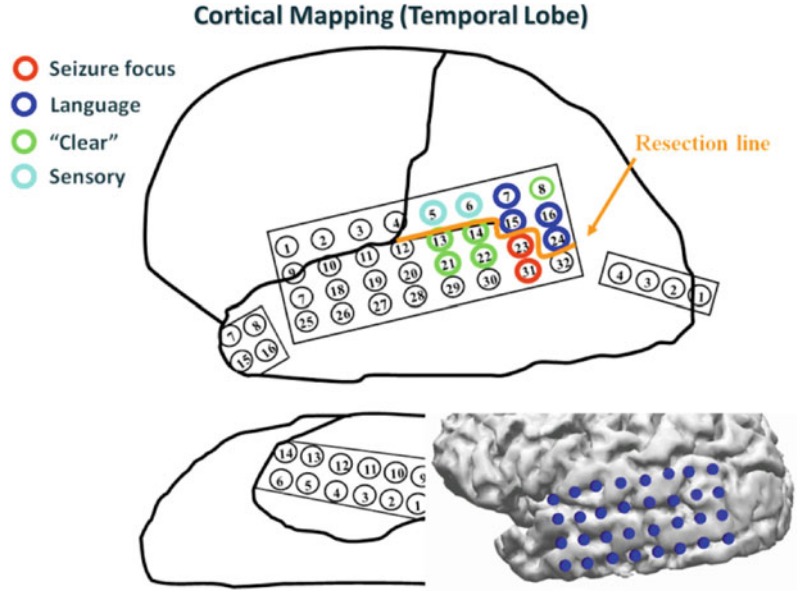

Fig. 25.6 Results of cortical mapping

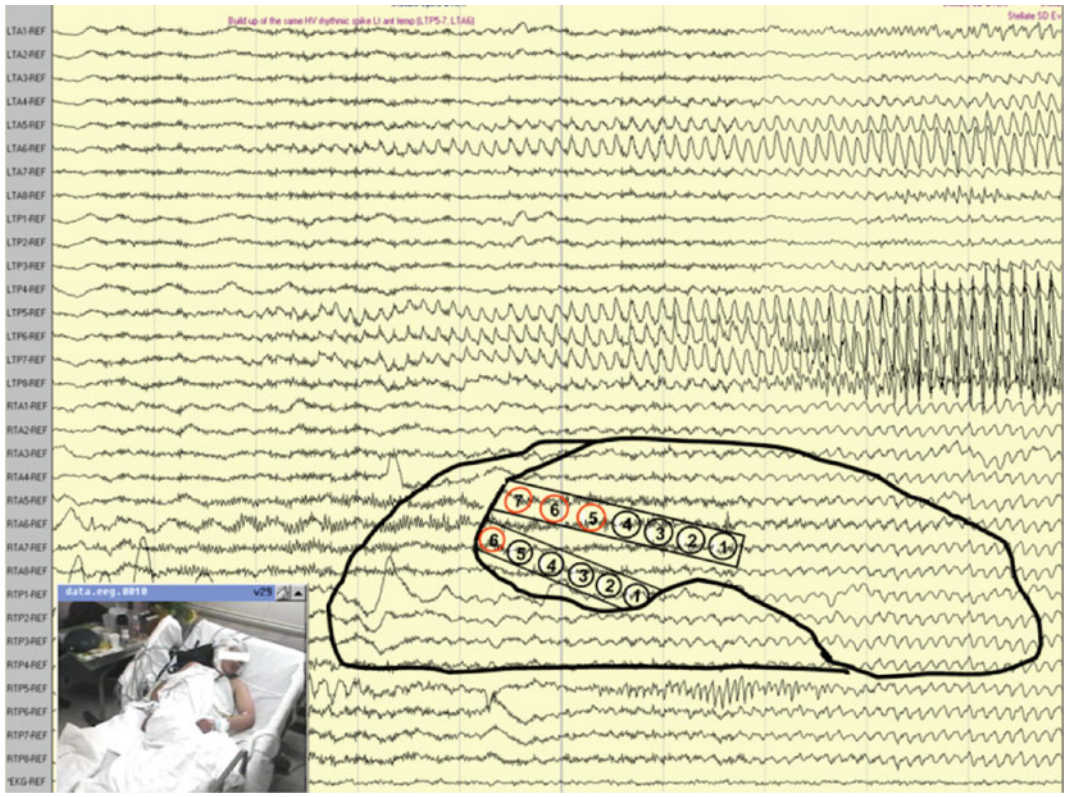

Fig. 25.7 Buildup of rhythmic ictal discharges in few left mesial–basal temporal electrodes. The patient underwent a standard left ATL and has been completely seizure free since the surgery with no new deficits (follow-up >5 years)

month). Her high-resolution brain MRI was normal. A routine EEG showed left temporal spikes and video-EEG monitoring revealed left temporal ictal onset, but there were a few seizures with indeterminate localization. An invasive monitoring using subdural strip electrodes was performed to confirm the localization (Fig. 25.7). Resective surgery was curative.

Outcome Following Nonlesional Partial Epilepsy Surgery

Surgical outcome following surgery in MRI-negative (nonlesional) patients with refractory partial epilepsy can result in favorable outcome. A review of 399 patients has shown positive long-term outcome after 0.5–15.7 year (mean 6.2) follow-up period [25]. The seizure types included focal dyscognitive seizures (complex-partial): 237 (59%), GTCS: 119 (30%), focal without alteration of awareness (simple-partial seizures): 26 (6%), and mixed: 17 (4%). Of these 372 (93%) had temporal lobe, and 27 (7%) extra-temporal lobe resections. The pathology showed MTS in 113 patients (28%), gliosis in 237 (59%), and normal tissue in 49 (12%). The overall Engel Class I outcome is given as follows:

- 81% at 6 months
- 78% at 1 year
- 76% at 2 years
- 74% at 5 years
- 72% at 10 years

Almost all seizures occurred during the first year after surgery. The positive predictive factor was seizure control during the first follow-up year. A Class I outcome at first year indicated

92% probability of seizure remission at 10 years. Negative risk factors included (1) extra-temporal seizure focus ($p < 0.001$), (2) previous surgery ($p < 0.001$), (3) male gender ($p = 0.035$), and (4) normal tissue in pathology ($p = 0.038$).

The negative predictors (risk factors) were (1) higher baseline seizure frequency and (2) preoperative generalized tonic–clonic seizures. Memory decline was reported with dominant hippocampus resections [26].

Outcome Following ATL in Nonlesional TLE Surgery

A normal MRI is not against surgery in patients with TLE. Sixty-four adult patients with refractory TLE but normal MRI who had underwent TLE surgery (1996–2009) were followed for 1–14.5 years (mean 4.1). Standard anterior temporal lobectomy was done in 84% and an unremarkable pathology was reported in 45% of the patients. Complete seizure freedom rates are given as follows:

- 1 year: 76% (Engel Class 1: 81%)
- 2 years: 66% (Engel Class 1: 76%)
- 7 years: 47% (Engel Class 1: 69%)

Case Presentation #4

For the past 20 years, a 45-year-old man would wake up soon after falling asleep screaming and flailing his arms and legs for 30 s before full recovery. He is otherwise healthy. Currently he is on 4 ASMs. He has been on most of the available ASMs, clonazepam, and SSRIs, for seizures, sleep disorders, and "pseudoseizures," respectively. In the past, he had experienced a few similar episodes during the day as well. His EEGs and polysomnogram have all been normal in the past. His current event frequency is 3–7 events per night. He is unemployed, does not drive, and his wife sleeps in a separate room (Figs. 25.8, 25.9, 25.10, 25.11, 25.12, and 25.13).

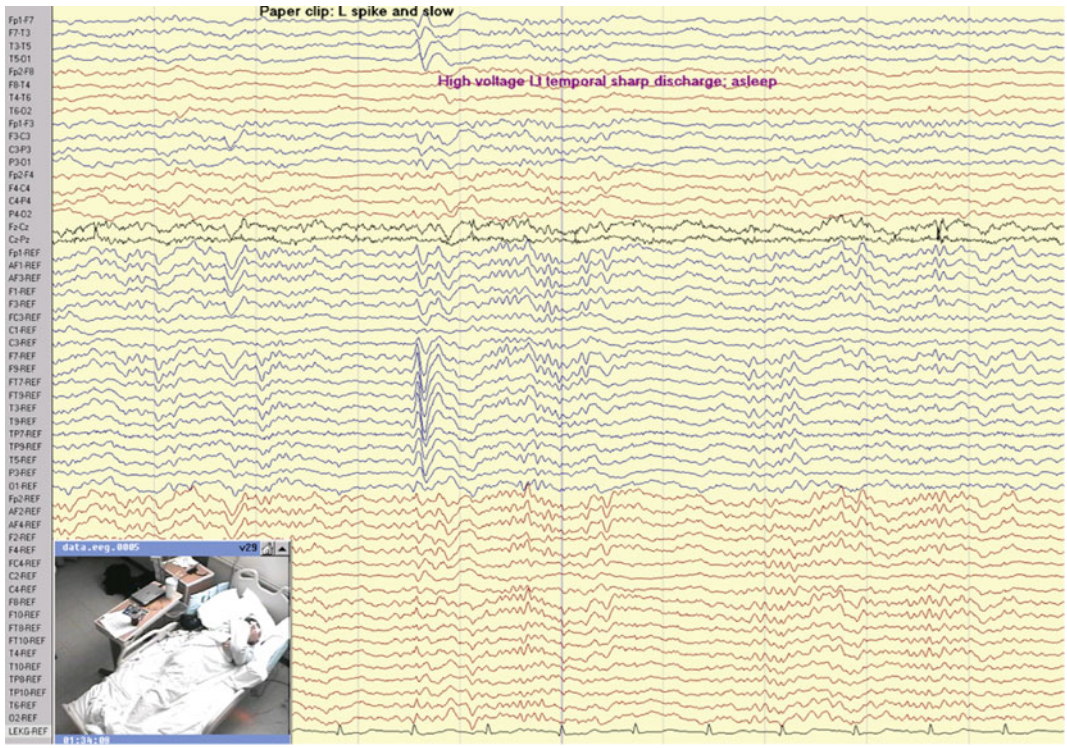

Fig. 25.8 Left temporal interictal spike during sleep

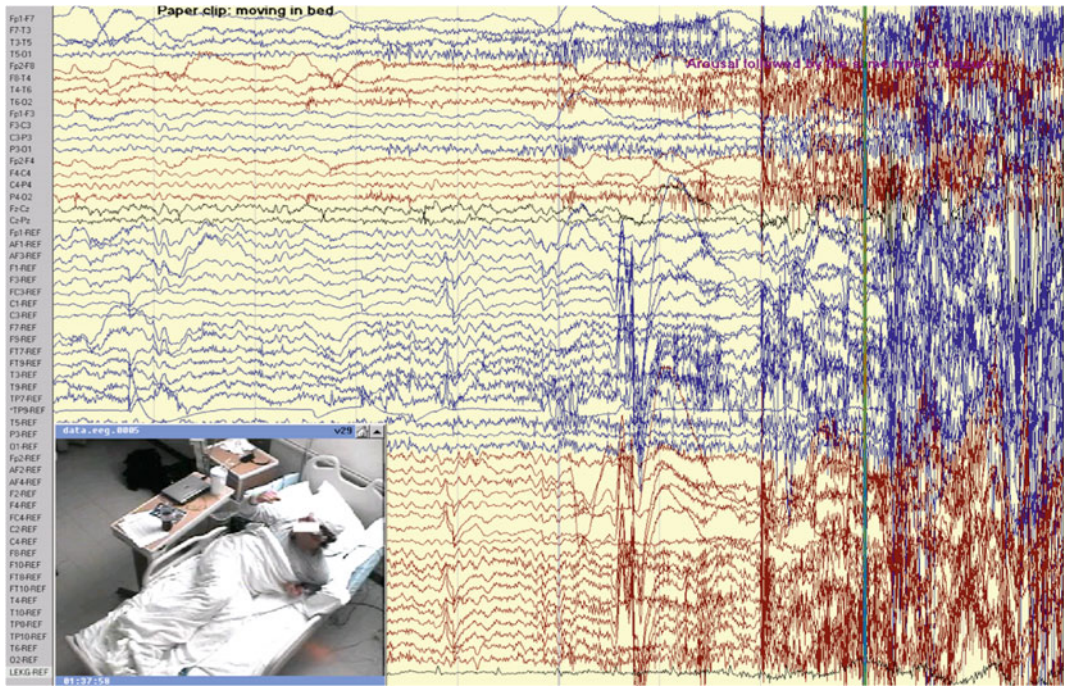

Fig. 25.9 Clinical seizure; arousal from sleep; movement artifact with no clear epileptiform discharges

