REVIEW ARTICLE

INVITED REVIEW:
Clinical and Basic Neurophysiology of Generalised Epilepsies

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ABSTRACT: Electroencephalography (EEG) clarifies several aspects of generalised epileptic seizures and epilepsies. For the clinician, it assists in the diagnosis of the epileptic condition and helps assign the disorder to an appropriate syndrome. This assignation and the quantity of epileptic discharges estimate severity and prognosis. When combined with relevant basic science investigations, EEG studies may disclose significant pathophysiological mechanisms. Therefore, this paper first describes EEG characteristics of the several disorders included under the broad category of "generalised". The review then relates these phenomena to germane experimental data intending that this binocular survey will provide a more meaningful perspective of these disorders.

RÉSUMÉ: Neurophysiologie clinique et fondamentale de l'épilepsie généralisée. L'électroencéphalographie éclaire plusieurs aspects des crises épileptiques généralisées et des épilepsies, guide le clinicien pour le diagnostic de la maladie épileptique et l'aide à assigner le désordre au syndrome approprié. Il est possible de déterminer la sévérité et le pronostic selon le syndrome et la quantité de décharges épileptiques. Quand cette information est associée aux investigations fondamentales pertinentes, les études ÉEG peuvent révéler des mécanismes physiopathologiques significatifs. Cet article décrit donc en premier lieu les caractéristiques ÉEG de plusieurs entités comprises sous la catégorie "généralisée". Une relation est ensuite établie entre ces phénomènes et des données expérimentales pertinentes afin que cette double perspective puisse fournir une perspective plus juste de ces désordres.

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Electroencephalography (EEG) may furnish the clinician several types of useful information in evaluating patients whose clinical picture suggests a "generalised" epilepsy.

According to the Oxford Dictionary, "generalised" means "including or affecting or applicable to all or most parts or cases or things".[1] Applying this definition to epilepsy designates epileptic conditions that: begin without specific warning; whose motor manifestations are usually symmetrically bilateral; in which awareness is usually impaired or lost; and which terminate without focal postictal manifestations. Electroencephalography (EEG) in such conditions may: 1) indicate if the disorder is primary- or secondarily-generalised, 2) help identify the epilepsy syndrome, e.g. Lennox-Gastaut (LGS), and 3) gauge its approximate severity.

Herein are described "generalised" epileptiform features and their association with certain epilepsies and epileptic seizures. Gradations between "generalised" and "focal" are also indicated. The clinical section therefore consists of four parts: 1) principal EEG patterns, 2) patterns in association with epileptic seizures, 3) EEG characteristics of selected epileptic syndromes and 4) photic stimulation in generalised epilepsies.

GENERALISED EEG EPILEPTIFORM ABNORMALITIES

Hypsarrhythmia

Hypsarrhythmia consists of high voltage 1-3 Hz waves with multifocal asynchronous spikes and sharp waves of varying morphology and amplitude. "Disorganised" and "chaotic" are appropriate terms here (Figure 1). Although continuous during wakefulness and light sleep, the pattern may become discontinuous and more synchronous in deep sleep. During slow wave sleep, the EEG may display bursts of synchronous irregular polyspike waves separated by epochs of low voltage amorphous activity. Spike discharges of hypsarrhythmia may be bisynchronous but never rhythmically repetitive or highly

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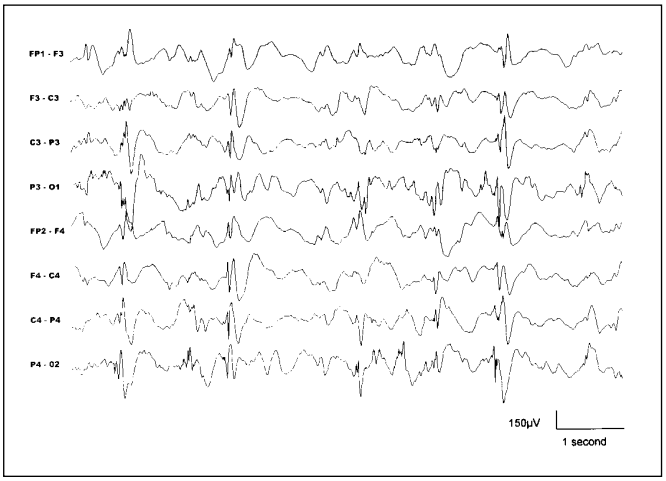

Figure 1: *Hypsarrhythmia. High voltage delta activity with multifocal spikes. Note the bilateral synchrony of spikes in this sleep recording.*

organised.[2] The quantity of rapid eye movement (REM) sleep may be less during the presence of hypsarrhythmia but this may increase if the patients improve with therapy.[3,4]

Interictal variants of hypsarrhythmia have been described.[5,6] These include hypsarrhythmia with: 1) increased interhemispheric synchronisation, 2) marked left-right asymmetry, 3) a consistent focus of abnormal discharge, 4) episodes of attenuation and 5) primarily high voltage slow activity with few epileptiform discharges. Focally accentuated hypsarrhythmia may correlate with a focal lesion in which case the epileptic spasms may appear maximally in the contralateral limbs. An additional hypsarrhythmia type is a modified hypsarrhythmia with preserved normal background.[7]

Despite the abundant epileptiform discharges, hypsarrhythmia is considered an interictal pattern. The spasms are associated with a sudden diffuse attenuation of activity termed "an electrodecremental event" which may be preceded by a high voltage wave with or without a spike (Figure 2). Low voltage high frequency waves are occasionally superimposed upon such electrodecremental events or these may predominate as the ictal pattern.[8] These may be superimposed upon a high amplitude slow wave.[9] Moreover, spasms can occur without any EEG change.[10] After a spasm, the EEG may appear normal for several seconds.

Hypsarrhythmia appears principally between the ages of three months and five years. Among patients who are thought to have a prenatal cause, initial EEGs may be normal or have focal spikes progressing to multifocal abnormalities before progressing further to hypsarrhythmia.[11] Among those with a perinatal central nervous system insult, initial EEGs have shown either a burst suppression pattern or very low voltage activity followed by focal or multifocal abnormalities. Patients with the Ohtahara Syndrome (see below) have burst suppression evolving to hypsarrhythmia. Prognosis is better among patients whose initial EEG demonstrates typical hypsarrhythmia than for those who evolve to this from other abnormal patterns.[12] A typical interictal hypsarrhythmia pattern is usually indicative of cryptogenic West syndrome and therefore a relatively benign evolution.[13] If less than 0.5 mg/kg of diazepam at 0.5 mg every 20 seconds abolishes hypsarrhythmia, the prognosis may also be more favourable.[14] As hypsarrhythmia resolves, its components decline in amplitude, spikes become less multifocal and more synchronous.[5] This evolution to slow spike-waves (SSW) may occur at age two to four years. Occasionally the hypsarrhythmia pattern may persist longer in non-REM sleep than in other states as polyspike bursts with low voltage activity between them.[12]

Clinical Correlates

Major authors equate hypsarrhythmia with epileptic spasms, suggesting high specificity.[15,16] Baird and Borofsky[17] reported that 51 of their 80 hypsarrhythmia patients had epileptic spasms, 20 had other seizure types and nine had no history of seizures.

