

Online brainmapping

Version 10

A Monthly Publication presented by Professor Yasser Metwally

February 2009

EEG SHARP ACTIVITY: MORPHOLOGICAL, NEUROPHYSIOLOGICAL AND BIOCHEMICAL FEATURES

Spike/sharp waves, morphological features:

The spike/sharp wave activity are hypersynchronous discharge pattern of large amount of epileptic neuronal aggregates.

◆ Spike

A spike is a pointed peak transient clearly distinguished from the ongoing EEG activity. The distinction between the spike and the ongoing activity is based upon the voltage and wave morphology. The spike stands out in clear contrast with the ongoing activity because of their higher voltage compared with the ongoing activity.

From the morphological point of view, the spike has a multiphasic feature, being composed of a minor positive, major negative and another minor positive component. The multiphasic characteristic of the spike is related to the fluctuating membrane potentials during the genesis of the hypersynchronous epileptic neuronal discharge.

The duration of the spike potentials ranges between 70-100 msec. The spike is usually followed by a large surface negative slow wave.

◆ Sharp waves

The only difference between spikes and sharp waves lies in their duration. While the spike duration does not exceed 100 msec. The sharp wave duration ranges between 100-200 msec. Otherwise no other differences exist between the spikes and the sharp waves. Both of them are frequently termed sharp activity. From the physiological view point, the sharp activity represents large excitatory post-synaptic potentials (EPSPS) called paroxysmal depolarization shifts (PDS), while the slow waves following them interictally represent inhibitory post-synaptic potentials (IPSPS).

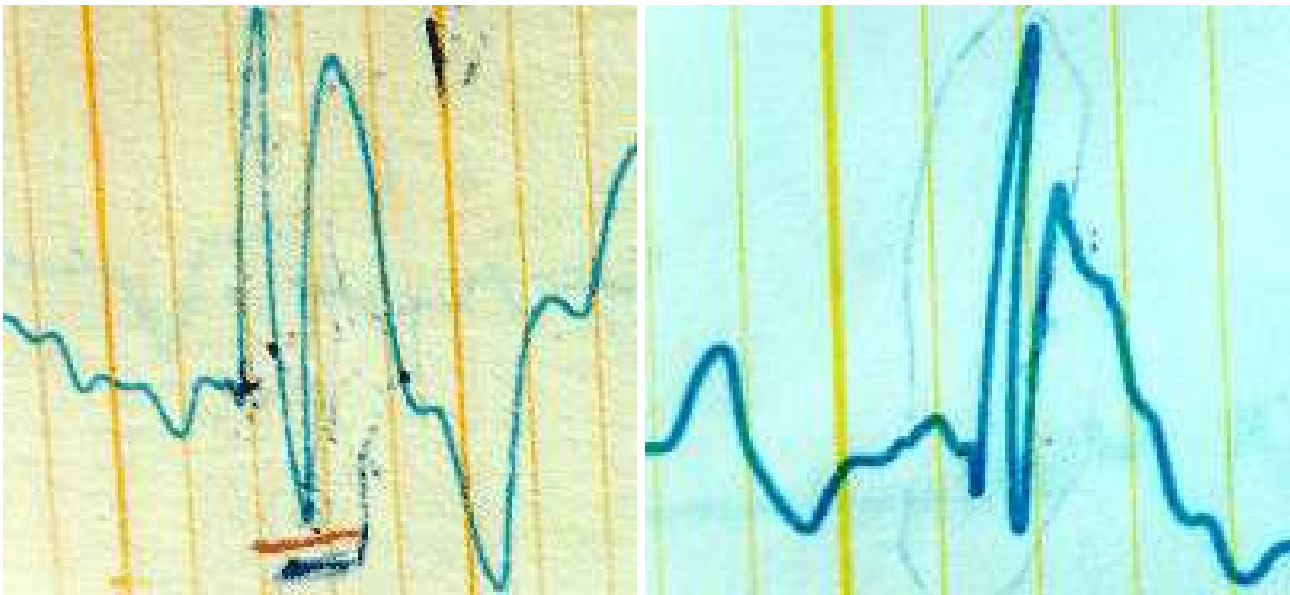


Figure 1. Examples of sharp waves [left] and spike [right]

Spike/sharp wave, a neurophysiological perspective:

The neuronal epileptic discharge consists of bursts of high voltage sustained and repetitive axosomatic unite spikes called paroxysmal depolarization shifts (PDS).