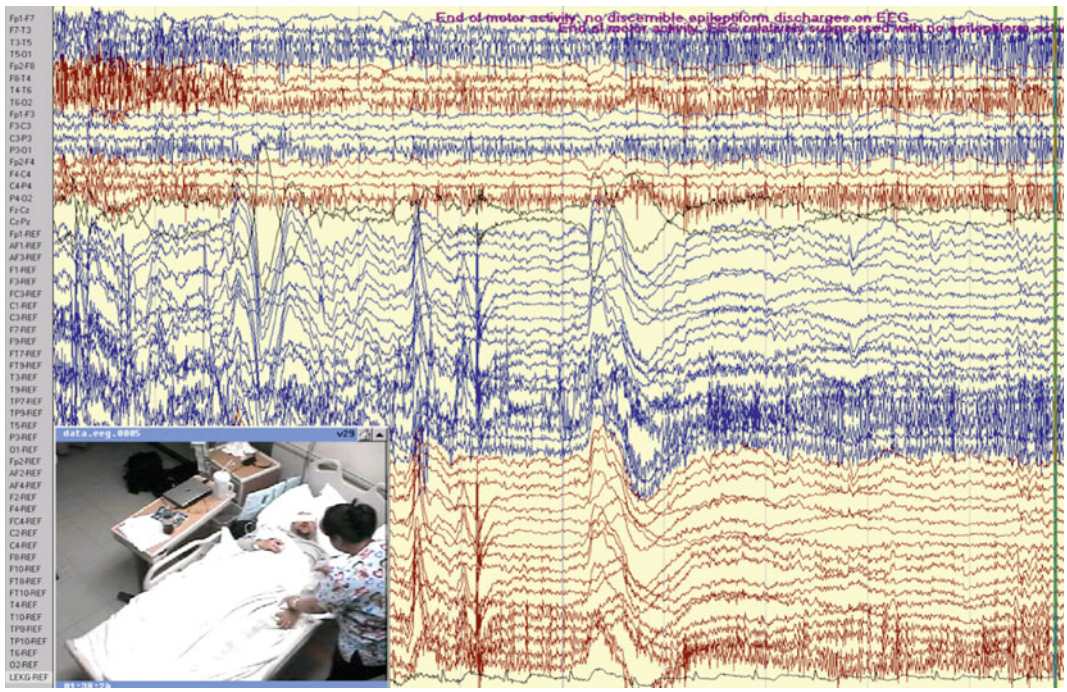

Fig. 25.10 Postictal EEG; no clear epileptiform discharges or postictal suppression

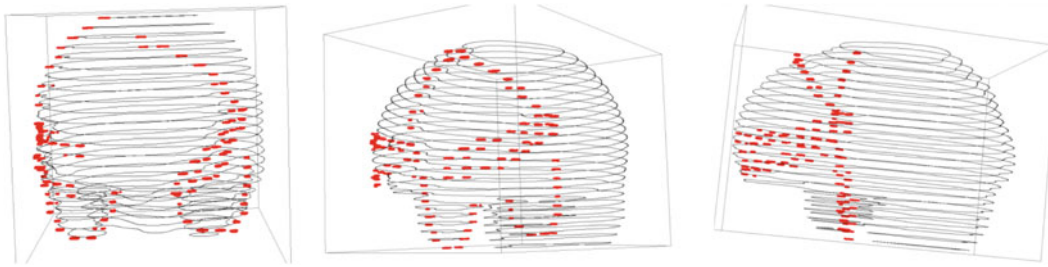

Fig. 25.11 Bilateral subdural strips placed through burr holes for seizure onset focus lateralization (Phase 2a). From left: frontal, left oblique, and left lateral views

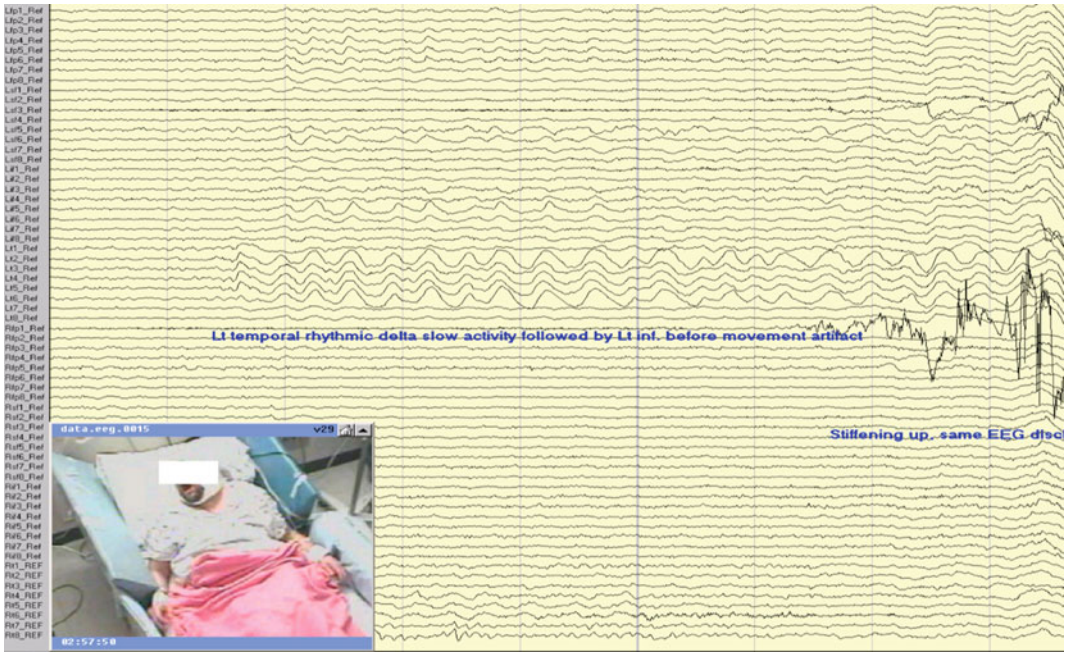

Fig. 25.12 Left temporal rhythmic delta discharges recorded 10 s from seizure onset, indicating a far-field recording from a remote focus (such as frontal lobe) that had spread to the temporal lobe

After lateralizing the seizure onset of the left hemisphere in Phase 2a through bilateral strips, the patient underwent a second surgery by placing more extensive grid electrodes to cover the medial inter hemispheric, fronto-polar, superior posterior, and inferior posterior frontal lobes on the left for accurate seizure localization as well as cortical mapping as indicated. EEG recording (not shown) indicated the seizure onset electrodes shown in red along with electrodes to which the seizures rapidly spread (brown and yellow) indicating the epileptogenic zone located on the edge of the fronto-polar electrode grid. Cortical mapping was performed on the most anterior row of the superior posterior frontal grid and did not reveal any eloquent cortex.

Figure 25.14 shows the 3D reconstruction of the seizure onset electrodes (red) and those to which seizures rapidly spread (brown and yellow). Since the seizure onset zone was located on the edge of the grid, the resection included the colored electrodes in the top two rows of the grid

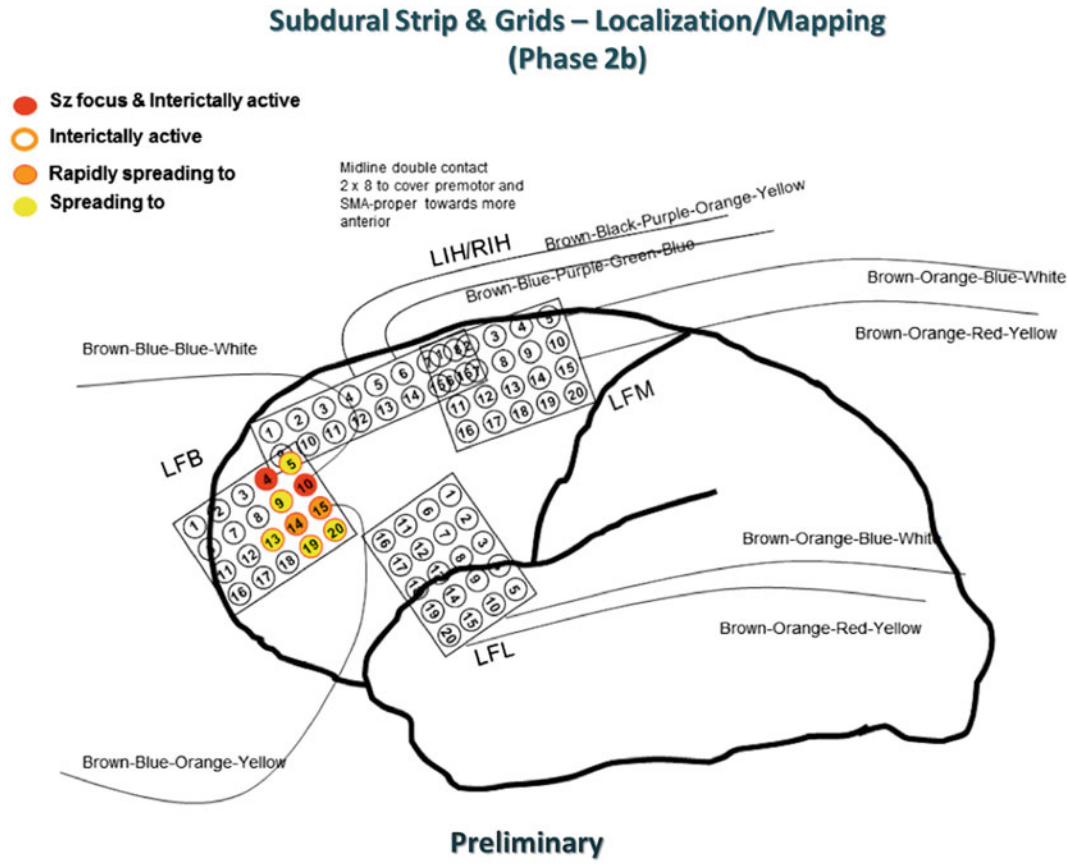

Fig. 25.13 Location of the seizure onset zone and interictal discharges on the intracranial electrodes

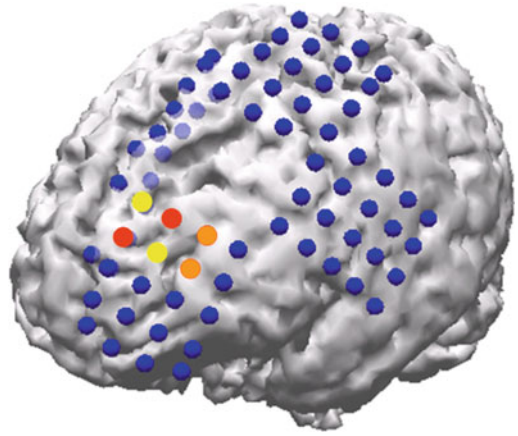

Fig. 25.14 3D reconstruction of the brain coregistered with the postoperative CT to localize the electrodes in relationship to gyral anatomy

as well as one row beyond that which was part of the same gyrus, to minimize the possibility of leaving part of the epileptogenic zone intact. The patient has been completely seizure free since the surgery with no deficits (follow-up >2 years).

Outcome Following Frontal Lobe Epilepsy Surgery

Patients with frontal lobe epilepsy (FLE) and an identifiable focal lesion are more likely to achieve seizure freedom than those with poorly defined seizure focus. A review and meta-analysis of 21 studies (total of 1199 patients) with FLE surgery including studies with ≥ 10 patient and follow-up period ≥ 48 months showed seizure freedom

(Engel Class I outcome) in 45.1%. Significant predictors of long-term seizure freedom included lesional origin, abnormal MRI, and localized frontal resection (vs. more extensive lobectomy). In patients with lesional FLE, improved outcome was more likely to be achieved after gross-total resection rather than subtotal lesionectomy [27].

In another study, 25 patients with history of resective surgery after intracranial EEG recording were reviewed. A seizure-free (Engel Class 1) outcome was seen in 15 patients (60%), while 10 patients (40%) continued to have seizures (Classes II, III, and IV). Risk factors for lack of seizure freedom included:

- Left frontal lobe epilepsy surgery;
- Dominant hemisphere;
- Patients without aura;
- Interictal epileptiform discharges in scalp EEG;
- Intracranial EEG widespread (>2 cm) in contrast to focal seizure onset;
- Shorter latency to onset of seizure spread; and
- Ictal involvement beyond frontal lobe.

Lack of seizure freedom is likely because of widespread epileptogenicity (as indicated by rapid spread of ictal activity). Early resection may improve seizure outcomes of FLE surgery, particularly in children [28, 29].

Case #5
A 52-year-old woman presented with seizures since age seven; she attributed her seizures to an accident two years earlier when an axe fell on her head. Her seizures presented as sudden arm and leg extension with no clear loss of awareness that happened up to 10 times day (mostly nocturnal). She had tried all available ASMs (had a pregnancy on phenytoin and phenobarbital with fetal in utero exposure and congenital defects in the baby). At the time of presentation, she was on 4 ASMs at high doses. Her EEGs had been always normal, and in the past she had been diagnosed with "pseudoseizures" by her neurologist.

Her scalp monitoring showed no interictal or ictal EEG discharges while numerous typical seizures were recorded. The seizure semiology indicated supplementary motor area (SMA)-type seizures. Her high-resolution MRI showed a small area of increased signal intensity in the bottom of a gyrus in the right mesial frontal area at the convexity, corresponding to the distal lower extremity on the left. Therefore, she underwent invasive recording using subdural grid electrodes covering the right frontal and temporal regions including motor and sensory cortex, and a dual-sided 2×8 strip to record directly from the SMA. Her invasive recording revealed very frequent interictal spikes and seizures onset zone at the juncture of motor cortex, pre-SMA but less in the SMA proper, with spread anteriorly. Of note, the ictal discharges consisted of very high-frequency (beta and gamma) discharges. After discussing the options, the patient underwent an awake surgery for a limited resection including the pre-SMA and part of the SMA proper preserving the motor (foot and leg) cortices. Pathology confirmed focal cortical dysplasia. She had a transitory left-sided paresis following the surgery with excellent recovery following rehabilitation. She remained seizure free for one year after which her nocturnal seizure resumed but at a significantly lower frequency (90% of decrease) and was milder in severity. She had no more diurnal seizures for 3 years but has had rare seizures during the day over the last 2 years (follow-up since surgery >6 years). Given her condition and the presence of comorbidities (obstructive sleep apnea and asthma requiring steroids and resultant weight gain complicating her apnea management), her medications have not been tapered.