Differential Diagnosis

Ohtahara[18] described an early infantile epileptic encephalopathy characterised by tonic spasms and an EEG burst suppression pattern with an unfavourable prognosis.

Electroencephalography (EEG) with a polygraph recording of limb muscle activity may help distinguish early myoclonic encephalopathy from epileptic spasms. The jerks are briefer than spasms and their EEG correlate is diffuse polyspike-wave discharges arising from relatively normal background activity.[19] This distinction is important as the prognosis with such myoclonic attacks is distinctly better than that of epileptic spasms.

Slow Spike-Waves

These are spike-waves with a repetition rate between 1 and 2 Hz and a total duration of each complex from 450 to 600 milliseconds.[20] The epileptiform component may be either a spike or a sharp wave (Figure 3). The complexes are usually bilaterally synchronous and symmetrical but they may be principally expressed in, or confined to, the anterior or the posterior head regions. Morphology, amplitude and repetition rate may vary between and within SSW bursts; shifting asymmetries may occur. Hyperventilation has little effect on

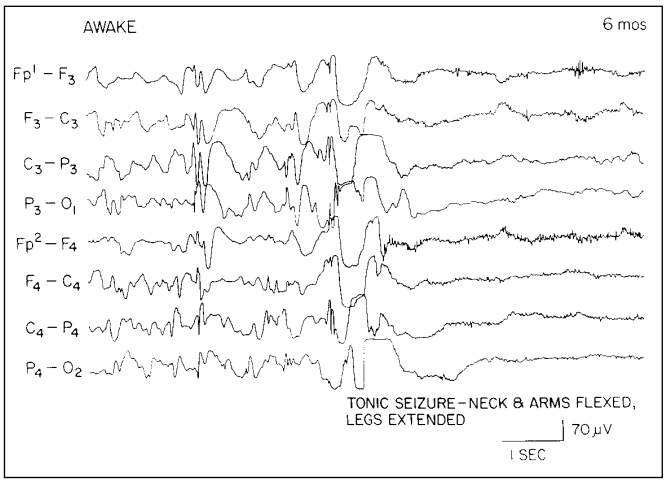

Figure 2: *Electrodecremental event from hypsarrhythmia. A spasm or tonic seizure is associated with a diffuse attenuation of ongoing activity, usually preceded by a single spike and slow-wave as seen here.*

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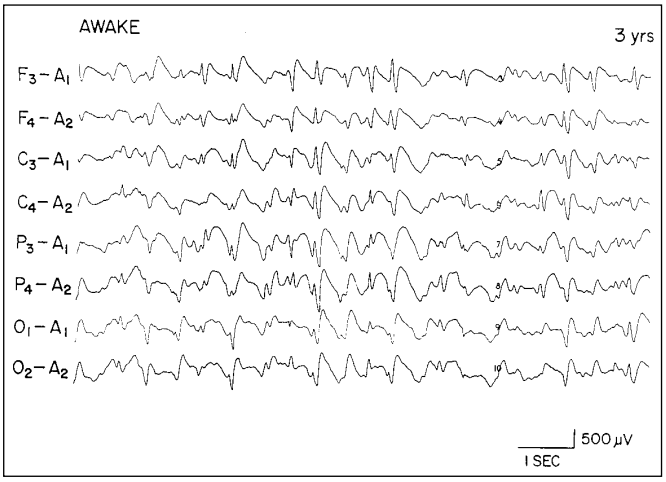

Figure 3: *Slow spike-waves. Bisynchronous slow spike-waves, some of which resemble triphasic waves.*

these discharges and photic stimulation has none. Sleep increases their abundance. During sleep, polyspike waves, generalised polyspikes, and 10-20 Hz rhythmic waves or even electrodecremental events (sudden attenuation for 1-2 seconds) may appear. Sleep spindles and V-waves may be absent.[21]. The maximum incidence of such discharges occurs between one and five years,[22] but SSWs may be mixed with hypsarrhythmia at the younger part of this range and with 3 Hz spike-waves at the later part. In contrast to recordings with 3 Hz spike-wave discharges, the interparoxysmal recording is usually abnormally slow. This phenomenon usually occupies a greater portion of the awake recording than generalised spike-wave complexes. No clinical alteration may be discerned in such patients at the onset of a burst of slow spike-waves in contradistinction to 3 Hz spike-wave discharges in which a closer EEG-clinical correlation occurs. However, in other instances "atypical absence" may coincide with SSWs.

Clinical Correlates

Seizures occur in about 98% of patients with SSWs; the most common are tonic seizures and also atypical absence attacks. Atonic, myoclonic, and tonic-clonic seizures are also seen.[20,22-24] Unfortunately, the majority of patients have more than one type of seizure and have daily attacks that are usually difficult to control. Tonic seizures are most often accompanied by diffuse electrodecremental events, fast rhythmic waves, or polyspikes.[22,23,25] Atypical absence may be detected at the onset of slow spike-waves or may accompany any of the patterns of tonic seizures. Myoclonic attacks occur in association with high voltage bisynchronous spikes.

Continuous or very abundant bisynchronous 2 Hz SSW in non-REM sleep in children between four and 12 years may represent a developmental or regressive cognitive disorder of infancy or childhood such as "encephalopathy with electrical status epilepticus during slow sleep" or "acquired epileptic aphasia".[26]

Spike-Waves

Each bilaterally synchronous complex consists of a single or multiple spike discharge followed by a rhythmic wave; both phenomena are surface negative. The complexes repeat at 2.5-5.0 per second (Figure 4). The repetition rate is highest at the onset of a spike-wave series and decreases towards its termination. Spike-waves usually begin and end abruptly. Their repetition rate may slow to 2 per second during absence status epilepticus. Further scrutiny revealed a more complex morphology to Weir[27] (Figure 5). Within a series of spike-wave complexes, each 200-500 msec negative wave is preceded by a 100-150 msec positive trough. The one or two negative spikes interrupt this positive trough, i.e. are superimposed upon it. The second, larger spike is the classic spike of the spike-wave complex.

Such "generalised" phenomena may be confined to the anterior head regions, to the posterior head regions, to one hemisphere, or even to a region of one hemisphere.[28] Spike-waves may begin 10-25 msecs earlier or may be maximally expressed in one hemisphere.[29] However, this predominance should shift from side-to-side during a single recording or over several recordings. Diffuse spike-waves are often maximum in the superior frontal regions (F3, F4) and this maximum usually differentiates spike-waves from triphasic waves which appear principally in the frontal polar regions. Fragments of spike-wave discharges, confined to one hemisphere or a region, appear commonly in recordings with typical spike-wave discharges, particularly on bipolar montages. The morphology of such discharges more closely resembles those of spike-wave discharges as compared to focal spikes: the spike component of spike-wave complexes is relatively small as compared to the wave.[28] The interparoxysmal "background" activity is normal.