A unite spike represents multiphasic membrane potential fluctuation, its chief component is a steep negative potential, this component is of

high voltage, sustained and repetitive quality. In general the main components of the membrane potential oscillation are.

- ◆ Steep depolarization, which when exceed the membrane potential will trigger a series of high voltage, repetitive action potentials (PDS).
- ◆ Steep repolarization phase.
- ◆ Hyperpolarization phase.

The initial steep depolarization is usually preceded by massive slow depolarization shifts of an amplitude reaching up to 30 MV and of duration that may exceed 100 msec.

The slow and fast depolarization shifts are usually ushered by prominent changes in the ultra-slow activity, those ultraslow shifts are strongly negative at the center and show positivity at the periphery .

The ultra slow shifts, fast and slow depolarization shifts, associated with repolarization and hyperpolarization will collectively give rise to the neurophysiological phenomenon of PDS, morphologically, by intracellular recording, it is represented as bursts of high voltage, high frequency unit spikes (bursts of high voltage, high frequency action potentials). Paroxysmal depolarization shifts constitute the spikes of the micro-EEG (the spikes of the micro-neurophysiologists).

In general paroxysmal depolarization shifts are a giant excitatory post-synaptic potentials (EPSPS). Paroxysmal depolarization shifts are the hallmark of an epileptic neuron, when aggregates of epileptic neurons fire simultaneously and in synchrony, the summated potentials of Paroxysmal depolarization shifts will give rise to the macro EEG spike/sharp wave potentials. In short, the summated Paroxysmal depolarization shifts of a large number of epileptic neuronal aggregates is the pathophysiological phenomenon which is represented graphically as spike/sharp wave in the EEG.

◆ Role of inhibition

The inhibitory system in the CNS are based upon three different neurophysiological mechanism

- The post-synaptic inhibitory activity via hyperpolarization of the post-synaptic membrane. This occurs selectively in the brain and is mediated by the GABA-BNZ receptor complex.
- Pre-synaptic inhibition, via depolarization of the pre-synaptic terminal, thus reducing the amount of neurotransmitter release.
- Recurrent collateral inhibition by which the cell regulate its own activity.

The brain is protected by powerful anticonvulsant inhibitory system. Paroxysmal depolarization shifts are invariably followed by post PDS after hyperpolarization representing inhibitory post-synaptic potentials (IPSPS). The persistence of this IPSPS is responsible for the overall duration of spiking (PDS) and contribute to its termination.

The post-depolarization shifts after hyper polarization (inhibitory post synaptic potentials, IPSPS) is mediated by the GABA-BNZ receptor complex in the post synaptic junction. This GABA mediated IPSPS is represented morphologically, in the EEG, as a large surface negative slow wave (the slow wave that commonly follows the spike/sharp wave). This slow wave represents, from the neurophysiological viewpoint, the GABA mediated inhibitory tone which prevents the spiking from becoming self sustained and generalized.

Transition from interictal spiking to ictal spiking with clinical tonic clonic fit is invariably associated with failure of the local inhibitory process that create the post-depolarization shift (PDS) after hyper polarization. The loss of this local protective mechanism signifies the imminent transition from interictal to ictal discharge.

From the EEG point of view transition from interictal to ictal spiking is characterized by loss of the inhibitory slow wave that follows the spiking interictally, and the discharge is replaced by fast rhythmic self sustained spiking with frontal predominance during the tonic phase. The clonic phase is characterized by reappearance of the rhythmic slow wave alternating with bursts of polyspikes. The polyspikes are synchronous with the clonic jerks and the slow waves are synchronous with the periods of relaxation in-between the jerks. Finally, the inhibitory activity overcome the excitatory activity resulting in termination of the grand-mal fit.

To sum up, failure of the GABA mediated inhibition signal the start of the tonic-clonic fits. The tonic phase is characterized by complete failure of the GABA mediated inhibition. The clonic phase is characterized by partial reappearance of the GABA mediated inhibition. Finally GABA mediated post-synaptic inhibitory mechanism is responsible for seizure termination. Failure of this inhibitory mechanism is responsible for the status epilepticus.

In general, in epileptic foci the excitatory activity (PDS) is strongly counterbalanced by the strong inhibitory anticonvulsant system of the brain. So that epileptic discharge remains constrained and subclinical (interictal). Temporary failure of the GABA mediated anticonvulsant system of the brain is responsible for the start of a grand mal fit.