Supplementary Motor Area (SMA) Seizures

These seizures presented with tonic posturing of the extremities, usually bilateral, and may appear as "fencer posturing." Awareness is typically retained during these seizures. The primary epileptogenic zone is usually outside the SMA with rapid spread to the SMA, hence the semiology. The interictal, and even ictal, EEG is often unrevealing. If the seizure onset focus is outside

the SMA, resection of epileptogenic zone alone, leaving the SMA intact, might be enough [30]. Synchronous interictal/ictal discharges in SMA and primary cortex with a time lag of 25/100 ms. have been reported [31]. Resecting the EEG onset zone within the SMA while sparing primary motor cortex may result in >90% seizure reduction [32]. Following the SMA resection, while preserving primary motor cortex, a transitory paresis or severe deficits without permanent loss of motor or speech functions may be seen (typically lasting 24 h), but favorable surgical outcome is common [33].

Multiple Subpial Transection (MST)

This technique was introduced to spare the eloquent cortex in patients in whom the epileptogenic zone lies in eloquent cortex. The NST is based on the notion that epileptogenic discharges require side-to-side (horizontal) interaction of cortical neurons while the major functional properties of cortical tissue depend upon the vertical fibers. Therefore, severing the tangential intracortical fibers in the seizure focus using a small blade is performed, while vertical fiber connections and blood vessels are preserved [34].

In a report of 21 patients (18 intractable epilepsy and 3 Landau–Kleffner syndrome (LKS)) who underwent either resection plus MST (12) or MST alone, in precentral and postcentral regions (follow-up: ~1–5 years), significant seizure reduction was seen in 11 of 18 patients (61%) and 3 LKS patients. The latter group who were mute before operation showed significant speech recovery. There were no chronic neurological deficits. Other studies have reported up to 56% seizure freedom and 95% seizure reduction in patients with intractable epilepsy arising from eloquent cortex following combined resection and MST versus no seizure freedom and >50% seizure reduction in those treated with MST alone. Predictor of complete seizure freedom appears to be the disappearance of epileptiform discharges in the post-op EEG. Subtle, but permanent deficits in about one-third of patients with MST performed in eloquent cortex. Therefore, MST surrounding a lesionectomy may minimize the excised volume and improve seizure control [35].

However, a meta-analysis of data from 6 major epilepsy centers (211 patients, 53 with MST alone) reported similar results between the MST plus resection and MST alone procedures: The MST plus resection resulted in >95% seizure reduction (GTCS 87%, CPS 68%, SPS 68%), compared to >95% seizure reduction (GTCS 71%, CPS 62%, SPS 63%) in MST alone group.

The outcome seemed to be independent of factors such as EEG localization, MST location, age at onset, or duration of epilepsy. These results suggest that MST may be efficient by itself, with minimal neurologic compromise, and should be investigated as a stand-alone procedure [36].

Overall Seizure-Free Outcome

The overall seizure-free rates following different types of surgery in different brain regions are reported as follows:

Temporal lobectomy: 55–80%
Frontal lobe resections: 5–18%
Frontal lobectomy: 23–68%
Parietal lobe resections: 45%
Occipital resections: 46–88%
Hemispherotomy: 60%

Epilepsy Surgery—Long-term Outcome ($\geq$ 5 Years)

Excellent short-term results of resective epilepsy surgery have been well established. Therefore, review and meta-analysis of long-term outcomes of largest case series of patients of any age after resective or non-resective epilepsy surgery have been attempted. After a mean follow-up of $\geq$ 5 years, resective surgery resulted in the following seizure freedom rates:

Temporal lobe resections: 66%
Occipital and parietal resections: 46%
Frontal lobe resections: 27%
Multiple subpial transections: 16%
Callosotomy (free of most disabling seizures): 35%

Therefore, long-term seizure-free rate following temporal lobe resective surgery appears to be favorable similar to that of short-term-controlled studies, but it is consistently lower after extra-temporal or palliative surgeries [37].

Failed Epilepsy Surgery and Reoperation

Reoperation following a failed previous surgery can be an efficacious and reasonably safe approach. Successful reoperation has been reported in patients with concordance between their postsurgical imaging and electroclinical findings, and no brain trauma or infection before their seizure onset. A review of 15 case series including 402 adult patients reoperated 2–5.5 years later (reoperation rate: 3.8–14%; follow-up of 6 months–4 years) post-reoperation seizure freedom was reported at 36.6% and complications rate at 13.5% [38].

It is also safe to use subdural grid electrodes in patients with prior craniotomy with favorable long-term seizure-free outcomes. In these patients, ictal onset at the edge of original surgical bed (more with lesional epilepsy) seems to be a predictor of seizure freedom [39].

Parietal Lobe Epilepsy

Auras are commonly present in these seizure; 94% of patients report somatosensory auras (painful dysesthesias), vertigo, aphasia, or disturbances of one's body image. The ictal propagation to the SMA may result in hypermotor manifestations while propagation to the temporo-limbic regions may result in complex visual or auditory hallucinations and automatisms.

Scalp ictal EEG is rarely localizing. Parietal lobe seizures have more variable scatter of interictal EEG discharges and less localizing ictal discharges compared to temporal or frontal lobe seizures. Overall, the semiology is of less value in these patients. High-frequency oscillations (HFOs) may be useful for localization as they more concentrated in seizure focus.

Postoperative sensory deficits such as temporary partial hemisensory or Gerstmann syndrome may be seen when corticectomy involves post-central gyrus. However, resective surgery can result in seizure freedom or significant seizure reduction especially when a lesion is present. The most common pathologies include low-grade tumors, cortical dysplasia, gliotic scars, or cavernous vascular malformations.

Complete or nearly complete seizure freedom has been reported in 65–67.5% of patients with favorable outcome factor being the absence of post-resection epileptiform discharges on the EEG [40–43].

Occipital Lobe Epilepsy

Auras are reported in 88% of these patients. The auras consist of elementary visual hallucinations, ictal amaurosis, eye movement sensations, early forced blinking or eyelid flutter, and contralateral visual field deficits. There is often eye/head deviation (usually contralateral to the side of seizure origin), loss of awareness, various types of automatism, fumbling (typical for temporal lobe seizures), and at times asymmetrical tonic or focal clonic motor patterns (characteristic of frontal lobe seizures). Medial or lobar lesions are more likely to cause visual field defects. The scalp EEG is rarely localizing [44, 45]. Intracranial EEG recording correctly identifies occipital lobe seizure origin in most, but not all of these patients. The variability in semiology depends on seizure spread patterns, i.e., medially, laterally, above/below the sylvian fissure, both ipsilateral and contralateral to the seizure origin.

After, focal resection seizure freedom is seen in 46–88% of patients. The most common pathologies include dysplasia, tumors, and gliosis. Following resection, about 50% of patients will not experience any new visual deficits while new quadrantanopia or hemianopia has been reported in 17%. Tailored resections (e.g., in lateral occipital lesions) may help preserve intact vision in about 38% of patient [46].

Insular-Opercular Seizures

These seizures usually present as nocturnal complex motor seizures. The auras include viscerosensitive or somatosensory symptoms. Ictal semiology consists of asymmetric tonic–dystonic posturing and/or hyperkinetic automatisms (bimanual/bipedal activity and ballistic movements). Simultaneous insular and opercular ictal discharges are present. Complex motor manifestations are seen when the seizure spreads to frontomesial regions (cingulum, superior frontal gyrus, and SMA) and/or mesial and neocortical temporal lobe structures.

Favorable outcome can be achieved with insular-opercular cortical resections. The most common underlying pathology is focal cortical dysplasia [47].

Epilepsy Surgery in Children

Epilepsy surgery is commonly performed in children. The long-term outcome (5–21 years) studied in 47 children with age at surgery ranging from 0.5 to 18.7 years (mean 8) reported 49% (23/47) seizure freedom and >75% seizure reduction in 13% (6/47). All of these children were assessed for cognitive function pre- and postsurgery and at follow-up. Twenty-one patients required a reoperation to achieve satisfactory seizure outcomes with low complications rate and no increase in seizures. Cognitive function was well preserved as 76% (34/47) followed their expected cognitive trajectory. Patients who were seizure free showed significant and long-term improvement in their cognitive processing speed, in particular those who were on no ASM [48].

Extra-temporal Epilepsy Surgery in Children

In general, surgical outcomes for extra-temporal lobe epilepsy (ETLE) are worse than those for TLE. A meta-analysis of the available literature (17 studies, 95 patients) reported that pathology (cortical dysplasia) and seizure type (CPS) were the positive outcome predictors. Factors contributing to less favorable outcome seem to be diffuse nature of pathology involved in ETLE, difficulty localizing the seizure focus in young children, and involvement of "eloquent" cortex [49].

Ictal Onset High-Frequency Oscillations

Retrospective review of high-frequency oscillations (HFOs > 80 Hz; sampling rate: 2000 Hz) recorded in intracranial EEG in pediatric patients suggest a high prevalence of ictal HFO zones in 93% of patients. Complete resection of ictal HFOs, regardless of the frequency bands, is highly correlated with a favorable surgical outcome. In one series, complete resection resulted in 82% seizure freedom versus 21% after incomplete resection. The most common pathology in these patients was cortical dysplasia [50].

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Procedures and Outcomes in Epilepsy Surgery

26

Ronald P. Lesser

Although surgery has risks, there are several reasons to consider it for patients with epilepsy. First is the possibility of harm to the patient if surgery is not done, because of continued seizures. In a study in 1997, Buck and coworkers [1] found that of 300 patients with at least one seizure in the previous year, 24% had sustained a head injury, 16% had burned or scalded themselves, 14% had a seizure while bathing or swimming with the risk of drowning, 10% had a dental injury, and 6% had a fracture.

Second, beyond actual injury is the important entity SUDEP (sudden unexpected death in epilepsy patients), an entity that may be more common in patients with more generalized convulsive seizures and in patients in their third through fifth decades of life. The reason for death in these patients is not known, but it is clear that patients with seizures, particularly with intractable seizures, can be found dead without a clear explanation other than the fact that they have epilepsy.

Third are the effects that ongoing seizures, particularly those affecting consciousness, have on a person's daily life. One cannot drive. One may have a seizure in public or in an unfamiliar situation and be unable to care for oneself. Those nearby might react in way that could add additional harm or danger.

Fourth are risks related to side effects of anticonvulsants, particularly if patients have frequent seizures with the need for higher doses or for additional numbers of medications. Additionally, for women of childbearing age, anticonvulsants impose risks on a developing fetus, and, for young children, seizures and medications impose risks on development.

Over the last several decades, there have been a number of new medications which can be used, but unfortunately, many patients continue to have seizures despite these. Overall, only 2/3–3/4 of patients can be seizure-free on medication [2]. Studies have shown that patients with intractable seizures undergoing surgery are significantly more likely to be seizure-free after surgery than if they continue on medication alone [3].

Before operating, however, we need to determine whether surgery is appropriate for the particular patient, and, if so, which. Less invasive evaluations should be performed first, with questions to answer including the following: What do the clinical symptoms suggest about region of seizure onset? Is there a focal lesion that can be resected? Is there a focus that can be found on EEG? Is the focus accessible surgically? Is the focus surgically separate from regions controlling important functions? Would a procedure other than focal resection be better? Because the symptoms of seizures can vary and because of the possibility of seizures beginning in one place but projecting to another, it is important to correlate the behaviors with the

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EEG findings during the episodes, and for this reason, patients should be referred for video EEG monitoring so that actual seizures can be recorded and patient behaviors during the seizures analyzed.

Symptoms

Temporal lobe seizures are the most commonly evaluated for surgery. Onsets of seizures from the temporal lobe can include epigastric, olfactory, and gustatory sensations, emotional changes, sense of familiarity or strangeness, hallucinations, staring, and automatisms, among others. One review [4] concluded that with temporal lobe epilepsy, abdominal aura had a 52% sensitivity and 90% specificity for localizing seizures to the temporal lobe. Seizures arising from temporal neocortex can have similar symptoms. For example, basal but not mesial temporal seizures can present with behavioral arrest or motor changes. Ictal theta activity was found to have an 85% probability for temporal lobe epilepsy and was 80–94% correct with respect to the side of seizure onset. Lateralized interictal spikes and possibly contralateral hand dystonia also were helpful. The authors thought that some of these also might help differentiate mesial from lateral temporal lobe epilepsy.

Febrile seizures are thought to have a relationship with mesial temporal sclerosis, as is found with mesial temporal lobe epilepsy; one report [5] found that only 2/21 patients with neocortical temporal lobe epilepsy had a history of febrile seizures. Seizure-free intervals were found to be less common with neocortical temporal lobe epilepsy than with mesial onset temporal lobe epilepsy. Despite neocortical onset, there nonetheless could be mild hippocampal atrophy. Patients could have tumors or heterotopias. About half could have decreased memory function on the Wada test. Independent contralateral spikes were rare. Some patients had experiential auras or motionless stares.

Frontal lobe epilepsy symptoms vary with the site of seizure onset [4]. With superior or interhemispheric onsets, there can be contralateral eye, head, or body turning with tonic or dystonic posturing. Orbital frontal seizures can include unusual behaviors including hypermotor activity such as rapid leg kicking or bicycling and can have autonomic findings, behavior arrest, and automatisms of other types. These characteristically occur frequently during sleep and last a relatively short period of time. Seizures from the frontal operculum can include salivation and swallowing. Inferior frontal onset can include findings referable to the face or to speech. Dorsolateral or dorsomedial onset seizures can include contralateral motor findings, premotor area seizures tonic version, and supplementary motor area seizures speech arrest, fencing postures, bilateral motor findings, and head version. It is important to note that frontal lobe regions can produce seizures that are similar to one another.