In some patients with absence attacks, only bursts of 3 Hz waves without spikes may appear. If clinically appropriate, their presence should encourage further measures to elicit spike-waves given their high specificity (see below). Such rhythmic waves may appear anteriorly or posteriorly and may gradually evolve to spike-wave discharges.

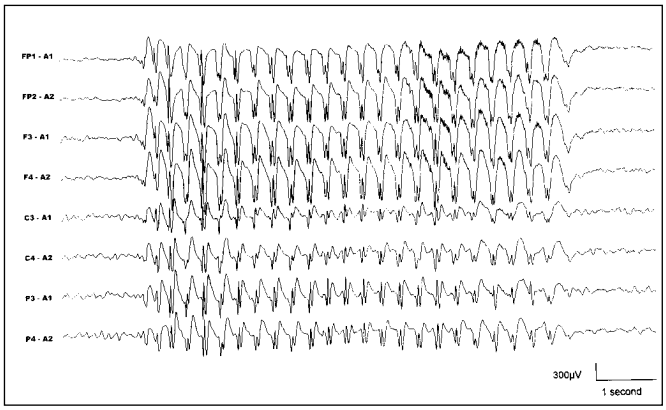

Figure 4: *Absence seizure with sequential spike-waves. Abrupt onset and offset of bisynchronous ~3 Hz spike-waves. Patient stared and eyes rolled upward.*

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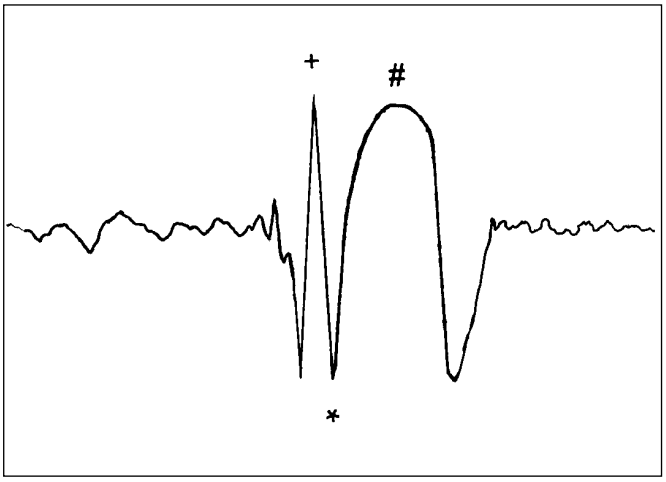

Figure 5: *Components of the spike-wave complex. Schematic referentially-recorded (F3-average) single spike-wave complex traced from the same spike-wave burst in Figure 4.*

+ spike ** trough* *# wave*

Hyperventilation may elicit spike-waves in about 50% of patients with absence[30] but it may require either prolonged hyperventilation or more than one hyperventilation episode to elicit their presence. The incidence may increase in non-REM sleep: the bursts are shorter, less regular, the repetition rate may vary from 1.5 to 2.5 Hz and the spike-waves may be converted to polyspike-waves.

Photic stimulation may elicit spike-waves (photoparoxysmal response) in about 10% of patients with epilepsy; such patients have one or more forms of primary generalised epilepsy: absence, myoclonic or tonic-clonic.[31] Eye closure during photic stimulation may elicit generalised spike-waves when they did not appear with eyes closed or open.

Clinical Correlates

About 97% of patients with bilaterally synchronous spike waves on a resting EEG or with HV have generalised seizure disorders.[32] Among various studies, about 26-70% of these patients have absence attacks, the incidence rising among patients with longer (more than 4 seconds) spike-wave series. As the quantity of interictal spike-waves correlates highly with the number of clinical absence attacks, the EEG may be used to assess effectiveness of therapy.[33] The incidence of generalised tonic-clonic seizures (GTC) is slightly greater among: 1) adolescents, 2) those with 3-6 Hz spike wave discharges, and 3) those with only the shorter bursts. Some younger patients with 3 Hz spike waves have principally myoclonic seizures.

A clinical absence attack is accompanied by sequential bisynchronous 3 Hz spike-waves which may slow in rate as the attack proceeds. The clinical and EEG signs of the seizure cease abruptly leaving no postictal slowing.

Three Hz or 4-6 Hz spike-wave discharges may appear in patients with myoclonic and generalised tonic-clonic epilepsy of adolescence (syndrome of Janz).[34] About 30-40% of these patients will have a photoparoxysmal response and a minority will have polyspike-wave discharges upon eye closure.

Bisynchronous myoclonic seizures usually occur with bisynchronous polyspike waves. These may appear in association with an otherwise normal EEG, with SSWs, or with other 3 Hz spike waves. Excess diffuse delta activity for age and state and an easy evocation of spike waves with photic stimulation both raise the possibility of a progressive myoclonic epilepsy.[35-37]

Fast Rhythmic Waves = Epileptic Recruiting Rhythm

These are bursts of sinusoidal waves at 8-30 Hz with a widespread or generalised distribution[38,39] (Figure 6). These may appear subtly and occasionally may be difficult to distinguish from ongoing beta activity.[38,39] The usual clinical accompaniment is tonic seizures when hypsarrhythmia or slow spike-waves appear in the recording. When spike-wave complexes appear in the same recording, the usual clinical accompaniment is absence.

Secondary Bilateral Synchrony

Secondary bilateral synchrony (SBS) refers to sequential focal spikes or sharp waves leading directly to bilaterally synchronous epileptiform paroxysms. The lead-in time may vary among patients but when it appears to be shorter than 200-400 msecs, the possibility of a transient hemispheric accentuation of essentially bisynchronous epileptiform paroxysms should be entertained as indicated above. Moreover, in SBS the morphology of triggering spikes should resemble other focal spikes in the same region and differ from that of the bisynchronous epileptiform paroxysms.[40]

There are several electrographic clues to the possible presence of secondary bisynchrony:

1. Frontal lobe foci more commonly trigger SBS than those from other lobes.[41]
2. Almost all patients with SBS have multiple spike foci in one or more recordings suggesting that SBS arises from an

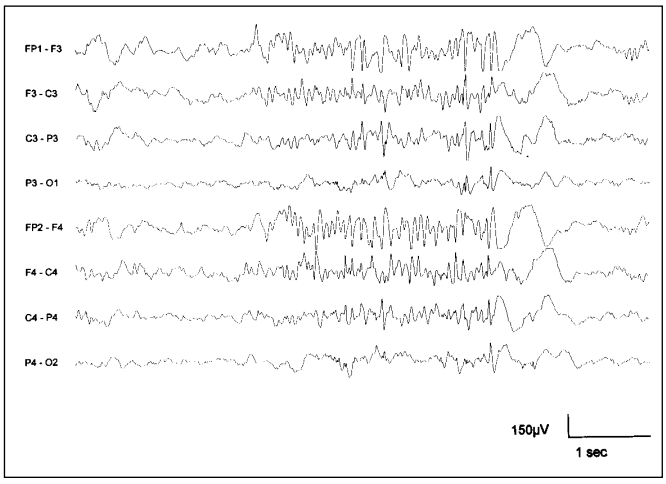

Figure 6: *Fast rhythmic waves = sequential polyspikes = epileptic recruiting rhythm. 12-15 Hz bilaterally synchronous, frontally predominant burst beginning suddenly from a slow background, persisting for about 3 seconds, and stopping abruptly. The post-burst delta activity likely represents diffuse inhibition (IPSPs).*

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interaction between such foci, possibly through the corpus callosum. The most active of such foci is usually the immediate origin of SBS.