To end up the following potentials are recorded at the epileptic foci interictally.

1. Ultra slow DC current.
2. Slow and fast depolarization shifts
3. Repolarization potentials.
4. Hyperpolarization potentials, this potentials is due to:
 - Electrogenic pumps.
 - Slow and fast GABA mediated IPSPS

Those potentials results in marked increase of power (voltage) in the whole EEG spectrum starting from 0.30 Hz (increase of power in the delta-theta-alpha and Beta frequency bands or increase of the full band power).

Neurobiochemistry of Paroxysmal depolarization shifts (EEG sharp activity)

- State of activation in focal epileptogenesis:

Paroxysmal depolarization shifts are associated with marked increase of calcium conductance through the cellular membrane resulting in increased cytosolic intracellular calcium concentration coupled with reduction of the extracellular calcium. Increased intracellular calcium is the hallmark of Paroxysmal depolarization shifts which are regarded as a calcium dependant pathophysiological process. Paroxysmal depolarization shifts of a single epileptic neuron and of epileptic neuronal aggregates is suppressed by calcium channel blockers.

The increased calcium conductance during the Paroxysmal depolarization shifts occurs mainly through the NMDA glutaminergic receptors. The NMDA operates on ionic calcium channels, when the NMDA receptor is stimulated the channel opens and closes rapidly resulting in massive influx of calcium intracellularly coupled with the discharge of bursts of high voltage repetitive action potentials (PDS).

Repetitive high frequency stimulation of the NMDA receptors condition the ionic channels, making the response to subsequent low frequency stimulation much greater, thus potentiating the efficiency of the NMDA synapses. This potentiation can last for weeks or months.

As activation of the NMDA receptors is coupled with increased intracellular calcium, this will ultimately results in the induction of the proto-oncogenes (cellular growth factors). So prolonged stimulation of the NMDA receptors results in increased in the number (hyperplasia) and the size (hypertrophy) of the NMDA synapses associated with sprouting of recurrent axonal collaterals making new synaptic contacts with the glutaminergic cell bodies, this will ultimately results in the establishment of closed excitatory circuits (self reverberating circuits or kindling).

This usually results in amplification of the excitatory impulses, so that the response to subthreshold stimuli will be amplified and much prolonged.

However progressive increase of the intracellular calcium beyond the buffering capacity of the calcium binding protein, will ultimately unleash a cascade of events that eventually results in neuronal death (excitotoxic neuronal damage). Those include activation of protease and lipase enzymes, liberation of cytotoxic free radicals, and uncoupling of the oxidative phosphorylation reaction.

- State of inhibition in focal epileptogenesis:

Increased intracellular content in GABergic interneurons, secondary to activation of the NMDA synapsis, is associated initially with reduction in GABergic neuronal sensitivity with subsequent reduction of the GABergic inhibitory tone. Progressive increase of the cytosolic calcium content of the GABergic interneurons ultimately results in excitotoxic GABergic neuronal damage so ultimately there is quantitative reduction in the number of the GABA-BNZ post synaptic receptors. This will lead to a state of disinhibition that can create the necessary condition for Paroxysmal depolarization shifts to become repetitive and self sustained.

To sum up, in focal epileptogenesis there are:

- Hypertrophy and hyperplasia of the excitatory NMDA glutaminergic synapsis with sprouting of recurrent axonal collateral establishing excitatory closed circuits (The kindling process).
- Reduction of GABergic interneurons with reduction of GABA and GAD activity and reduction of the BNZ receptors post synaptically.
- Reactive gliosis.