Seizures from the insula can include visceral, gustatory, and somatosensory symptoms, including laryngeal constriction or paresthesias [4]. Parietal lobe seizures can begin with somatosensory phenomena, and occipital lobe seizures can begin with visual auras and phenomena. However, both parietal and occipital lobe seizures can be locally silent, with symptoms related to the area of projection. For example, parietal lobe seizures can imitate superior frontal lobe seizures or can have sensorimotor symptoms.

Noninvasive Evaluations

Neuropsychological evaluation is important both in assessing baseline functioning and in determining whether there are aspects of function, which are below expectations. At times, these functions can be localized to specific regions of the brain, which in turn might be the sites of origin of the patient's seizures.

The intracarotid sodium amobarbital or Wada test is performed less frequently now than had been the case in the past. When used, it has two purposes. With the test, a medication, which traditionally had been amobarbital, but now can be another such as midazolam, is injected so as to

"anesthetize" one hemisphere for a few minutes while the other is tested. One looks for language function during the period of "anesthesia," to see whether speech remains while the hemisphere is not functioning, and one presents items for the patient to remember. One also tests recall memory after the effects of the medication wear off, to see whether new memories could be encoded during the period of hemisphere inactivation. The idea is that if a function is intact during the period of drug-induced inactivation, the tested function is likely to be supported by the non-inactivated hemisphere.

Imaging is increasingly important in evaluating patients with intractable seizures, with magnetic resonance imaging (MRI) being the most important; one should always be performed if possible. Important findings include evidence of mesial temporal sclerosis or other abnormality, as well as evidence of tumor, dysplasia, vascular anomaly, developmental defects, or other changes. For patients with temporal lobe epilepsy, it is important to keep in mind that there can be bilateral atrophy on MRI in some patients, perhaps 20% [4]. Sometimes, surgery can nonetheless be performed on one side, if seizures only originate on that side, but it adds a consideration before deciding whether to operate and a consideration when counseling the patient with respect to possible postoperative memory problems. Neuroimaging [4] can show amygdala abnormalities in 55% of patients and changes in the enterorhinal cortex in 25% and in the fornix in 86%. In one study of patients with temporal lobe epilepsy and tumors [6], astrocytomas were found in 46%, gangliogliomas in 21%, oligodendrogliomas in 18%, dysembryoplastic neuroepithelial tumors in 6%, anaplastic astrocytomas in 6%, and meningiomas in 3%.

Dual pathology can occur in 15–52% of patients with hippocampal sclerosis, with etiologies including heterotopias, cortical dysplasia, and tumors. Vascular lesions including cavernous malformations and arteriovenous malformations can occur in about 5% of patients [4]. Although the term has often been used to describe the combination of hippocampal sclerosis plus another lesion, it also is used to describe the occurrence of two potentially epileptogenic lesions regardless of type.

Causes of extra temporal seizures in a series of 133 consecutive cases included [7] cortical dysplasia in 38% and tumor in 28%. They reported that 10/50 patients with cortical dysplasia also had tumors; 11/50 had infarcts or remote ischemic lesions. They found four with arteriovenous malformations, 3 with Sturge–Weber malformations, and 2 with Rasmussen's encephalitis. 17% had no significant findings.

Positron-emission tomography (PET) scans can point to areas of decreased metabolic function which in turn can be area of epileptogenesis. Single-photon emission computed tomography (SPECT) studies can point to areas of altered function in a similar way with similar inferences regarding whether these might indicate where seizures are originating. Magnetic resonance spectroscopy (MRS) can point to areas with altered chemistry. fMRI is being developed as a possible alternative to the Wada test, using it to localize language, which has been relatively successful, as well as memory, which has not been as successful thus far.

Invasive Evaluations

Often noninvasive evaluation is sufficient to determine how and where to operate, but some patients need implanted electrodes as well. Depth and subdural electrodes are the ones principally used. Depth electrodes are thin "tubes," each usually containing several electrodes and electrode wires, and which are directed through the skull and through the outer cerebral tissues, aiming at more medial locations such as mesial temporal lobes. However, there are electrodes along the tube so that more lateral locations including neocortex are recorded at the same time. Subdural electrodes are flat disks, usually a few millimeters in diameter, imbedded in Silastic or other plastics and placed over and around areas of interest. Both depth and subdural electrodes are used to localize the area of seizure onset. Subdural electrodes are commonly, and depth electrodes less commonly, stimulated

electrically to determine the relationship of the area of seizure onset to regions controlling important functions such as movement, sensation, and language.

Complications of depth electrodes include asymptomatic subdural bleeding gliosis, degeneration, and microabscesses along electrode tract [8–10]. The incidence of bleeding or infection is between 0.5 and 5%. There can be a 25% overall rate of complications with subdural electrodes [11], including 12% infection, 11% transient neurological deficits, 2.5% epidural hematoma, 2.5% increased intracranial pressure, 1.5% infarction, and 0.5% death. Cerebrospinal fluid leakage also was common. The authors found that complications were more likely if there were more than 60 electrodes and if the grid was left in more than 10 days. Other risks included older patients, left-sided placement, and additional burr holes. They observed that complication risk likely was less now with improved technique.

Testing the Brain—Functional Localization

Functional localization can be performed in one of two ways. One can alter the brain, for example with cortical stimulation, and assess the behaviors that occurred during the alteration. An example would be to see whether there is hand or other movement during stimulation. One also can alter behavior and then assess the brain during the behavior. An example might be asking the patient to begin to read and then seeing whether there is reading arrest during stimulation. Cortical stimulation is generally performed with recurrent pulses. These should be alternating in polarity, so that the resulting stimulation is charge-balanced, to avoid complications due to metal deposit on an electrode. We [12] have used 0.3-ms duration alternating polarity square wave pulses, delivered at 50 pulses per second, with stimulation duration varying but generally 1–2 s initially and then up to about 5 s for language testing. Intensities that are needed to obtain stimulation-induced changes vary; with the device we use, they can go up to 17.5 mA. It is important to emphasize that the reliability of results can depend on the intensity of stimulation. If you stimulate at too low an intensity, you can get a false-negative result. If you stimulate at too high an intensity, you can get afterdischarges which can produce false positives because of the spread of the afterdischarges and also can cause seizures. One should begin at a low intensity, 0.5–1 mA, and increase in increments of 0.5–1 mA. Keep in mind that the above is in milliamps, but the important parameter is charge density, which depends on not only current but also electrode surface area.

It is also important to emphasize that stimulation only assesses the cortex directly under the stimulated electrodes. Charge density drops relatively rapidly with increased distance from the actual location of the electrodes. Also, 7/8 of the current is shunting through the cerebrospinal fluid [13, 14].

In addition to stimulation, one can analyze the brain function with a variety of methods based on frequency or power analysis. In summary, one asks the patient to perform an activity which can be something simple such as moving the tongue, making a fist, or wiggling the toes. One then records brain activity before during and after this activity and sees whether there are changes in particular regions of the brain which might point to the area participating in controlling this activity. There [15, 16] is a relatively good correlation between the results of such analyses and the results of cortical stimulation, but the two methods are slightly different so that the regions localized with one technique or the other might be expected to, and in fact do, differ.

Temporal Lobe Surgical Resections

Seizure Control

There are controversies regarding what to remove. For example, for anterior temporal lobectomy, some perform the same standard resection on each patient, while others tailor the resection based upon the specific findings during evaluation, particularly evaluation with

implanted electrodes. Some surgeons perform an amygdalohippocampectomy with lateral temporal structures left relatively intact. Some will do a hippocampectomy alone. There has been interest in the use of radiosurgery and laser surgery as noninvasive ways of resecting only mesial temporal structures.

In a prospective study [17], Wiebe et al. compared 40 patients who underwent temporal lobectomy to 40 who were on a surgical waiting list for a year. The surgery was an en bloc resection of 4–4.5 cm of the dominant and 6–6.5 cm of the non-dominant, temporal lobe, with removal of amygdala and 1–3 cm hippocampus. One year later, 58% of patients with surgical treatment but only 8% of patients with medical treatment alone were free of episodes with loss of consciousness. Quality of life also improved in patients who had surgery. However, simple partial seizure may continue: This group previously found [18] that 93% of surgical and 13% of medical patients had a 90–100% reduction of seizures after 6 months but only 35% of the surgical patients (and 6% of the medicine alone patients) were completely seizure-free. Also, seizures can recur over time. In one review [19] of patients seizure-free at one year, 87–90% were seizure-free at 2 years, 74–82% at 5 years, and 67–71% at 10 years. Among patients who were seizure-free at 2 years, 95% were seizure-free of 5 years, 82% at 10 years, and 68% at 15 years. Therefore, with time, seizure control decreases, but the longer the patient was seizure-free, the better the outcome. This review noted that more than half of the patients would have their seizure recurrence in the first 6 months and 95% in the first 5 years. They found that incomplete resection was more likely in patient with seizure recurrence. They also noted the possibility of a "running-down" phenomenon with initial seizure recurrence followed by seizure control. Good prognostic factors included early onset of seizures, mesial temporal sclerosis with ipsilateral interictal EEG discharges, unilateral MRI, PET, and SPECT findings with a single lesion, and greater than 90% of the interictal EEG findings originating in one place. Poor prognostic factors included a long duration of seizures and the occurrence of generalized tonic–clonic seizures. If patient has a normal MRI, outcome can be good if there are ipsilateral interictal EEG discharges and a history of febrile seizures. Outcome can be worse in patients with tumors, cortical dysplasia, vascular disease, and a longer duration of epilepsy [4].

One review [4] concluded that after surgery for temporal lobe tumors, 65% of patients became seizure-free and 82–86% of patients were free of disabling seizures. For mesial temporal sclerosis, 75% of patients became seizure-free with 41–79% free of disabling seizures. Among patients with normal MRIs, 56–62% of patients became seizure-free. For patients with cortical dysplasia, 38–54% became seizure-free. For patients with dual pathology, in this case mesial temporal sclerosis plus another lesion, 73% became free of disabling seizures if both pathological areas were removed but only 20% if only one of the areas was removed.

Schmidt et al. [20] reviewed previous reports of a total of 1658 patients who had been off medication for 5 years. They found that 25% of adults and 31% of children became seizure-free and remained off medication for 5 years.

Surgery outcome has long been classified using a system devised by Engel [21]. In this, Class I is for patients "free of disabling seizures," but the subcategories include completely seizure-free since surgery, non-disabling simple partial seizures only, some disabling seizures but none for 2 years, and generalized convulsive seizures with medication discontinuation. Class II was for patients with rare disabling seizures, with subcategories of initially free of disabling seizures, rare seizures now, rare disabling seizures since surgery, more than rare disabling seizures but rare for the last two years, and nocturnal seizures only. Class III was defined as worthwhile improvement, with subcategories of worthwhile seizure reduction and prolonged seizure-free intervals of greater than half the follow-up period and at least two years. Class IV was for patients with no worthwhile improvement, with subcategories of significant seizure reduction, no change, or worsening of seizures. The classification system was revised by a committee of the International League Against Epilepsy [22]. In

this classification, Class 1 was for patients completely seizure-free with no auras beginning one month after surgery, Class 2 for patients with auras only, and class 3 for patients with 1–3 seizure days per year. Class 4 was for patients with seizures ranging from 4/year to 50% decrease in days with seizures. Class 5 was for patients with a 50% reduction to 100% increase in days with seizures. Class 6 was for patients with a greater than 100% increase. Classes 3–6 included patients with or without auras.

Other Outcomes

Memory often can be worse [23]: (a) after a dominant hemisphere temporal lobe resection, (b) if the MRI does not show exclusive unilateral mesial temporal sclerosis, and (c) if preoperative immediate and delayed recall memory is intact. In particular, there can be declines in object naming and similar functions. Memory can improve, however, if a nondominant resection is performed. Surgery can be successful [19] if depth recordings show a unilateral ictal onset, if there is ictal spiking but not a rhythmic fast pattern, if there is no evolution to a distinct contralateral seizure pattern, and if there is an interhemispheric propagation time greater than 8 s. As expected from the last of these, a longer duration of ictal EEG activity before clinical onset may at times point to a more successful surgical result. Also, results of temporal lobe surgery are better if the onset of the seizure is not diffuse on the recordings and does not begin in the posterior temporal regions where resection is more difficult [19]. With bilateral ictal onset, surgery can still be successful if greater than 50% of seizures originate from the resected side, and if the Wada test shows adequate memory on the other side with no extra temporal focus [24]. In this study, 9/11 operated patients had no seizures and one of 11 had a 75% reduction in seizure frequency. Explanations for the findings included the possibility of a mirror focus, disconnection, or bilateral disease which was nonetheless responsive to unilateral surgery.

Adverse effects [4] after temporal lobe epilepsy surgery can occur in about 2% of patients including quadrantanopsia and memory problems. There can be other field deficits as well as motor, sensory, or speech deficits. With anterior choroidal artery or other occlusions, there can be significant problems including strokes. Some patients have had cerebellar hemorrhages. Death has been reported to occur in 0.24% of patients. One review [25] found less than 1% morbidity including hemorrhage, infarction, pulmonary embolus, and pseudogout. There was a 2.4% incidence of hemiparesis and 50% incidence of visual field defects with 2–4% hemianopia. Less than 2% of patients had infection and epidural hematoma or transient third nerve palsy, 20% transient anomia, 1–3% persistent dysphagia, and 2–20% transient psychosis or depression.