3. Regular 3 Hz spike waves usually represent primary bilateral synchrony. In contrast, SBS may produce irregular 2-3 Hz SSWs. The EEGer must be careful to distinguish these from regionally-appearing "fragments" of essentially primary generalised epileptogenic paroxysms; these retain the morphology of primary generalised discharges.[40,41]
4. Interparoxysmal abnormalities are usually present: unilateral delta or an attenuation of background activity, such as beta, may be seen. These would be unusual in primary bisynchrony.

Most patients with apparently primary generalised seizure disorders obtain adequate control with therapeutic amounts of a single appropriate anticonvulsant medication. Two major exceptions of this are those with LGS and patients with progressive myoclonic epilepsies.[36] If such conditions can be excluded on clinical grounds, the possibility of an occult secondary bisynchrony should be entertained.

EEG CHARACTERISTICS OF GENERALISED EPILEPTIC SEIZURES

Epileptic Spasms (formerly Infantile Spasms) (West Syndrome)

See EEG in some Generalised Epilepsy Syndromes (below).

Tonic Seizures

Sequential bilaterally synchronous spikes at 10-25 Hz accompany a tonic seizure, occasionally preceded by a brief, diffuse, attenuation.[38,39,42]

Interictal EEG patterns correlate with whichever syndrome contains the tonic seizures as a component. This most likely would be the bisynchronous slow spike-waves of the LGS.

Myoclonic Seizures

Interictally and ictally, syndromes containing myoclonic seizures have bilateral and symmetrical spike-waves or polyspike-waves repeating at 3 Hz or greater but usually lasting less than 4-5 seconds.[43] Doose et al[44] also described excess theta activity either diffusely or maximally in the posterior head regions.

Atonic Seizures

These are best depicted by polygraph recordings involving the EEG and involved muscles. Such recordings may demonstrate either atonic or myoclonic-atonic components. During episodes when muscle tone is diminished or lost, bisynchronous polyspike-waves may appear.[45] This loss of tone is principally associated with the wave component of the polyspike-wave discharges but a strict correlation between central and peripheral manifestations may not always be evident. Interictally, such patients may have bilaterally synchronous polyspike-waves, 3 Hz spike-waves or slow spike-waves.

Absence Seizures

An absence seizure tendency may be suspected by the presence of bisynchronous 2.5 per second - 3.5 per second spike-wave discharges which classically begin and end abruptly. Fragments of such spike-waves are common, particularly in sleep. Hyperventilation may precipitate 3 Hz spike-waves. The lack of spike-wave discharges on a "resting" awake recording or with hyperventilation in an untreated patient renders the diagnosis of absence attacks unlikely.[46] Bisynchronous 3 Hz slow-waves may appear in 10-20% of patients with typical absence attacks. Photic stimulation may elicit spike-waves or polyspike-waves in 10-20% of cases.[46] The interparoxysmal EEG may be normal or show sporadic theta bursts.

Spike-wave sequences exceeding 3-4 seconds characterise a clinically-apparent absence attack if the spike-wave paroxysms are sufficiently diffuse. However, cognitive disturbances may occur during shorter spike-wave paroxysms.[47]

Absence Status Epilepticus

Absence status epilepticus, a rare condition manifesting as impaired cognition with or without facial or limb myoclonus, may occur at any age, including the elderly. Similarly, non-convulsive seizures may follow generalised or focal convulsive seizures in acute care situations.[48,49] When generalised, these conditions are principally expressed as prolonged sequential 2-3 Hz bisynchronous spike-wave discharges. They may complicate metabolic or anoxic encephalopathies.

Generalised Tonic-Clonic Seizures

The waking EEG in patients with only GTC may be normal although slight nonspecific abnormalities of background activity may occur and antiepileptic drugs may slow the background slightly.[50] Some patients with a long history of generalised convulsive seizures may have excess bitemporal theta.

Interictal epileptiform abnormalities are usually bilaterally synchronous spike-wave discharges which may appear principally, or only, on hyperventilation. "Fragments" of such spike-wave discharges occur not uncommonly in the interictal recording as spike-waves limited to one hemisphere or to a portion thereof with shifting focality. Sleep recordings may increase the yield of such epileptiform activity. If absence or myoclonic attacks co-exist, the patients more likely will have paroxysmal rhythmic frontal delta activity or spike-wave discharges. Polyspike and wave discharges or 4-6 Hz spike-waves may be seen with juvenile myoclonic epilepsy. Photic stimulation may elicit spike-waves in some patients (see below).

As the ictal EEG of GTC may be obscured by muscle and movement artefact, little additional data are present unless a focal onset can be identified before the artefact occurs. Bilateral polyspike-wave discharges may be associated with any early bilateral myoclonic jerks. The tonic phase is associated with a brief diffuse attenuation or with low voltage 20 to 10 Hz waves. This pattern evolves to bilaterally synchronous high voltage spike-wave discharges in a subsequent clonic phase.[51] The postictal EEG may show a paucity of activity and diffuse delta but should not show any clear lateralising features.[51]

EEG IN SOME GENERALISED EPILEPSY SYNDROMES

Febrile Seizures

Frantzen et al[52] and Kuturec et al[53] found excess delta activity in a third of patients during the first week after a febrile seizure. This activity was either diffuse and maximum posteriorly, or confined to the posterior head regions. Such delta waves

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appeared more prominently if the convulsion exceeded 30 minutes or was associated with electrolyte abnormalities. Regional or hemispheric delta activity should raise suspicion of a structural lesion causing a seizure that is provoked by fever. Such delta waves may also represent the hemiconvulsion-hemiplegic-epilepsy syndrome of Gastaut.[54]

Spike-waves may be seen in the EEGs taken beyond the acute post-ictal phase in a minority of patients.[52] Such spike-waves are rare before age one year but are found in over half the patients with an EEG after age four years.[55] The number of febrile convulsions is greater among those with spike-waves than those without.

Most prospective studies have found no correlation between the presence of EEG paroxysms and the later emergence of non-febrile seizures.[52] However, a great abundance of spike-waves suggests to me that the febrile seizure is the first manifestation of an afebrile generalised seizure disorder.