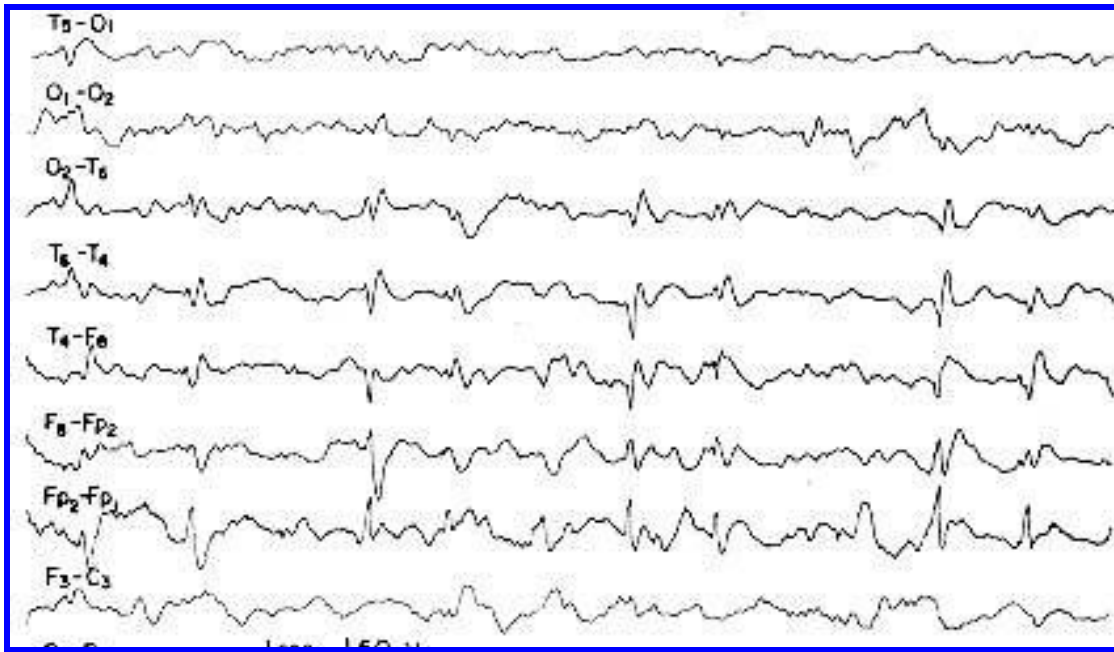


Figure 2. Typical anterior temporal spikes in a patient with temporal lobe epilepsy

Table 1. Electroclinical criteria of spike/ sharp wave discharge

- A spike is a transient, clearly distinguished from the background activity, with pointed peak at conventional paper speeds and a duration from 20 to under 70 msec; the main component is generally negative. Amplitude is variable. Spikes represent the basic element of paroxysmal activity in the EEG
- A sharp wave is a transient, clearly distinguished from background activity, with pointed peak at conventional paper speeds and duration of 70 to 200 msec. The main component is generally negative relative to other areas.
- Both spikes and sharp waves have multiphasic characters, being composed of a sequence of a minor positive, a major negative, and a second minor positive component is typical in most instances. The long duration of a sharp wave permits better insight into the multiphasic character of this potential.
- The spike/sharp wave potentials are reliable indicators of a potential seizure focus because they result from the characteristic neurophysiological event "the paroxysmal depolarization shift" (PDS). This phenomenon consists of thousands of neurons simultaneously undergoing large depolarization with superimposed action potentials. Both synaptic events and intrinsic cellular currents have been implicated in this process. EEG spikes/sharp waves are due to the slow depolarization currents in the PDS. Neurons surrounding the focus are inhibited during the paroxysmal depolarization shift, and within the focus the the paroxysmal depolarization shift is followed by a hyperpolarization potential. Both an increase in depolarizing events and a loss of inhibitory mechanisms can lead to persistence and propagation of the discharge as a seizure.
- Spikes and sharp waves are neurophysiologically closely related phenomena; both of them are typical paroxysmal discharges and highly suggestive of an epileptic seizure disorder, although both phenomena may occur in patients without a history of seizure disorder.
- The largest and most pronounced spikes are not necessarily associated with more serious epileptic seizure disorders. On the contrary, Rolandic spikes in a child age 4 to 10 yr are very prominent; however, the seizure disorder is usually quite benign or there may be no clinical seizures at all. low voltage spiking in the frontal or anterior temporal regions is highly epileptogenic even though its amplitude can be so low to the point that these spikes might be completely drowned within the background waves and subsequently can not be easily detected.