Depression is commonly present prior to temporal lobectomy and is more common afterward if present prior to surgery. Patients with a history of depression are less likely to become seizure-free after surgery. Moreover, there is a risk of postsurgery suicide, with an age- and sex-adjusted mortality ratio of 13.3 compared to the US population as a whole [26]. On the other hand, a study found that 45% of a group of patients experienced remission of psychiatric symptoms, no longer needing psychotropic medication, after epilepsy surgery [27].

Other Surgical Resections

In one survey [19] of frontal lobe surgery patients, at one year 49.5% of patients had Class I onsets with 55.7% of these patients seizure-free. In 5 years, 47% had Class I seizure control and 30.1% of these were seizure-free. At 10 years, 41.9% had Class I outcome. 80% of recurrences were in the first 6 months. If there were recurrences, patients were less likely to become seizure-free. The running-down phenomenon was less frequent. Good prognostic factors included MRI lesions and complete resection. With these, the likelihood of good prognosis was 72% versus 41% if these were not present.

The same authors concluded that with parietal and occipital lobe seizures, 73.1% of patients were seizure-free in 6 months, 68.5% in one year, and 54.8% in 6 years. Circumscribed lesions conveyed a good prognosis. The authors noted that side effects such as dysphagia or Gerstmann's syndrome could occur and they discuss the importance of sparing the calcarine cortex and speech areas.

Patients with bilateral temporal lobe onsets were discussed above. In addition, several authors have commented on the importance of considering that some patients with infantile spasms and apparent bilateral ictal onset on EEG may show unilateral PET hypometabolism and then may be found to be the candidates for focal surgery. Similar situations may occur with patients with focal hamartomas or other unilateral MRI lesions but apparently multifocal seizures. In many cases, the lesions are congenital or acquired early [28].

When a region of seizure onset cannot be removed completely, **multiple subpial transections** can be considered [29, 30]. This involves separating the superficial cortical horizontal connections within a gyrus while preserving the vertical pathways. Often, this is performed adjacent to an area of resection. Transections are typically performed at approximately 5-mm intervals, with the cuts extending 1–3 mm. The concept is that this disrupts "horizontal" epileptogenic propagation while preserving "vertical" axonal connections. One should keep in mind that this affects the gyral crown but not the sulci because of the way this is done. Reports describe that 1/3–2/3 of patients become seizure-free, but later recurrences also are possible. Although the major gyral sulci are well known, it is important to realize that there are microsulci throughout the cortex which are not readily seen from the cortical surface and that fibers in the microsulci are not affected by this technique. Also, microscopy shows that transections produce not only fiber separations but also microlesions [31].

Hemispherectomy is a useful for seizure control in a small group of patient who have problems such as Rasmussen's syndrome, hemimegalencephaly, Sturge–Weber syndrome, or lesions such as porencephaly with seizures that have become intractable to medication [32]. Often, these patients have multiple seizures per day and have a complete or progressive hemiparesis. There are widespread areas of potential epileptogenesis in a single hemisphere. The entire hemisphere is removed in the classic procedure, but there are modifications including a functional hemispherectomy, in which the hemisphere is left in place but disconnected from the opposite hemisphere by section of pathways such as the corpus callosum. To avoid postoperative complications, some surgeons will collapse the subdural space by fixing the dura to the falx. Corticectomy plus disconnection has been performed as well as corticectomy plus lobectomy. 70–80% of patients become seizure-free. Because of the reduction in seizures, intellectual function often improves. Despite removal of a hemisphere, patients can walk or even run although they may need an ankle brace. The hand contralateral to the resected hemisphere has no fine finger and has little wrist movement but can function as a "helper hand." Possible complications include subarachnoid bleeding, hemosiderosis, cerebrospinal fluid block, and hydrocephalus.

Multilobe resections can be performed as well. For example, this can be done in patients with Sturge–Weber syndrome, or with cortical dysplasia, with the dysplasia removed as an addendum to temporal lobe resection. These methods have not been helpful in patients with Rasmussen's syndrome; hemispherectomy is the surgical treatment of choice. As expected, functional complications of hemispherectomy or multilobar resection often relate to the location of the area of surgical removal. In particular, removal of the perirolandic area is more likely to result in a permanent motor deficit. (But patients with Rasmussen's syndrome often are already hemiparetic when surgery is performed.)

Corpus callosotomy has been particularly helpful for atonic, "falling," seizures as well as for tonic seizures, with electrodecrement at seizure onset, and for generalized tonic–clonic seizures. While "falling" seizures may benefit, other seizure types may remain, so generally this should be thought of as a palliative rather than

curative procedure. Focal seizures can become more severe after section, and in experimental models, kindling can occur more rapidly [33, 34]. It may be that this occurs because seizures were originating in one hemisphere and the homologous region in the opposite hemisphere was helping to control, limit, or stop the actual seizure progression. After callosal section, the contralateral homologous region can no longer suppress the region of epileptogenesis.

There can be an acute disconnection syndrome after callosal section, with akinetic mutism, incontinence, apraxia, or the alien hand syndrome. It is thought that this is more likely if the entire corpus callosum is sectioned initially. For this reason, many prefer to do an anterior 2/3 section first. The posterior third can be sectioned later if necessary, with a lower likelihood of adverse postoperative effects. However, in addition to the amount of callosal fibers resected, it is possible that pressure on the brain or vascular compromise, for example due to retraction, might explain the acute effects of disconnection just described.

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Quality of Life in Epilepsy

27

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Restrictions: Patients at risk for seizures should be warned that all environments or situations that could cause harm to the patient or others, should a seizure occur, must be avoided. Specifically:

- No working at "unprotected" heights, including roofs and ladders.
- No working around heavy machinery with moving parts.
- No construction equipment use.
- No use of manufacturing equipment, including, among others, fork lifts, heavy presses, and conveyor belt systems.
- Avoid known environmental triggers: heat, cold, humidity, dust, and fumes.
- Shower or bathe in minimal amounts of water in order to avoid drowning in case of loss of consciousness.
- Swim only when supervised by someone who is aware of seizure history and is capable of helping should a seizure occur.
- No cooking or working around open flames.
- NO DRIVING!

These restrictions stay in effect until released at the discretion of the provider or the stipulations of the state.

Driving: Without a doubt, the loss of driving privileges has the greatest overall impact on those with epilepsy. Each state has regulations and some leave the decision to the discretion of the provider. Driving restriction typically ranges between three and 12 months. Tennessee, for example, requires six months of seizure freedom, whereas Kentucky requires three months. The loss of driving means relying on others for transportation whether this is to school, work, shopping, or to go on a date! The loss of a license may mean the loss of employment for those that drive a truck or captain a boat for a living.

Commercial Truck Drivers: The restrictions are placed by the Federal Motor Carrier Safety Administration:

Current recommendations are that restrictions should be determined on an individualized basis. The nature of the seizure and risk of recurrence should be considered when determining fitness for specific job requirements.

- Persons with diagnosed epilepsy who are seizure-free and off medication for 10 years may be considered for licensure to operate a commercial vehicle.
- Onetime event thought to be nonepileptic and requiring no antiseizure medication will possibly allow for return to driving after six months of seizure freedom.
- Single unprovoked seizure with no recurrence may be considered for reinstatement following a five-year period off medication. A waiver to this determination may be made

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if the individual has a normal EEG and has been evaluated by a neurologist that specializes in epilepsy.
- Acute symptomatic seizures in the presence of acute structural insults to the central nervous system with low risk for recurrence; there should be no restriction after they have been seizure-free for two or more years off antiepileptic drugs.
- Persons that have undergone any procedure that penetrates the dura should not be considered eligible for commercial licensure [1].

Merchant Mariners Including Riverboat Captains: According to the US Department of Homeland Security and the United States Coast Guard under COMDTMOTE 16700.4, NVIC 04-08, Enclosure (8) Mariners, including commercial ship captains and riverboat captains, are controlled by the Coast Guard.

- Those mariners that have seizure(s) determined to be low risk of recurrence may be considered for a waiver to return to duty when they have been seizure-free and off medication for a minimum of one year.
- Those with seizures considered as high risk of seizure recurrence must be seizure-free for a minimum of eight years [on or off medication]. If they continue on medication their dose regimen must be stable for two years. If they are off medication, they must be seizure-free for eight years from the time they stopped the medication [2].

Aircraft Pilots: Neurological disorders: epilepsy, seizures, stroke, paralysis, etc. The applicant should provide history and treatment, pertinent medical records, current status report, and medication. The Examiner should obtain details about such a history and report the results. An established diagnosis of epilepsy, a transient loss of control of nervous system function(s), or a disturbance of consciousness is a basis for denial no matter how remote the history. Like all other conditions of aeromedical concern, the history surrounding the event is crucial. Certification is possible if a satisfactory explanation can be established.

Guide for Aviation Medical Examiners:

- A disturbance of consciousness without satisfactory medical explanation of the cause must submit all pertinent medical records, current neurological report, to include name and dosage of medication(s) and side effects. This requires Federal Aviation Administration (FAA) decision.
- Rolandic seizure must submit all pertinent medical records, current status report, to include name and dosage of medication(s) and side effect. Rolandic seizures may be eligible for certification if the applicant is seizure-free for 4 years and has a normal EEG.
  This requires FAA decision.
- Febrile seizure (single episode) must submit all pertinent medical records and a current status report if occurred prior to age 5, without recurrence and off medications for 3 years of issue.
  Otherwise, this requires FAA decision.
- Transient loss of nervous system function(s) without satisfactory medical explanation of the cause, e.g., transient global amnesia must submit all pertinent medical records, current status report, to include name and dosage of medication(s) and side effects. This requires FAA decision.
- Unexplained syncope, single seizure. An applicant who has a history of epilepsy, a disturbance of consciousness without satisfactory medical explanation of the cause, or a transient loss of control of nervous system function(s) without satisfactory medical explanation of the cause must be denied or deferred by the examiner. Consultation with FAA is required.
- Infrequently, the FAA has granted an authorization under the special issuance section of part 67 14 CFR 67.401 when a seizure disorder was present in childhood, but the individual has been seizure-free for a number of years. Factors that would be considered in determining eligibility in such cases would be age at onset, nature, and frequency of

seizures, precipitating causes, and duration of stability without medication. Follow-up evaluations are usually necessary to confirm continued stability of an individual's condition if an authorization is granted under the special issuance section of part 67 14 CFR 67.401 [3].

Common Seizure Triggers: Stress (positive or negative), fatigue, medication compliance, excessive alcohol use, and sleep deprivation. Positive stress usually relates to vacation time or cheerful events causing change of daily routine including change in food and alcohol intake, reduced sleep time, and changing time zones. Negative stress mostly relates to bad news and grief resulting in reduced sleep and poorer AED adherence.

Accommodations: According to the United States Department of Labor:

> A job accommodation is a reasonable adjustment to a job or work environment that makes it possible for an individual with a disability to perform job duties. Determining whether to provide accommodations involves considering the required job tasks, the functional limitations of the person doing the job, the level of hardship to the employer, and other issues. Accommodations may include specialized equipment, facility modifications, adjustments to work schedules or job duties, as well as a whole range of other creative solutions.
>
> The Job Accommodation Network (JAN), a service of the Office of Disability Employment Policy (ODEP), provides a free consulting service on workplace accommodations [4].

Accommodations may be needed at work or school. Looking at the classic triggers, recommendations, and restrictions, it is simple to justify the accommodations often needed for the patient to function in their environment. The individual must understand that accommodations are not always possible.

A letter, worded carefully, should assure that the individual's needs are addressed without violating HIPAA rules, or requesting accommodations that are unreasonable.

Accommodations in the work place include the following:

- Minimize excessive stress,
- Limited work hours to 8–10 h/day,
- No third or midnight shift,
- No working at unprotected heights,
- No working around heavy moving machinery,
- Avoid environmental situations that are known triggers or that should a seizure occur could cause harm to the individual or others, and
- Provide assistive technology (AT) that can improve productivity of the individual coping with any cognitive issues.

College students with epilepsy should register with Student Health, protecting themselves should a need arise either physically or educationally. Seizure activity frequently escalates during the college years. Students in both high school and college may need assistance with recording lectures, extra time to prepare for examinations, and accommodations for missed classes secondary to seizure activity. Accommodations frequently requested include the following:

- Leniency on attendance.
- If seizures are active, they may have to rely on others for transportation.
- Seizures can result in an assignment not being completed or a class missed.
- All night study sessions are not possible due to risk of sleep deprivation.
- Avoidance of multiple examinations on the same day [frequently during mid-term and finals].
- Understanding that an assignment given one day and expected back the next might not be possible as it is imperative that the student gets adequate rest. All night study sessions can only produce negative outcomes.
- Short-term memory loss is not uncommon so "pop quizzes" will be difficult and the student may need other means of meeting the needed results.
- Assistance with reading, taking notes, or recording lectures.

- Single college room—allowing for adequate rest and no late night interruptions by roommates.

Other accommodations occasionally requested:

- Dogs/pets—both trained seizure dogs or companions that may stay in their dorm room or apartment;
- Request for single-level housing;
- Use of elevators when available rather than open stairwells;
- Access ride or other forms of discounted public transportation; and
- Use/purchase of wheelchairs, manual or motorized.

Disability: According to the Social Security Official Web site: [5]

SSR 87-6: TITLES II AND XVI: THE ROLE OF PRESCRIBED TREATMENT IN THE EVALUATION OF EPILEPSY

> POLICY STATEMENT: As a result of a modern treatment which is widely available, only a small percentage of epileptics, who are under appropriate treatment, are precluded from engaging in substantial gainful activity (SGA). Situations where the seizures are not under good control are usually due to the individual's noncompliance with the prescribed treatment rather than the ineffectiveness of the treatment itself. Noncompliance is usually manifested by failure to continue ongoing medical care and to take medication at the prescribed dosage and frequency. Determination of blood levels of anticonvulsive drugs may serve to indicate whether the prescribed medication is being taken. In a substantial number of cases, use of alcohol has been found to be a contributory basis for the individual's failure to properly follow prescribed treatment. In such cases, the individual's alcohol abuse should be evaluated. (See SSR 82-60, PPS No. 83, Titles II and XVI: Evaluation of Drug Addiction and Alcoholism.)