Infantile Encephalopathy with Suppression-burst Pattern (Ohtahara Syndrome)

These unfortunate children have several hundred per day of tonic seizures in flexion lasting a few to 10 seconds occurring during wakefulness or in sleep and therefore represent epileptic spasms in this respect.[18] Diffuse cortical dysgenesis and neonatal asphyxia are the two etiologies. Their EEGs consist of bursts of spikes, sharp-waves and slow-waves lasting 1-5 seconds alternating with periods of electrical attenuation, i.e. "suppression". These bursts may appear asymmetrically or symmetrically, synchronously or asynchronously but the individual spikes and waves are never bilaterally synchronous either during wakefulness or sleep. Such "suppression-bursts" occur during wakefulness or sleep and therefore are distinguished from hypsarrhythmia which has similar bursts only in non-REM sleep. The ictal phase is manifested by diffuse desynchronisation and sequences of low voltage fast activity and therefore resemble somewhat that of epileptic spasms. The burst-suppression pattern may progress to hypsarrhythmia via a gradual increase in voltage of the suppression phase which first appears in the awake state. A second outcome is progression to focal spikes.

These infants, manifesting evidence of severe cerebral dysfunction, may progress to the West Syndrome at about age four months; but all become handicapped or die.

Epileptic Spasms

Hypsarrhythmia is the most remarkable but not the only EEG pattern associated with epileptic (infantile) spasms. It appears in 40-70% of cases,[56] but is the most characteristic interictal EEG pattern seen with epileptic spasms. According to Jeavons and Bower,[57] about two-thirds of first EEGs done for epileptic spasms contain hypsarrhythmia; other EEG abnormalities occur in 30% while only 2% of first EEGs are normal. All subsequent EEGs of these 2% are abnormal. Be alert to the possibility of pyridoxine dependancy or deficiency in this condition.

During the spasm, a widely synchronous single spike is followed by diffuse attenuation upon which may be a superimposed high frequency low amplitude rhythmic waves.[38,39]

Myoclonic Epilepsies of Infancy and Early Childhood

These patients have myoclonic seizures characterised by very brief shock-like muscle contractions and 3-4 Hz spike-wave or polyspike-wave complexes. This syndrome superficially resembles the LGS as the patient falls during the seizures and mental subnormality or deterioration occurs in both entities. However, the clinical and EEG manifestations differ.

Some investigators, cited by Aicardi,[58] divide these syndromes into benign and severe forms whereas Lombroso[59] believes that a spectrum of myoclonic syndromes exists. In the benign form, polyspike-waves or spike-waves are virtually the only EEG abnormality as the EEG background activity is relatively normal. Severe myoclonic epilepsy shows bursts of 3-4 Hz spike-wave complexes, multifocal spikes, and an abnormally slow background activity. Photosensitivity is present in 25% of these more afflicted patients, some of whom may self-precipitate their seizures.

The Lennox-Gastaut Syndrome

This syndrome consists of an intractable generalised seizure disorder of childhood onset consisting of multiple seizure types including tonic, atonic, and atypical absence attacks. Some patients may have tonic or non-convulsive status epilepticus. EEG criteria include bilaterally synchronous slow spike-waves and 10-20 Hz epileptic recruiting rhythm, the latter appearing principally in sleep. According to Genton et al[60] both the slow spike-waves and the paroxysmal 10-20 Hz activity must be present in the same recording in any given patient to satisfy the diagnosis of the syndrome. Therefore, a sleep recording should be carried out in any patient suspected of having the LGS in whom the 10-20 Hz activity does not appear in the awake state.

To document EEG-clinical correlations, particularly subtle attacks, polygraph recordings are often valuable. These would include: EEG, video, axial and deltoid EMG, and monitors of respiration and ocular movements.

Slow spike-waves, a principal electrographic characteristic of this syndrome, occupy a far higher percentage of awake recordings than do 3-4 Hz spike-wave discharges. In contrast to the latter, their onset and offset may be gradual. Myoclonic seizures of LGS are associated with bilateral and symmetrical spikes superimposed onto the characteristic diffuse slow spike-waves. Multifocal spikes may also be seen. Rapid (10-20 Hz) rhythms and bursts of generalised polyspikes with attenuation may characterise sleep recordings. These rapid rhythms may consist of high amplitude polyspikes or low voltage electrodecremental events with superimposed fast activity; these last up to several seconds and may disrupt sleep continuity. Polygraph recordings will reveal an alteration in breathing pattern or slight to moderate tonic events.

The awake background activity is virtually always slower than normal and contains excess delta activity for age and state. Multifocal spikes may appear.

Adolescents who have had the LGS may continue to have atypical absence, generalised tonic-clonic seizures and atonic seizures. Although their EEGs retain slow spike-waves, rapid rhythms and tonic seizures become rare to absent.

EEG Differential Diagnosis

Characteristics of the severe myoclonic epilepsy of infancy[61]

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have been described above. Secondary bilateral synchrony with a predominant frontal epileptiform and nonepileptiform focus and a consistent lead-in to bisynchronous discharges may resemble slow spike-waves. Evolution from infantile encephalopathy with suppression burst pattern (Ohtahara syndrome) is an important distinction as its prognosis is even worse than is the LGS. Obtaining prior EEGs may assist in this distinction. Electrographic status epilepticus of sleep shares some of the features of LGS (see below).

Encephalopathy with Electrical Status Epilepticus during Slow Sleep (ESES)

This syndrome consists of a seizure disorder beginning between ages two months and 12 years with a peak of four to five years as focal motor, absence and/or generalised tonic-clonic seizures. About one-third of patients have a pre-existing encephalopathy or pre- or perinatal abnormalities.[26]

Such patients have normal or slightly abnormal awake background activity and some have bursts of generalised spike-wave discharges. Fragments of these may also appear as regional spike-waves. Some patients, during the period of ESES, may show more abundant spike-waves at 2-3 Hz during wakefulness. However, as soon as non-REM sleep occurs, 1.5-2 Hz SSWs appear, persisting through all non-REM sleep stages. Such spike-waves may occupy 85-100% of non-REM sleep.[62]

Patients with "acquired epileptic aphasia", i.e. Landau-Kleffner syndrome, may also have profuse bilateral SSWs in non-REM sleep. Several other clinical and electrographic aspects are shared by these two syndromes.[26]

Childhood and Juvenile Absence

See section on Epileptic Seizures.

Progressive Myoclonus Epilepsies

Slowing of background activity and generalised spike-wave discharges characterise this group of disorders. In mitochondrial encephalopathy with ragged red fibres, focal abnormalities and photosensitivity may appear. Normal physiological sleep patterns may be abolished.[37] In neuronal ceroid lipofuscinosis low frequency flashes may elicit high voltage posterior polyphasic spikes. Visual evoked potentials are also of high amplitude in this disorder. In Lafora's disease, focal occipital paroxysms may be seen in the same recording that demonstrates generalised polyspike waves. In Unverricht-Lundborg disease, photic stimuli may elicit polyspike-wave discharges in about 90% of patients, particularly in early phases of the disease.