THE BRAINMAP COUNTERPART OF EEG SHARP ACTIVITY

The introduction of power spectral analysis and subsequent brain electrical activity mapping (BEAM spectral studies) has further extended the clinical utility of the classical EEG as an investigatory tool in epileptology. BEAM spectral studies is now considered as an important contribution towards localization and characterization of epileptic foci, especially when the standard EEG is considered as within normal or showing non specific changes. In this respect, BEAM was capable of uncovering cases of covert epilepsy and of detecting subclinical epileptogenic foci. As atated above

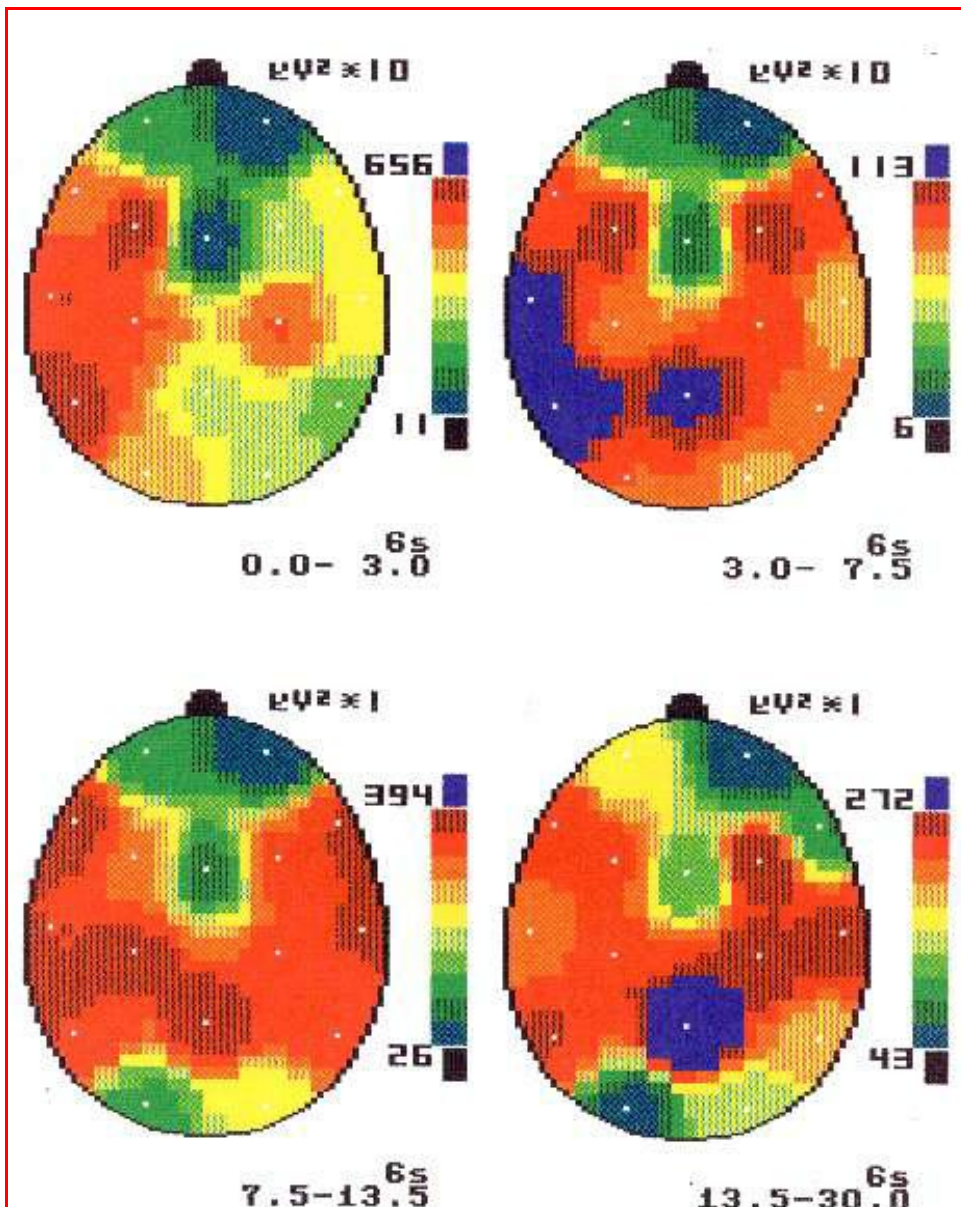
As atated above the following potentials are recorded at the epileptic foci interictally.