Documentation needed in the medical record:

EEG—Corroborating the nature and frequency of seizures;
Detailed description of typical seizure pattern including associated phenomena:

- Professional observation,
- Observation of a third party, and
- Description by the patient is not acceptable for social security requirements;

History of treatment, response and any recent changes;
Consistency in therapy:

- Attending regular clinic visits/ communications and
- Details regarding seizure history and responses to therapy;

Major motor seizures must be occurring more frequently than once a month—on medication;
Minor motor seizures must be occurring more frequently than once weekly in spite of being on prescribed treatment for at least 3 months;
Establish whether the seizures are due to factors beyond the individual's control or to noncompliance with prescribed therapy:

- Record of AED blood levels,
- Low levels must be explained,
- Noncompliance,
- Abnormal absorption or metabolism, and
- The dosage is not optimal.

Medications:
Insurance plans are becoming more complicated. A secondary program such as Medco/Express Scripts, CVS Caremark, Optum, EnvisionRxPlus, and many more generally processes prescriptions. This secondary program determines coverage and responses to appeals. Each program has its own formulary and appeals process. It is important to understand their requirements for coverage as often there are ways to successfully work around their roadblocks. These are only a few of the restrictions on prescriptions that may be encountered:

- generics only—often no appeal process,
- generics preferred—appeal process available,
- quantity limits—appeal possible letter of medical necessity,
- formulary/nonformulary,
- tiering/levels of coverage: anywhere from 2–4 tiers with the expense going up with each tier,

- tier exception—often requires letter of medical necessity requesting the medication be covered at a lower tier,
- percentage of cost,
- percentage of the total cost of the medication: 20, 50%,
- co-pay plus percentage,
- co-pay plus the difference in cost of generic versus nongeneric,
- controlling the dose by maximum milligrams allowed/day—not always associated with FDA recommendations:
  - use a mixture of strengths so that no one "medication" equals more than the allowed milligrams—Example,
  - needing 1000 mg but insurance only allows 600 mg, and
  - Use 3–200 mg tabs plus 4–100 mg tabs.
- limiting the number of tablets—this limitation is the most difficult to comprehend, it may require a maximum of two tablets per day, and it does not matter if they are 50 or 200 mg. It is important to understand this concept as the dose is increased.
- This same concept is involved when increasing doses. In order to get a larger dose, it may be necessary to use a combination of strengths merely to meet the number of tablets restriction.

The appeal process is often offered with particular programs and you must be able to demonstrate the step therapy and titration process.

Information that you should have ready anytime an appeal is submitted:

- all previously tried AEDs,
- dates used,
- reason for termination, and
- proof of previous use of the generic formulation.

Medications Affordability

Medications are frequently too expensive for the patient to afford. It is difficult to accept that the medication that is best for the patient is unavailable to them because of cost. There are programs that can assist patients with their medication costs. If the patient has no insurance or at least no medication coverage, they might be eligible for a pharmacy assistance program through the manufacturer. The same is true for those falling into the donut hole with Medicare. The easiest method to determine what programs are available to the patient is to access rxAssist.org. This Web site will advise of programs available and any necessary qualification. Discount cards are also available on many medications. The $4.00 programs offered by select pharmacies often provide a very limited number of AEDs. A program called RxOutreach has generic medications, including many controlled drugs at a price often cheaper than the usual insurance co-payment.

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Multiple Choice Questions for Part V

1. Computed tomography most reliably identifies which of the following epileptogenic pathologies?

   A. Hippocampal sclerosis
   B. Focal cortical dysplasia
   C. Subacute stroke
   D. Low-grade glioma
   E. Hippocampal atrophy

2. Magnetic source modeling refers to

   A. Modeling the cortical generators of neuromagnetic events
   B. Modeling the microscopic neural circuitry that generates brain electrical signals
   C. Modeling the various sources of interference in the MEG system
   D. Modeling the anatomy of the brain from MRI
   E. Modeling the magnetic properties of the head and brain tissue

3. The purpose of neuropsychological examination in epilepsy includes all of the following, except:

   A. Assess cognitive difficulties resulting from seizures or antiseizure medications
   B. Establish baseline of functioning for systematic comparisons across time
   C. Provide treatment for comorbid depression
   D. Provide evidence for localization of function and dysfunction

4. All of the following are true about MRI features of Dyke–Davidoff–Masson syndrome (DDMS), *except*?

   A. Enlargement of the frontal sinus
   B. Polymicrogyria
   C. Falcine displacement
   D. Thickening of the skull vault
   E. Capillary malformations

5. All of the following are associated with intellectual deficiencies in individuals with epilepsy, except:

   A. Frequent episodes of status epilepticus
   B. Focal epilepsy with a localizable focus
   C. Polytherapy
   D. Early onset of seizures
   E. West syndrome

6. Selective amygdalohippocampectomy provides:

   A. Better neurocognitive outcome compared to en bloc temporal resection
   B. Worse neurocognitive outcome compared to en bloc resection
   C. Its neurocognitive advantage is not well established

D. Better but seizure freedom chances than temporal lobectomy
E. Worse but seizure freedom chances than temporal lobectomy

7. All of the following is true about hemimegalencephaly, *except*?

A. White matter volume in enlarged hemisphere is normal
B. Hemispheric growth is hamartomatous
C. There is agyria
D. There is polymicrogyria
E. There is lissencephaly

8. Where in the hippocampus are sclerotic changes typically found in MRI-negative (1.5T) temporal lobe epilepsy?

A. CA1
B. Hippocampal tail
C. CA3
D. CA4
E. Subiculum

9. Neuromagnetic signals from the brain are of the order of:

A. Nanoteslas
B. Milliteslas
C. Microteslas
D. Femtoteslas
E. Picoteslas

10. Which of the following is true about driving restrictions in the USA?

A. Uniform across all states
B. Minimal seizure freedom is 3 months
C. Does not apply to provoked seizures
D. Excludes brief absence seizures
E. None of the above

11. Which of the following best characterizes MRI findings in focal cortical dysplasia?

A. MRI findings can be detected in 90% of patients with FCD
B. Transmantle sign is seen in patients with cytoarchitectural dysplasia
C. Architectural dysplasia is the subtype of FCD that is most often missed on MRI imaging
D. FCD is seldom seen with dual pathology of HS
E. In neonates, FCD is usually hyperintense in T2-weighted images and hypointense in T1-weighted images

12. Intracarotid amobarbital procedure (Wada test) can be helpful in terms of:

A. Lateralizing seizure focus
B. Lateralizing memory
C. Lateralizing language dominance
D. Predicting surgical outcome
E. All of the above

13. Which of the following is true regarding diffusion MRI findings in the epileptogenic zone during the ictal phase?

A. During the ictal period, diffusion MRI abnormalities are found equally in both the gray and the white matter
B. Ictal onset is followed by an immediate increase in the ADC signal
C. Following the short initial phase of ictal onset, the ADC signal is highest due to vasogenic edema
D. With continued seizure activity, there is eventual cytotoxic edema and the ADC signal increases
E. During the postictal phase, if there is irreversible injury due to seizure activity, the ADC signal decreases compared to neighboring tissue

14. In drug-resistant epilepsy, deep brain stimulation targets which of the following structures?

A. Cingulate gyrus
B. Reticular formation of the thalamus
C. Anterior nucleus of the thalamus
D. Hippocampus
E. Outer globus pallidus

15. The antiepileptic effects of vagus nerve stimulation (VNS):

    A. Increases indefinitely over time until complete seizure freedom is achieved
    B. Reaches its peak in 3 months
    C. Remains the same throughout the course of treatment
    D. Shows improvement over a ≥ 2 year course as compared to the initial 3 months
    E. Is highest initially

16. Which of the following is associated with poor verbal memory outcome after left temporal lobectomy?

    A. Left mesial temporal sclerosis on MRI
    B. Adult seizure onset
    C. Left temporal hypometabolism on FDG-PET
    D. Poor preoperative scores on the Rey Auditory Verbal Learning Test
    E. Poor preoperative scores on Boston Naming Test

17. The typical SPECT pattern in a mesial temporal lobe foci during the ictal (0–2 min from seizure onset) and subsequent peri/postictal (2–6 min from seizure onset) period is characterized by which of the following?

    A. During the ictal state, there is marked ipsilateral hyperperfusion with a surrounding smaller region of hypoperfusion
    B. During the ictal state, severe ipsilateral hyperperfusion involves the entire temporal lobe
    C. During the peri-ictal/postictal state, severe contralateral hypoperfusion involves the entire temporal lobe
    D. During the peri-ictal/postictal state, severe ipsilateral hyperperfusion involves the entire temporal lobe
    E. During the ictal period, there may be bilateral temporal lobe hypoperfusion

18. Free consulting service on workplace accommodations is provided by:

    A. FDA
    B. Job accommodation network (JAN)
    C. "No epileptic left behind" association
    D. Accommodation for all office
    E. This service is not free

19. A patient who continues to have focal and secondary generalized seizures despite trying 7 different antiseizure medications

    A. Is likely to become seizure-free after trying more ASMs
    B. Is unlikely to become seizure-free after trying more ASMs
    C. Must be referred for presurgical evaluation
    D. Is very likely to become seizure-free with deep brain stimulation (DBS) therapy
    E. 2 and 3

20. Which of the following MRI techniques has the highest relative sensitivity for detection of mesial temporal sclerosis?

    A. A.T2 relaxometry
    B. Inversion recovery
    C. Visual atrophy
    D. Inversion recovery + visual atrophy
    E. Hippocampal volumetry

21. Which of the following percentages is the closest approximation of the false lateralization rate for PET in patients with unilateral temporal lobe epilepsy?

    A. 1–2%
    B. 5%
    C. 10%
    D. 20%
    E. 30%

22. Which of the following is true with PET imaging in temporal lobe epilepsy?

    A. Decreased monoamine oxidase-B ligand binding in cases of pathologically proven temporal lobe epilepsy

B. Ipsilateral to the seizure foci, there is increased μ-opiate receptor binding, decreased σ-opiate receptor binding, and decreased K-opiate receptor binding
C. Increased D2/D3 binding in the epileptogenic temporal lobe
D. Decreased benzodiazepine receptor binding ipsilateral to the temporal epileptic foci
E. Increased serotonin-1A (5-HT1A) receptor binding ipsilateral to the temporal epileptic foci

23. All of the following are true about neuropsychological tests, *except*:

A. Working memory can be assessed by Digit Span Backwards
B. Grooved Pegboard Test or Purdue Pegboard Test assesses visual memory
C. Set-shifting can be assessed by Trail Making Test
D. Stroop Color Word Test assesses executive function
E. Rey–Osterrieth Complex Figure Test assesses planning

24. Most common adverse events of vagus nerve stimulation (VNS) includes:

A. Tachycardia
B. Bradycardia
C. Cough
D. Hoarseness
E. Asystole

25. All of the following are MRI findings of the affected side in mesial temporal sclerosis except?

A. Loss of internal architecture of the hippocampus
B. Collateral white matter atrophy of the temporal lobe
C. Extratemporal enlargement of the caudate
D. Extratemporal atrophy of the fornix
E. Dilation of the temporal horn

26. All of the following are common pitfalls in erroneously diagnosing epileptic lesions in normal hippocampi except?

A. Vertically oriented hippocampus erroneously suggests hippocampal dysplasia
B. The hippocampus is normally hyperintense on T1, misleading to a diagnosis of bilateral MTS
C. Artifactual size asymmetry can easily be caused by head rotation as the hippocampus is large anteriorly and tapers progressively posteriorly
D. Hippocampal sulcus remnant is a normal variant that occurs in 10–15% of normal hippocampi
E. A choroid fissure cyst expands the choroidal fissure and compresses the hippocampus, erroneously suggesting hippocampal atrophy

27. Which of the following statements about MEG source modeling is *incorrect*?

A. The problem of determining the cortical generators of MEG activity is considered an "ill-posed" inverse problem
B. "Ill-posed" inverse problems have a unique solution
C. "Ill-posed" inverse problems have an infinite number of possible solutions
D. The "*forward model*" is a physical model of neural sources in the brain and how these sources generate electromagnetic fields outside the head
E. The "*head model*" is a component of the forward model

28. Which of the following is the most common neoplastic lesion associated with new onset seizures in older adults?

A. DNET
B. Ganglioglioma
C. Low-grade glioma
D. High-grade glioma
E. Cerebral metastasis

29. Which of the following is true about efficacy of responsive neurostimulation (RNS)?

    A. Seizure reduction in the 12 week blinded phase of RNS is 17.3%
    B. Seizure reduction 5 months postimplantation of RNS is 25%
    C. 50% responder rate is 55% after two years
    D. Seizure freedom reaches 75%
    E. None of the above

30. All of the following are true regarding postictal diffusion changes except?

    A. If ictal activity subsides without causing irreversible injury, a complete resolution with no residual diffusion change is noted.
    B. During the immediate postictal period, there is a decrease in the ADC.
    C. ADC is increased with continued seizure activity due to neuronal cell death, acute inflammatory changes, and gliosis.
    D. During the immediate postictal period, there is decreased DWI signal in the epileptogenic area.
    E. If injury due to seizure activity progresses, the ADC increases compared to the preictal state and to the neighboring normal tissue.