Juvenile Myoclonic Epilepsy

The interictal background activity is normal; 4-6 Hz spike-waves and 2.5-3 Hz spike-waves occur approximately equally often but such spike-waves appear interictally in only about 5-10% of all patients with juvenile myoclonic epilepsy. Hyperventilation, sleep deprivation, and photic stimulation may elicit such epileptiform paroxysms. The myoclonic episodes are accompanied by a burst of bisynchronous spikes followed by slow-waves, all lasting about 2-10 seconds.[63]

Hemispheric Epilepsy

Rarely, patients may have a clinical-electroencephalographic semiology occupying an intermediate position between focal and generalised epilepsy.[64] Although most such patients have bilaterally symmetrical motor seizures and absence attacks, the most frequent interictal EEG abnormality is unilateral spike-waves that occurred consistently over the same hemisphere on multiple recordings (Figure 7).

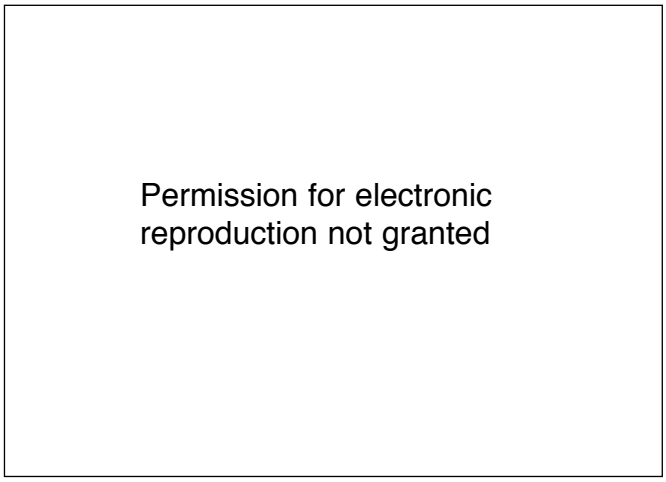

Figure 7: *Hemispheric polyspike-waves. Right hemisphere spike-waves and polyspike-waves with occasional bilaterally synchronous polyspike-waves in this awake patient. Note the medium-voltage right hemisphere delta (1-3 Hz) activity with slight expression on left. Reprinted from Blume WT. Hemispheric epilepsy. Brain 1998; 121: 1937-1949 by permission of Oxford University Press.*

PHOTIC STIMULATION IN GENERALISED EPILEPSIES

The most clinically valuable phenomenon elicited by photic stimulation is the photoparoxysmal response which consists of bisynchronous polyspikes or spike-waves. The spike repetition rate varies within the burst, is unrelated to the flash rate, and may extend beyond the flash stimuli. Such phenomena are diffuse with an anterior or posterior maximum expression. Photic stimuli during eye closure or with eyes closed most readily elicit the photoparoxysmal response. It is most frequently induced by 15 flashes per second with eye closure or eyes closed or 20 flashes per second with the eyes open.[65-67] The tendency to evoke a photoparoxysmal response increases with prolonged or repeated flash epochs.

The most common relevant clinical phenomena in association with the photoparoxysmal response are generalised myoclonias, absence, and generalised tonic-clonic seizures. The EEG technologist should proceed with photic stimulation at intervals and watch carefully the elicitation of the photoparoxysmal response to avoid a generalised tonic-clonic seizure.

Clinical Correlates

Photoparoxysmal responses may appear in between 0.5-5% of normal children and adolescents.[68,69]

Photic-induced generalised spike-wave discharges may occur in myoclonic epilepsy of infancy. Childhood and juvenile absence are accompanied by photoparoxysmal response in 13-18% and 8% of patients respectively.[30,31] Thirty to thirty-five percent of patients with juvenile myoclonic epilepsy have a photoparoxysmal response.[31] Epilepsy with generalised tonic-

clonic seizures on awakening is accompanied by a photoparoxysmal response in 13%.[70]

The presence of a giant visual evoked response to low flash rates in a patient with myoclonic seizures should raise the possibility of a progressive myoclonus epilepsy.[36,71]

PATHOPHYSIOLOGY OF GENERALISED SEIZURES

This review focuses on the spike-wave complex, the principal and best-studied generalised epileptiform phenomenon.

The Spike-Wave Complex

Several studies have demonstrated the close association between bisynchronous epileptiform discharges and generalised seizure disorders. Jasper and Kershman[72] correlated clinical seizure manifestations with interictal EEG abnormalities: bilaterally synchronous spike-wave discharges occurred in 84% of their patients with absences and in 48% of patients with generalised tonic-clonic seizures. Bilaterally synchronous epileptiform paroxysms occurred in all 90 children with myoclonic epilepsy studied by Aicardi and Chevrie.[73] Conversely, 80% of patients with bisynchronous paroxysms had generalised seizures in the Jasper and Kershman series.[72] Ninety-eight percent of children with bilaterally synchronous slow spike-waves have generalised seizures which are most commonly tonic.[22,23]

Spike-waves, the most common bisynchronous epileptiform discharge, consist of one or more electronegative spikes within a positive trough followed by a broad negative wave[27] (Figure 5). Bilaterally synchronous spike-waves are usually maximally expressed over the frontal regions.[74] Sequential field plots of evolving spike-wave discharges confirm this location over the frontal lobes corresponding principally to the premotor and prefrontal cortices.[29] Bancaud et al[75] and Goldring,[76] recording from implanted electrodes in humans, found that generalised motor seizures originated principally from the frontal cortex and that subcortical structures became involved secondarily.

Gloor et al[77] correlated EEG features in patients with diffuse encephalopathies with their histopathological abnormalities. Patients with both cortical and subcortical grey matter disorders developed bisynchronous bursts, either as slow spike-waves, sharp waves or delta. Such abnormalities rarely appeared among those whose lesions involved only the cortical grey matter.

Cortical Participation

The feline generalised penicillin epilepsy model[78] disclosed several, similar, properties of bisynchronous spike-wave discharges. Bilateral participation of both the thalamus and cortex are required for development of the spike-wave complex. Parenteral penicillin injection produced epileptiform activity in the cortex before subcortical regions.[79,80] Moreover, Fisher and Prince[79] produced spike-wave discharges by bilateral cortical penicillin application but thalamic application did not elicit spike-waves. However, inactivation of the thalamus by potassium chloride can abolish spike-wave discharges.[81]

The neuronal aggregates participating in the spike-wave phenomenon include: corticothalamic neurons and their axons (excitatory), thalamocortical relay neurons (TCR) and their axons (excitatory), adjacent cortical and thalamic gabaergic interneurons (inhibitory), and thalamic reticular nucleus neurons (inhibitory) (Figure 8). Corticothalamic axons release glutamate to excite: 1) TCR cells (excitatory), 2) cortical and thalamic gabaergic interneurons (inhibitory) and 3) thalamic reticular nucleus neurons (inhibitory). Thalamocortical relay cells cells excite related cortical neurons, adjacent inhibitory interneurons and thalamic reticular neurons.[82,83]

Micro-electrode recordings reveal that the negative spikes of spike-wave complexes are associated with depolarising potentials resembling excitatory post-synaptic potentials in upper cortical layers while positive troughs are linked with excitation in lower cortical layers.[84,85] Kostopoulos et al[86] found the peak incidence of cortical action potential firing to coincide with the junction of the spike and positive trough of the spike-wave complex. Similarly, Elger and Speckmann[87] found that corticofugal potentials correlate with excitatory discharges in deeper cortical layers. Although the latter work was performed in the primary motor cortex, its finding combined with the field distribution of spike-wave discharges may lead one to postulate that the junction of the electronegative spike and positive trough is that point in the spike-wave complex that correlates with corticofugal discharges from the premotor and prefrontal areas. In contrast, cortical action potential firing virtually ceases during the wave.[88] This oscillatory pattern of alteration between a high incidence of action potential discharge (spike and trough) and longer periods of near neuronal silence (wave) was found in both cortex and the thalamus.