1. Ultra slow DC current.
2. Slow and fast depolarization shifts
3. Repolarization potentials.
4. Hyperpolarization potentials, this potentials is due to:
 - Electrogenic pumps.
 - Slow and fast GABA mediated IPSPS

Those potentials results in marked increase of power (voltage) in the whole EEG spectrum starting from 0.30 Hz (increase of power in the delta-theta-alpha and Beta frequency bands or increase of the full band power). Focal increase of power (spectral energy) in all frequency bands is the hallmark of focal epileptogenesis in in brainmapping studies and quantitative EGG analysis. In the author experience increase of the full band power (between 0-30 c/s) precisely map the epileptic cerebral lesions

Focal increase of the spectral energy in all frequency bands signals epileptogenic cortex. Increased spectral energy might involve the whole power spectrum, or it might be localized to the beta band. Occasionally, the focal increased energy in the beta band might be associated with decreased energy in the Delta, theta and alpha bands either at the site of the beta focus or in the nearby cortex. Focal beta hyperactivity (Focal increase of the beta spectral energy) is a manifestation of a seizure focus. In less irritable foci, the power increase is limited to the beta band while more excitable epileptogenic foci show a BEAM spectral profile characterized by focal increase of the spectral energy in all frequency bands (Delta - theta, alpha as well as beta bands). In patients where the enhanced beta focus is associated with power reduction in the alpha, theta and delta bands, a pattern of diminished and augmented activity in close proximity, might suggest a region of atrophy and gliosis surrounded by epileptogenic cortex. The diminished power in the delta band might, in this respect, indicates functionally destructive cortex.

Various provocative techniques were used in conjunction with the power spectral analysis and BEAM studies to enhance the visualization of epileptic foci. As focal beta abnormality is found to be the BEAM substrate of epileptic foci, beta enhancing medications are subsequently used to enhance the localization of epileptic foci. Fast EEG activity induced by barbiturate could be used to localize brain lesions, where lesioned area does not respond by increased beta activity.



The spatial distribution of the EEG beta activity induced by thiopental - a beta enhancer -can change in 3 different ways:

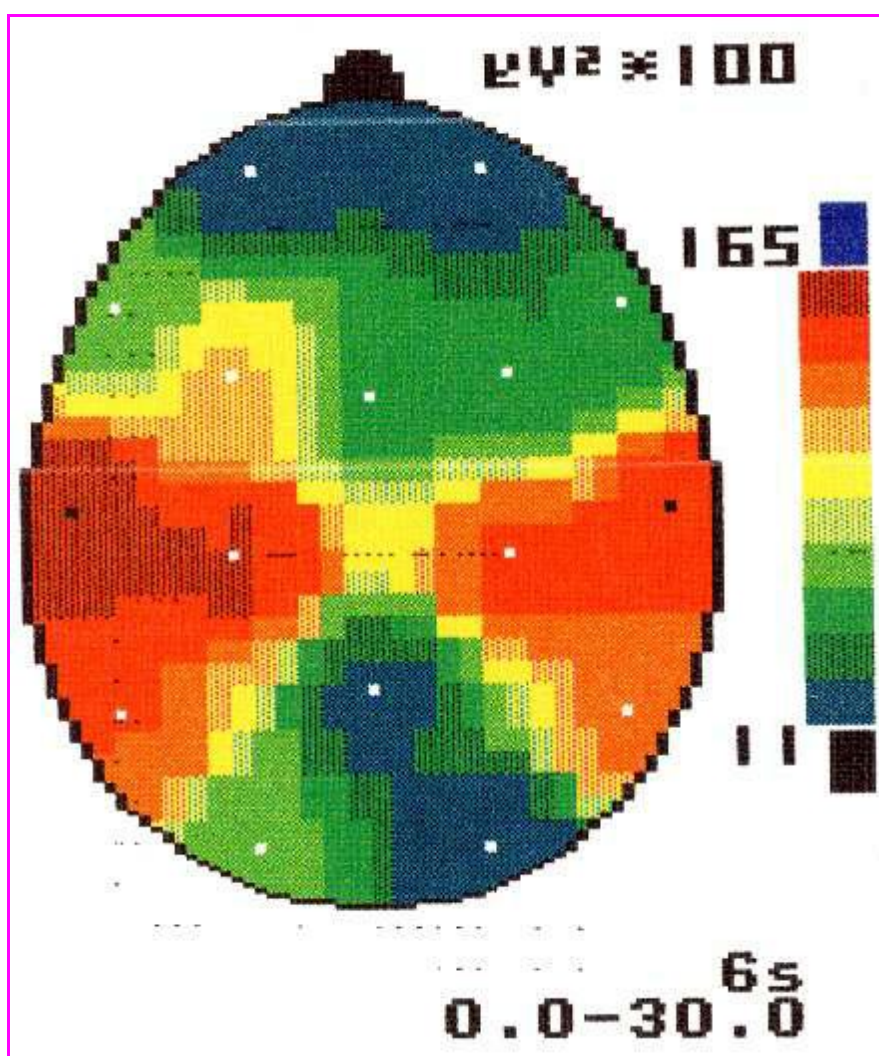
1. Diffuse symmetrical and frontally maximal which is the normal response.
2. Generalized lack of response seen in diffuse encephalopathic process.
3. Regional or focal paucity of augmented beta activity seen over focal, often atrophic lesions.