31. Which of the following intracranial vascular malformations is most commonly associated with seizures?

    A. Arteriovenous malformations
    B. Cavernous hemangiomas
    C. Epidural hematoma
    D. Venous angiomas
    E. Capillary telangiectasias

32. Recent studies suggest that high-frequency oscillations (HFOs) are:

    A. Most abundant in the frontal lobes
    B. Are present in the epileptogenic zone
    C. Signify functional cortex and must not be resected
    D. Can be recorded with scalp EEG in the absence of muscle artifact
    E. Are seen only ictally

33. Which of the following is an appropriate use of CT in patients with epilepsy?

    A. Acute emergency for evaluation of new onset seizures in patients with symptomatic causes.
    B. Postoperative follow-up for tumor recurrence.
    C. Defining topographic relationships of epileptogenic lesions to functional cortex and cortical white matter tracts.
    D. Detection of mesial temporal lobe sclerosis.
    E. Pediatric new onset seizures without apparent symptomatic cause.

34. A 45-year-old pilot experiences a brief episode of "losing track of conversation" after a prolonged flight. His routine EEG reveals occasional left temporal rhythmic delta activity but is otherwise normal. His brain MRI is normal. The most appropriate counseling step is to:

    A. Have the pilot continue the regular flight schedule
    B. Restrict the pilot from long flights for at least 6 months
    C. Indefinitely stop piloting
    D. Refer to psychiatry for possible malingering
    E. Offer few weeks of rest before resuming regular flight schedule

35. Which of the following is *not* true about ADHD in individuals with epilepsy?

    A. ADHD is seen in 20–40%
    B. In epilepsy, ADHD affects males and females equally
    C. Temporal lobe epilepsy is associated with higher rates of attention problems than frontal lobe epilepsy
    D. Nocturnal seizures exacerbate inattention
    E. Stimulants do not lower the seizure threshold

36. At present, MEG has an approved clinical indication for all of the following, *except*:

    A. Localizing cortical generators of interictal epileptic spikes in patients being evaluated for epilepsy surgery
    B. Lateralizing language dominance prior to brain surgery
    C. Localizing somatosensory cortex prior to brain surgery
    D. Confirming a diagnosis of epilepsy in a patient with negative EEG studies
    E. Localizing primary auditory cortex prior to brain surgery

37. Magnetic source modeling refers to

    A. Modeling the cortical generators of neuromagnetic events
    B. Modeling the microscopic neural circuitry that generates brain electrical signals
    C. Modeling the various sources of interference in the MEG system
    D. Modeling the anatomy of the brain from MRI
    E. Modeling the magnetic properties of the head and brain tissue

38. Which of the following statements represents a limitation of MEG in the presurgical evaluation of patients for epilepsy surgery?

    A. MEG cannot accurately localize primary sensory cortices for functional mapping
    B. In patients with multifocal spikes, magnetic source modeling cannot accurately localize the events
    C. In some patients, no interictal spikes or ictal events may be captured during the MEG study
    D. Ictal rhythms cannot be localized using magnetic source modeling methods

39. Which statement is correct about patients with vagal nerve stimulation (VNS)?

    A. May not have an MRI
    B. May have an MRI after turning off the normal mode
    C. May have an MRI after turning off the magnet mode
    D. May have an MRI after turning off the normal and magnet mode
    E. Refer for CT scan instead

40. For lateralizing language, what is the concordance rate between neuromagnetic responses to auditory language stimuli and the Wada test?

    A. <10%
    B. 25%
    C. 50%
    D. >70%

41. Which of the following is true about side effects of responsive neurostimulation (RNS)?

    A. Intracranial hemorrhages occurred at a rate of 10%
    B. Mood worsening was noted
    C. Cognitive function worsened
    D. Quality of life improved
    E. None of the above

42. Very frequent VNS magnet activation in the setting of high-frequency stimulation ($\geq$ 50 Hz) can result in:

    A. ON time $\geq$ OFF time that does not result in degenerative nerve damage in laboratory animals and is safe
    B. ON time $\geq$ OFF time is not technically possible to induce
    C. ON time $\geq$ OFF time that can result in degenerative nerve damage in laboratory animals and therefore should be avoided
    D. OFF time $\geq$ ON time that would be ineffective and therefore should be avoided
    E. No effect

43. A 34-year-old woman started having episodes of confusion and lip smacking. Her EEG showed left temporal spikes. She was initially started on levetiracetam but failed to achieve good seizure control. In

spite of adding lamotrigine, she continued to have occasional disabling seizures. Her antiepileptic blood levels are therapeutic. The best next step is to:

A. Add clobazam
B. Refer to RNS
C. Refer to VNS
D. Admit for inpatient video EEG
E. Start citalopram

44. A 30-year-old female patient with chronic refractory temporal lobe epilepsy is typically more likely to become seizure-free after:

A. Several attempt of polytherapy with combination of old and new generation antiseizure medications (ASMs)
B. Temporal lobectomy
C. Repeated attempt of polytherapy with synergistic generation ASMs
D. Vagus nerve stimulation
E. Responsive neurostimulation

45. Patients with intractable temporal lobe epilepsy who have normal high-resolution brain MRIs:

A. Are not candidates for presurgical evaluation because of a possible poor outcome
B. Must undergo presurgical evaluation
C. Have better outcome than those with abnormal brain MRI
D. Are unlikely to have hippocampal seizure onset
E. Are likely to have concomitant psychogenic non-epileptic episodes

46. Which of the following is most associated with an increased risk of suicidality in patients with epilepsy?

A. Coexistent depression
B. Higher absence frequency
C. Male sex
D. Lower quality of life
E. Generalized onset seizures

47. A patient with history of prior left temporal hemorrhage and refractory left temporal lobe epilepsy may undergo temporal lobectomy:

A. After subdural grid electrode placement localizes seizure onset zone and language mapping is done
B. If the Wada test establishes that verbal memory lateralizes to the right
C. Based on an MRI that confirms the presence of encephalomalacia in the left lateral temporal area and ictal scalp EEG that localizes seizures to the left temporal region
D. If PET shows left temporal hypometabolism
E. If ictal SPECT shows seizure onset in the left temporal lobe

48. Which of the following is not a typical aura in insular seizures?

A. Abnormal taste
B. Contralateral somatosensory symptoms
C. Contralateral head version
D. Laryngeal constriction
E. Visceral symptoms

49. An adult patient with frequent nocturnal events soon after falling asleep, consisting of arousal from sleep and violent movements for 30 s with full recovery, most likely has:

A. Insular epilepsy
B. REM sleep behavior disorder
C. Frontal lobe epilepsy
D. Psychogenic non-epileptic seizures
E. Temporal lobe epilepsy

50. Which of the following is true about corpus callosotomy?

A. It does not help control atonic seizures
B. May worsen focal seizures
C. Akinetic mutism is not a complication
D. Apraxia is not a complication
E. Incontinence is not a complication

51. Patients with extratemporal lobe epilepsy:

    A. More likely need invasive recording before epilepsy surgery
    B. More likely to be surgical candidates without invasive recording
    C. More likely to need subdural recording unless there are frontal lobe discharges consistent with frontal lobe epilepsy
    D. More likely to be surgical candidates without invasive recording, only if brain MRI shows a frontal lobe lesion
    E. More likely to be surgical candidates without invasive recording, only if brain MRI shows a parietal lobe lesion

52. Which of the following is true regarding abdominal aura?

    A. It has a sensitivity of 90% for localizing seizures to the temporal lobe
    B. It has a specificity of 90% for localizing seizures to the temporal lobe
    C. It indicates insular seizure onset
    D. It is non-specific in localizing seizure onset
    E. None of the above

53. Stimulation of either of superior and inferior cervical cardiac branches of the vagus nerve during system diagnostics (lead test) may cause:

    A. Bradycardia and/or asystole
    B. Tachypnea
    C. Hiccups
    D. Respiratory distress
    E. Diarrhea

54. Which antidepressant is least likely to aggravate seizures?

    A. Bupropion
    B. Citalopram
    C. Clomipramine
    D. Amoxapine
    E. Venlafaxine

55. When comparing results of temporal lobectomy to medical treatment in intractable epilepsy, patients treated with surgery are how many times more likely to be seizure-free?

    A. 3 times
    B. 7 times
    C. 15 times
    D. 20 times
    E. 25 times

56. Which of the following is true about hemispherectomy?

    A. About 25% of patients become seizure-free after hemispherectomy, but intellectual function worsens
    B. About 25% of patients become seizure-free after hemispherectomy, and intellectual function improves
    C. About 75% of patients become seizure-free after hemispherectomy, but intellectual function worsens
    D. About 75% of patients become seizure-free after hemispherectomy, and intellectual function improves
    E. About 50% of patients become seizure-free after hemispherectomy, with no change in intellectual function

57. When ictal theta activity is recorded, temporal lobe epilepsy is present in:

    A. Less than 10%
    B. 10–25% of cases
    C. 25–50% of cases
    D. 50–75% of cases
    E. More than 75% of cases

58. Extrahippocampal abnormalities in patients with temporal lobe epilepsy

    A. Are rare
    B. Include atrophy of lateral temporal structures
    C. Often include cortical dysplasia

D. Correlate with favorable surgical outcome if hippocampal atrophy is not present on presurgical MRI
E. None of the above

59. Which of the following is false about Rasmussen encephalitis?

A. Bilateral disease is rare
B. May present in adolescents or adults
C. Developmental delays do not precede presentation
D. Multilobar resections are a useful alternative to hemispherectomy
E. Progressive hemiparesis will ensue

60. Which of the following psychiatric conditions is most common in patients with epilepsy?

A. Bipolar II
B. Attention deficit disorder
C. Paranoid delusions
D. Depression
E. Post-traumatic stress disorder

61. Lifting driving restrictions of epilepsy patients operating large commercial vehicles require:

A. Same rule as for private car
B. A minimum of two-year seizure freedom
C. A minimum of ten-year seizure freedom
D. Being off antiepileptic drugs
E. C and D

62. All of the following may exclude patients from disability benefits except:

A. Chronic alcohol consumption
B. Low antiepileptic blood levels
C. Twice-weekly minor motor seizures
D. Seizure freedom for more than three months
E. Nocturnal seizures

63. In the newly diagnosed epilepsy, almost half patients will have seizure freedom with the first antiepileptic drug. What percentage will achieve seizure freedom with the second antiepileptic drug?

A. 5%
B. 15%
C. 25%
D. 40%
E. 50%

64. Stimulation of the region anterior to the premotor cortex will likely cause:

A. Salivation
B. Eye deviation
C. Sensory derangement
D. Behavioral change
E. Tinnitus

Answers

1. (C). CT scans provide better details about bony structures and can easily detect hemorrhages, calcifications, strokes after 24 h, and large tumors. However, CT may fail to recognize commonly encountered lesions in patients with epilepsy such as hippocampal atrophy, hippocampal sclerosis, cortical dysplasias, or low-grade gliomas (LGGs).
2. (A). Magnetic source modeling or magnetic source imaging (MSI) refers to the process of generating best-fitting hypotheses about the cortical generators of recorded neuromagnetic signals. Source modeling does not attempt to model the microscopic neural circuitry that generates brain signals, but assumes elementary sources comprised of one or many current dipoles. Structural models of the head and brain are requisites for source modeling but not the objective.
3. (C). Unlike general psychological practice, a neuropsychologist does not necessarily diagnose psychiatric conditions or provide treatment and may not assess specific vocational skills (driving, interest inventory, etc).
4. (B). Dyke–Davidoff–Masson syndrome (DDMS) presents with seizures, facial

asymmetry, contralateral hemiparesis, and mental retardation. Radiologic features include thickening of the skull vault, enlargement of the frontal sinus and the ethmoidal and mastoid air cells, elevation of the petrous ridge, ipsilateral displacement of the falx, and capillary malformations. Hemispherectomy may be recommended.

5. (B). Risk factors for intellectual deficiencies in epilepsy include primary generalized epilepsy, West syndrome, Lennox–Gastaut syndrome, localization-related epilepsy but seizure focus difficult to isolate; severe volumetric abnormalities; early onset of epilepsy; frequent seizures and more episodes of status epilepticus; polytherapy; and comorbid diagnoses (e.g., autism).
6. (C). Selective amygdalohippocampectomy provides similar seizure freedom chances to those of temporal lobectomy, but it is unclear whether it is superior to lobectomy in terms of neurocognitive outcomes; some studies reported better outcomes and others reported worse.
7. (A). Hemimegalencephaly refers to unilateral hamartomatous excessive growth of all or part of one cerebral hemisphere at different phases of embryologic development. MRI reveals an enlarged hemisphere with increased white matter volume, cortical thickening, agyria, pachygyria, polymicrogyria, or lissencephaly and blurring of the gray–white matter junction. Often, there is a large, ipsilateral irregularly shaped ventricle.
8. (D). In MR-negative MTLE, sclerotic changes are limited to or predominately in the CA4 region (endfolium) of the Ammon's horn.
9. (D). Neuromagnetic signals from the brain are typically of the order of 10^{-15} T (femtotesla). MRI scanners have static field strengths of the order of 1 T. The heart generates magnetic field of the order of a nanotesla.
10. (B). Driving restrictions apply to both provoked and unprovoked seizures. Each state has specific regulations, and some leave the decision to the discretion of the provider. Driving restriction typically ranges between 3 and 12 months.
11. (C). MRI is unrevealing in up to 34% of patients, especially those with architectural dysplasia only. Transmantle sign is seen in patients with Taylor-type dysplasia. FCD is the most common dual pathology with HS. The signal intensity of FCD varies with the age of the patient. In neonates and young infants, FCD is usually hypointense in T2-weighted images and hyperintense in T1-weighted images. After white matter myelination has reached significant levels (24 months), the hyperintensity is easily seen in FLAIR and T2-weighted images.
12. (E). The Wada test can help lateralize language and visual or verbal memory by inhibiting the function of one hemisphere at a time by amobarbital and assessing the function of the other hemisphere. The test also helps lateralize the seizure focus and predict surgical outcomes in terms of cognitive deficits as discussed in Chap. 25.
13. (C). During the ictal period, diffusion MRI abnormalities are primarily found in the gray matter. Immediately at seizure onset, there is an increase in electrical activity, leading to increased cellular metabolism and subsequent hyperperfusion. During this phase, there is no apparent change in the tissue microarchitecture detectable by diffusion MRI due to lack of significant edema. As seizure activity progresses, there is initially vasogenic edema (peak of ADC signal changes) followed by cytotoxic edema (decreased ADC activity). With irreversible neuronal injury, the ADC signal is increased compared to the preictal state and to the neighboring normal tissue.
14. (C). Deep brain stimulation has shown efficacy in patients with drug-resistant epilepsy when targeted to the anterior nucleus of the thalamus.
15. (D). Efficacy of VNS increases with time. Data showed improvement in seizure control over a ≥ 2 year course as compared to the initial 3 months of therapy.