Animal models of generalised spike-wave seizures have disclosed an increased effectiveness of cortical glutamatergic neurotransmission mediated by amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors that may adopt characteristics of an N-methyl D-aspartate-receptor-like response.[89,90] Additionally, a possible decrease in the density of gamma-aminobutyric acid $(GABA)_A$ receptors in the cortex of the genetic absence epilepsy rat from Strasbourg (GAERS) may

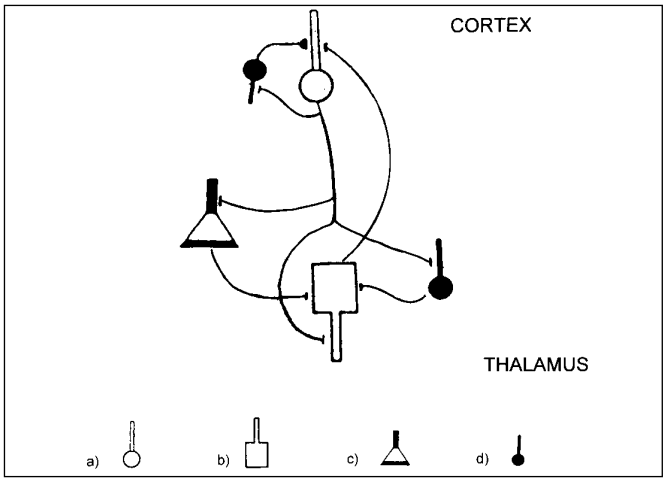

Figure 8: *Corticothalamic relationships in spike-wave generation. Components of the cortex and thalamus involved in the generation of bisynchronous spike-waves. Only principal connections shown.*
a) cortical pyramidal cell
b) thalamocortical relay neuron
c) thalamoreticular neuron
d) inhibitory interneurons

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make more GABA available to $GABA_B$ receptors that are not decreased in this absence model. This may enhance $GABA_B$ mediated inhibitory post-synaptic potentials (IPSPs) there.[90] The aforementioned oscillation corresponds to the intracellular correlates of spike-waves as alternating sequences of depolarising and hyperpolarising potentials.[84] Further mechanisms underlying these sequences are discussed below.

Thalamic Participation

As the thalamic neuronal aggregates creating sleep spindles play a crucial role in this oscillation, the relationships of its relevant components are significant.

The "nonspecific" thalamic nuclei, a rostral portion of the ascending reticular activating system, comprise the intralaminar nuclei, the midline nuclei, and the reticular thalamic nucleus.[91] Midline and intralaminar nuclei, which receive reticulothalamic connections from the reticular formation of the brain stem, project onto the thalamic reticular nucleus. Neurons of these nuclei resemble those of the reticular formation of the brain stem and their richly branching axons enter neighbouring "nonspecific" and "specific" thalamic nuclei.[91] These latter are relay nuclei.

Single shock stimulation of these "nonspecific" nuclei trigger widely distributed "spindle bursts" in the cortex.[92] Dempsey and Morison[92] found that repeated stimulation of these nuclei, at rates close to those of spontaneous cortical rhythms, would produce long latency, monophasic, surface negative, widely distributed association cortex responses. They termed this phenomenon the "recruiting rhythm" as the response increased in amplitude with successive stimuli.[92] This contrasts to stimulation of "specific" thalamic sensory relay nuclei that produces a short latency, diphasic "augmenting" response, restricted to the relevant projection area.[93] By blocking local cortical $GABA_A$ inhibition, bilateral application of penicillin over the cerebral cortex transformed the stimulation-induced thalamocortical response from a spindle or recruiting rhythm to spike and wave discharges.[94,95] Spike-waves in the penicillin model could only be elicited by stimulation of those thalamic nuclei ("nonspecific") that elicited the recruiting rhythm or spindles before penicillin. However, no spike-waves occurred when penicillin was injected into the thalamus.

Thalamic relay cells and thalamic reticular neurons each possess a unique type of calcium channel, so-called "T" channels, which are typically closed at resting membrane potentials.[82,90] T-type calcium channels are activated by first hyperpolarizing this type of cell through GABAergic interneuron innervation. Such hyperpolarisation "de-inactivates" T-type calcium channels. De-inactivation allows calcium to enter the thalamic relay cell whenever any afferent input slightly depolarises the neuron. This calcium current allows thalamic relay neurons to possess, in normals, two distinct responses to stimuli depending upon the resting membrane potential and corresponding to level of awareness. The "relay mode", predominant during wakefulness, occurs at intracellular membrane potentials positive to -60mV (depolarised): action potential rates of 1-200 Hz occur corresponding to stimulus intensity. Intracellular membrane potentials more negative than -60mV (hyperpolarised) convert the "relay mode" to a "burst firing" mode. In this mode, characteristic of sleep but occurring in wakefulness, 300-500 Hz bursts of action potentials occur, only weakly related to input strength.[96] Depolarisation from the burst deactivates T-type calcium channels so on termination of the burst there is less depolarising influence allowing the cell to hyperpolarise. Moreover, the action potential burst, associated with calcium entry, activates calcium-dependent potassium conductances producing an after-hyperpolarisation that, in turn, de-inactivates the "T" calcium-current completing the cycle. This sequence occurs in both thalamic relay and thalamic reticular neurons. The "relay mode" provides an accurate reconstruction of the afferent stimulus while the "burst firing" mode indicates that something has changed in the environment.[97] The mechanism of generalised spike-wave and seizure generation appears to represent an accentuation of this normally-occurring "burst firing mode." In the GAERS model, reticular thalamic nucleus lesions abolish spike and wave discharges.[98] The selective inhibition of such "T" calcium channels by the anti-absence drugs ethosuximide and valproic acid supports the essential role of such channels in spike-wave generation.[99,100]