Area with poor response to diazepam or any beta enhancer (lesser increase of the beta activity) always coincides with the area of maximum spiking.

Figure 3. A patient presented clinically with temporal lobe epilepsy. A brainmap study showing Bitemporal increase of power in all frequency bands with maximum involvement of the left temporal area. The full band power increase also involves the posterior frontal and the centroparietal areas

Thiopental activation and brain electrical activity mapping (BEAM) can be combined to accurately localize and characterize epileptic foci.

1. Lesions which showed augmented focal beta activity on the BEAM profile following thiopental administration contained an irritable often epileptogenic cortex.
2. Epileptic foci showing diminished response to thiopental in the delta range are found to be more



spatially extensive or functionally destructive.

BEAM spectral studies always localized the epileptic foci in an objective, quantitative and easily interpretable fashion. In some epileptic patients BEAM might be the only convincing evidence of focal disorder. Subclinical epileptic foci as well as residual cortical irritable foci in patients properly controlled by medications are clearly visualized on the BEAM spectral profile. In this respect, even transphenoidal electrodes failed to demonstrate convincing evidence of focal disorders in some temporal lobe epileptic patients whereas BEAM clearly visualized the epileptic foci in those patients.

Figure 4. A patient presented clinically with temporal lobe epilepsy. A brainmap study showing Bitemporal increase of the full band power with maximum involvement of the left temporal area

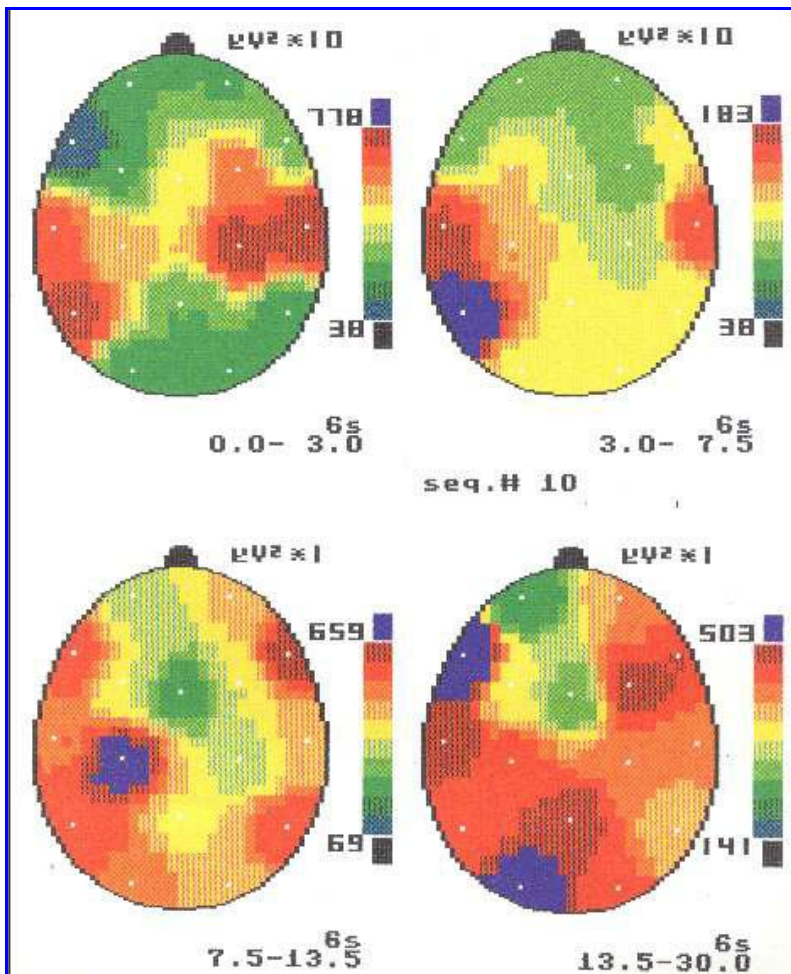


Figure 5. A patient presented clinically with temporal lobe epilepsy. A brainmap study showing Bitemporal increase of power in all frequency bands with maximum involvement of the left temporal area. The full band power increase also involves the posterior frontal and the centroparietal areas