16. (B). Early age of onset increases the chances that the brain will functionally rearrange. Mesial temporal lobe sclerosis on MRI and hypometabolism on PET suggest poor functioning and thus less risk of decline after surgery. Poor preoperative performance on naming and verbal memory makes suggest lower chances of further postoperative decline
17. (A). During the ictal state, there is ipsilateral temporal hyperperfusion with surrounding severe hypoperfusion. In the peri-ictal state, there is a "postictal switch" during which there is severe ipsilateral hypoperfusion throughout the temporal lobe, with the exception of persistent hyperperfusion in the mesial temporal region. Bilateral temporal lobe hyperperfusion is only seen in seizures of lateral temporal origin.
18. (B). The job accommodation network (JAN), a service of the Office of Disability Employment Policy (ODEP), provides free consulting services on workplace accommodations. Accommodations may be needed at work or school depending on classic seizure triggers, recommendations, and restrictions.
19. (E). Medically intractable epilepsy is defined as failure of two adequate trials of antiseizure medications to achieve seizure freedom. Patients who have failed to medications must be referred for surgical evaluation since additional medication regimens will have very low chances of achieving seizure freedom.
20. (E). Hippocampal volumetry, sensitivity of 97%.
21. (A). Unrecognized ictal activity during FDG injection could make temporal lobe contralateral to the focus appear falsely depressed. Prior depth electrode implantation could lead to contralateral hypometabolism. Increased interictal metabolism ipsilateral to an epileptic focus has been described in large cortical malformations.
22. (D). Monoamine oxidase-B binding increases with increasing gliosis in temporal lobe epilepsy. Ipsilateral to the seizure focus, there is increased μ-opiate receptor binding, increased σ-opiate receptor binding, and decreased K-opiate receptor binding. There is decreased D2/D3 binding in the epileptogenic temporal lobe. C-flumazenil PET is very sensitive in MRI-negative temporal lobe epilepsy given reduced benzodiazepine receptor binding. There is decreased serotonin-1A receptor binding in patients with TLE.
23. (B). Please refer to the table in Chap. 22.
24. (D). The most common adverse effect of VNS is hoarseness. Most of the VNS adverse effects have a negligible impact on the quality of life of treated patients and are reported as mild in most instances.
25. (C). There is extratemporal atrophy of the caudate.
26. (B). The hippocampus is normally hyperintense on FLAIR, misleading to a diagnosis of bilateral MTS. Amygdala and hippocampus are isointense on all other MR pulse sequences.
27. (B). The problem of MEG or EEG source modeling is considered an "ill-posed" inverse problem. "Ill-posed" inverse problems do not have unique solutions, but rather an infinite number of possible solutions.
28. (E). Metastatic lesions are the most frequent epileptogenic neoplasms in older adults.
29. (C). Seizure reduction in the 12-week blinded phase of RNS was 37.9% compared with 17.3% for sham. At 5 months postimplantation, 41.5% seizure reduction was seen in the stimulation group compared to a 9.4% reduction in the sham group. Two years after implantation of RNS, 50% responder rate was reported in 55%.
30. (D). During the immediate postictal period, the DWI signal is increased in the epileptogenic zone.
31. (A). Seizures occur in 24–69% of arteriovenous malformations and 34–51% of cavernous hemangiomas. The vast majority of capillary telangiectasias and venous angiomas are clinically silent. Epidural hematomas are not considered intracranial vascular malformations.

32. (B). HFOs are oscillation in the gamma band that are recorded with intracranial electrodes at high digital sampling frequencies. They have been studied and found to be abundant in the epileptogenic zone ictally and interically. Resection of the areas where HFOs are seen correlated with better surgical outcome.
33. (A). MRI is indicated for all of the other answer choices.
34. (C). The clinical history and the described EEG abnormality (rhythmic temporal delta activity) are both suggestive of partial (focal) epilepsy. Piloting an aircraft, either private or commercial, is completely prohibited for anyone with a history of seizures.
35. (C). Prevalence of ADHD in epilepsy is 20–40%. Inattentive presentation is more common, and the boys and girls are equally represented, which is different from developmental ADHD with no seizures. There may be higher rates of attention problems with FLE and CAE. Associated issues like nocturnal seizures or medication side effects may be the primary cause of inattention. Studies have shown that stimulants used for ADHD symptoms do not lower seizure threshold.
36. (D). MEG is not clinically indicated at this point for the evaluation of a patient with new onset seizures, or to confirm a diagnosis of epilepsy. MEG and source modeling of epileptic spikes or evoked responses is indicated as part a presurgical evaluation prior to epilepsy, tumor, or vascular surgery.
37. (A). Modeling the cortical generators of neuromagnetic event
38. (C). MEG studies aimed at localizing interictal epileptic spikes may sometimes fail to record any epileptic events for source modeling ($\sim$20% of cases) given the relatively short duration of the recording. In these situations, it may not contribute to localizing epileptic dysfunction. Multifocality of spikes does not undermine the accuracy of the source modeling. Ictal MEG recordings are relatively infrequent, but early ictal rhythms can be modeled with good accuracy to predict seizure onset zones.
39. (D). Patients with vagal nerve stimulators can undergo MRI imaging if both normal and magnet modes are turned off.
40. (D). For lateralizing language, neuromagnetic responses to auditory language stimuli were found to be concordant with the Wada test in 87% of patients. Other investigators found a concordance rate of 86% with the Wada test in 35 patients with a sensitivity of 80% and specificity of 100%. Several smaller studies have reported MEG–Wada concordance rates between 69 and 100% using a variety of paradigms and analysis methods.
41. (D). In a 2-year follow-up study of RNS, 50% responder rate was reported in 55% of patents. Intracranial hemorrhages and infections each occurred in about 2% of implanted patients, neither mood nor cognitive function worsened, and quality of life improved.
42. (C). When using high-frequency stimulation (>50 Hz), frequent VNS magnet activation can result in nerve damage and thus should be avoided.
43. (D). This patient likely has drug-resistant partial epilepsy of left temporal lobe origin. He has failed two antiepileptic drugs at therapeutic doses and appropriate drug levels. The next step is to consider epilepsy surgery for which an inpatient video EEG study is part of the workup.
44. (B). Temporal lobe resection has been shown to be superior to continued medical therapy in refractory temporal lobe epilepsy in a controlled trial. The rate of seizure freedom with vagus nerve stimulation or response for stimulation is much less than that of lobectomy.
45. (B). Although the surgical outcomes in non-lesional epilepsy are generally less optimal than those of lesional epilepsy, this must not deter the epileptologist from performing the surgical evaluation. In these patients, sometimes intracranial monitoring may help localize the seizure focus, and the surgical outcomes are often favorable. Hippocampal seizures occur in patients with normal MRI, which can be confirmed with

depth electrode recordings. In these patients, the pathology often shows neuronal loss in the CA4 region of the Ammon's horn.

46. (A). Patients with epilepsy have higher risks of suicidality than the normal population. This is mainly due to the coexistent depression. Antiepileptic adverse events have also been linked to higher suicidal ideations in patients with epilepsy.
47. (A). In such a patient, right hemispheric verbal memory lateralization improves surgical candidacy in terms of memory outcome, but is not enough because of the risk language deficits if language is on the left. Ictal scalp EEG is not totally localizing. Functional neuroimaging is important but will not provide the details as regards the relationship of the seizure onset zone to the eloquent cortex as with intracranial monitoring.
48. (C). Seizures from the insula can include visceral, gustatory, and somatosensory symptoms, including laryngeal constriction or paresthesias.
49. (C). This presentation is typical of frontal lobe epilepsy. Insular and temporal lobe epilepsy may have similar presentations, but they are much less frequent causes of this seizure semiology. Although non-REM parasomnias may have similar presentations, REM sleep behavior disorder presents differently. The brief duration of the seizure, its stereotypical nature, nocturnal occurrence, and the full recovery make psychogenic seizures less likely.
50. (B). Corpus callosotomy has been particularly helpful for atonic, "falling," seizures as well as for tonic seizures, with electrodecrement at seizure onset, and for generalized tonic–clonic seizures. While "falling" seizures may benefit, other seizure types may remain, so generally this should be thought of as a palliative rather than curative procedure. Focal seizures can become more severe after section, and in experimental models, kindling can occur more rapidly. There can be an acute disconnection syndrome after callosal section, with akinetic mutism, incontinence, apraxia, or the alien hand syndrome. It is thought that this is more likely if the entire corpus callosum is sectioned initially. For this reason, many prefer to do an anterior 2/3 section first.
51. (A). In extratemporal lobe epilepsy, invasive recordings are often used for localizing the seizure focus and mapping the brain, thus defining the surgical borders in a manner that maximizes tissue resection and minimizes functional deficits. While in frontal lobe epilepsy the ictal EEG can be non-lateralizing, a lateralizing EEG or seizure semiology is helpful primarily in guiding the implantation of the intracranial electrodes for further localization and mapping. Similarly, lesions are helpful in this regard, but do not obviate the need for monitoring as the seizure focus often is close to, though not within, the lesion, and nearby cortex can be eloquent.
52. (B). Abdominal aura had a 52% sensitivity and 90% specificity for localizing seizures to the temporal lobe (Velasco, T. R. and Mathern, G. W. in Wyllie's Treatment of Epilepsy: Principles and Practice (ed Cascino GD Wyllie E, Gidal BE, Goodkin HP) Ch. 82, 922–936 (Wolters Kluwer/ Lippincott Williams & Wilkins, 2011).
53. (A). The VNS lead electrodes must be placed below where the superior and inferior cervical cardiac branches separate from the vagus nerve. Stimulation of either of these two branches during the system diagnostics (lead test) may cause bradycardia and/or asystole.
54. (B). Selective serotonin reuptake inhibitors (such as citalopram) are the preferred first-line antidepressant therapy for patients with epilepsy. The other listed drugs may aggravate seizures especially at higher doses.
55. (B). In the controlled trial of temporal lobectomy versus continued medical treatment in intractable temporal lobe epilepsy, one year later 58% of patients with surgical treatment but only 8% of patients with medical treatment alone were free from episodes with loss of consciousness.

56. (D). After hemispherectomy, 70–80% of patients become seizure-free. Because of the reduction in seizures, intellectual function often improves.
57. (E). Ictal theta range organized spike discharge was found to have an 85% probability for temporal lobe epilepsy and was 80–94% correct with respect to side of seizure onset.
58. (B). Quantitative analysis of MRIs in patients with temporal lobe epilepsy shows frequent atrophy in medial as well as lateral temporal structures. A non-sclerotic hippocampus correlated with less optimal surgical outcome after lobectomy than hippocampal sclerosis.
59. (D). Rasmussen encephalitis (RE) is a rare, progressive, chronic disease characterized by seizures, progressive hemiparesis, and cognitive loss. It occurs mainly in children with a peak of incidence at the age of 6–7 years. However adolescent and adult cases have been reported accounting for about 10% of all cases of RE. RE occurs usually in healthy children, adolescents, and adults. RE usually affects only one hemisphere of the brain; bilateral disease is very rare.
60. (D). Depression affects at least one-third of patients with epilepsy and is considered to be the most common psychiatric comorbidity that needs early identification and treatment. The relationship of seizure and epilepsy is bidirectional, and depression may precede epilepsy and is considered to be a risk factor for epilepsy. In addition, depression is often associated with anxiety symptoms or full-blown anxiety disorder.
61. (E). A diagnosis of epilepsy and the use of antiepileptic medications (AEDs) preclude the individual from driving a commercial motor vehicle. In order to even be considered for reinstatement of commercial driver's licensing (CDL), an individual with epilepsy has to be off AED(s) and seizure-free for at least 10 years.
62. (C). Patients with epilepsy may be granted short- or long-term disability if their seizures remain uncontrolled despite appropriate therapy, strict compliance, and absence of known controlled triggers such as alcoholism. In the particular case of motor seizures, major motor seizures must be occurring more frequently than once a month and minor motor seizures must be occurring more frequently than once weekly.
63. (B). The first antiepileptic drug achieves seizure freedom in 47% of patients, and the second antiepileptic drug achieves seizure freedom in only 14%.
64. (B). During electrocorticography, stimulation of the frontal eye fields (Brodmann area 8) which is situated just anterior to the premotor cortex, will likely cause contralateral eye deviation.

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Note: Page numbers followed by *f* and *t* indicate figures and tables, respectively.

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