The pattern of corticothalamic action potentials influences this mechanism. Recall that the same thalamocortical network that generated spindle waves could switch to spike-wave activity in the feline generalised penicillin epilepsy model. Spindle waves are generated through a reciprocal interaction between excitatory thalamocortical cells and inhibitory gabaergic thalamic reticular neurons and depend upon fast (100-150 msec) $GABA_A$ receptor-mediated IPSPs in the thalamocortical cells, setting the oscillation frequency at about 6-14 Hz. Blocking $GABA_A$ receptors in the thalamocortical relay cells can convert spindles to 3-4 Hz activity.[83] Blumenfeld and McCormick[83] and Kim et al[101] found that brief bursts of action potentials in thalamic reticular cells produces fast (100-150 msec) IPSPs in thalamocortical cells mediated by $GABA_A$ receptors. However, more sustained bursts in thalamoreticular cells elicit, in addition to $GABA_A$ IPSPs, slow (approximately 300 msec) $GABA_B$ receptor-mediated IPSPs in thalamocortical cells. Blumenfeld and McCormick[83] demonstrated that increased firing in the corticothalamic pathway can actually transform the thalamoreticular cell discharge from brief to sustained bursts thereby effecting conversion to $GABA_B$ IPSPs. A possible decrease in thalamic $GABA_A$ receptors in the GAERS absence model may contribute to this conversion to the $GABA_B$ mechanism. The slow metabotropic IPSPs are particularly effective in removing inactivation of the low threshold calcium current and therefore in generating large delayed rebound bursts of action potentials that initiate the next cycle of the oscillation.[97] Clinically, most GABA-enhancing drugs, such as Vigabatrin, worsen absence.[90] That only $GABA_B$ antagonists can reliably block experimental absence seizures in the rat, while both $GABA_A$ and $GABA_B$ agonists prolong such attacks, argues for a primal role of $GABA_B$ in this phenomenon.[102] However, the role of $GABA_B$ receptor mechanisms in absence remains to be clarified (see Avoli et al[103] for discussion).

The TCR excitatory output propagates to the cortex where both regularly spiking and intrinsically bursting pyramidal neurons are excited synchronously. Such synchronous excitation results from the aforementioned enhanced post-synaptic AMPA receptor-mediated response and the reduced $GABA_A$ neurotransmission in the cortex. The feedback excitation from

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the cortex would reach the thalamic reticular neurons during the repolarising part of their cycle producing reactivation of the low threshold calcium-mediated burst, restarting the next spike and wave.[90]

Determinants of Generalised Seizure Type

Manifestations of generalised seizures depend principally upon 1) the region of epileptogenesis, 2) the maturity of the brain at seizure onset and currently, and 3) the physiological state of the system at any point.

Region

Motor seizures and their electrographic correlates in generalised epilepsy represent epileptogenic mechanisms principally in the brain stem and thalamic reticular system as well as association cortex, principally frontal.

Studies in the Rhesus monkey and the cat found that cortical projections to the pontine and medullary tegmental fields arise principally from area 6, the rostral part of area 4, the prefrontal cortex and the supplementary motor area.[104-107] The premotor cortex sends its most prominent corticofugal projections to the medullary reticular formation.[104] These corticoreticular fibres terminate at or near the regions from which the reticulospinal tract originates. Reticulospinal tracts descend in the ventral and ventral lateral spinal funiculi, terminating in the intermediate zone of the spinal cord where they connect with long propriospinal interneurons and motor neurons of proximal limb muscles.[108] The most powerful excitatory influences over spinal neurons originate from large cells in the upper pontine reticular formation.[109] In contrast, that portion of the reticulospinal tract arising from the medial medullary reticular formation inhibits motor neurons.[110] These distinctly different effects underlie some of the various manifestations of bilateral motor seizures.

Corresponding with these data are effects found by Velasco and Velasco[111] in stimulating the brain stem of cats with pentylenetetrazol (PTZ). Perfusion of PTZ in the rostral part of the mesencephalic reticular formation produced myoclonic seizures with bursts of action potentials. More caudal mesencephalic PTZ perfusion led to tonic seizures with sustained action potentials. Pontine PTZ perfusion produced hypotonia, likely by stimulating the medullary inhibitory system (above). Increases in activity in the mesencephalic and pontine reticular formations occurred in association with tonic-clonic seizures induced by systemic PTZ.[112]

Mechanisms in the forebrain appear to be crucial for triggering facial and forelimb clonic convulsions.[113] Site of neocortical involvement may also affect generalised seizure phenomena. Thus, Marcus et al,[114] using bilateral acute epileptogenic foci in the frontal cortex of monkeys, correlated seizure type with epileptic focus localisation. Anterior foci gave absence whereas progressively more posterior foci gave increasing motor components from myoclonic events to generalised tonic-clonic seizures.

Ontogenesis

A caudal-to-cranial progression of epileptogenesis appears to occur with age. Chevrie and Aicardi,[24] studying childhood epileptic encephalopathy with slow spike-waves, found that tonic seizures began at a mean age of 16.6 months whereas atypical absences began at 32 months, myoclonic attacks at 39 months, and clonic or tonic-clonic seizures at 42 months. These correlate well with the localisation data described above. However, the rare onset of myoclonic epilepsy in early infancy indicates that this principle cannot be uniformly applied.

Physiological State

Modifications of pathophysiology in a component of generalised seizures may convert one seizure type to another: an absence or myoclonic seizure may evolve to a generalised tonic-clonic event. This transition from an absence attack to a generalised tonic-clonic seizure has been associated with a progressive decrease in recurrent $GABA_A$ inhibition in the cortex.[115] In several models of seizure activity, cortical extracellular potassium levels rise.[116] This rise causes a shift of the chloride equilibrium potential in a positive (depolarising) direction thus decreasing the hyperpolarising effect of $GABA_A$ activity. A higher extracelllar potassium level also decreases the normally hyperpolarising outward potassium current from $GABA_B$ receptor activation.[115]

Gradations Between Focal and Generalised Epilepsies

Several clinical entities straddle the two current pillars of the classification system.[117] Benign childhood epilepsy with Rolandic spikes comprises both partial and generalised epileptic seizures.[118] Disparate sensory symptoms may appear in patients with bisynchronous spike-waves.[119] Gastaut et al[120] described hemigeneralised epilepsy consisting of tonic-clonic or clonic phenomena resembling those of "generalised epilepsy" but confined to or appearing principally on one side. Blume[64] described "hemispheric epilepsy" in which spike-wave discharges consistently appeared principally in the same hemisphere over sequential recordings, but whose clinical ictal manifestations were mostly bilateral (Figure 7). Lombroso[121] found consistent focal abnormalities in over half of EEGs among patients whose clinical and EEG features otherwise conform to those of primary generalised epilepsy. The co-existence of regionally-accentuated and bisynchronous epileptiform discharges in acquired epileptic aphasia (Landau-Kleffner Syndrome) was discussed above. Lemieux and Blume[29] found hemispheric frontally-predominant onsets in one-third of apparently "generalised" spike-waves.

Secondary bilateral synchrony is an electrographic entity in which a focal epileptiform discharge consistently leads to bilaterally synchronous epileptiform discharges.[122,123] Widely synchronous regional spike discharges appear more likely to produce SBS than discrete foci.[124] Frontal lobe spikes have a greater propensity to develop widely synchronous regional spikes than those from other areas.[41] Mesial frontal lesions may be particularly apt to produce secondary bisynchrony.[123,125] Interaction of multiple cortical epileptiform foci may also facilitate the production of SBS.[41]

The foregoing data illustrate the blurred distinction between focal and generalised epilepsy in many instances.

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