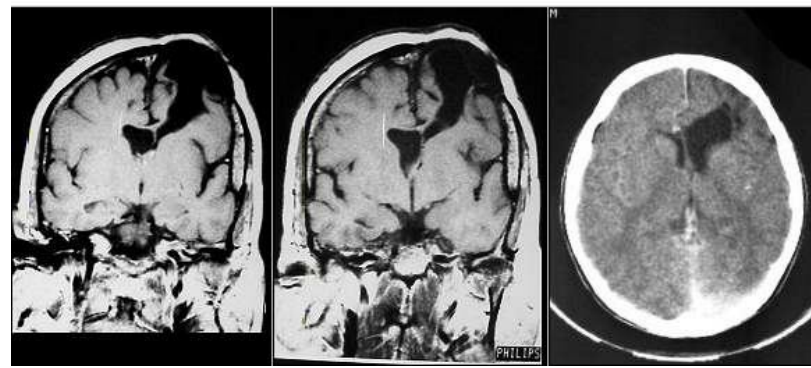
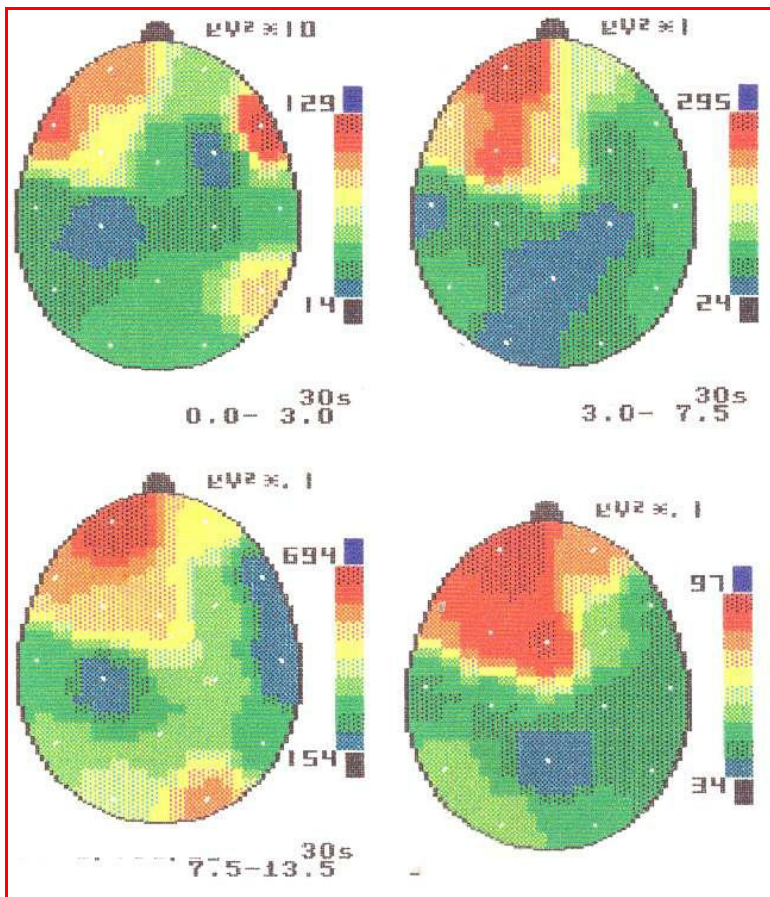


Figure 6. A child with cortical dysplasia (lissencephaly, schizencephaly and septo-optic dysplasia. The schizencephalic cleft involved the left frontal area and is seen extending between the subarachnoid spaces and the frontal horn of the lateral ventricle on the left side. Brainmap study in this patient showed a left frontal increase of the full band power that precisely mapped and localized the schizencephalic cleft and the area of maximum sharp activity recorded in the conventional EEG.

THE SPATIAL DISTRIBUTION OF FOCAL EPILEPTIC DISCHARGE

The preferential localization of local epileptic discharge is related to a number of factors that include :

- The patient's age:
 - There is a tendency of some form of focal discharges to be localized to certain brain areas depending on the state of maturation and the age of the patient.
- The site of the pathological lesions producing the seizures.
- The degree of epileptogenicity of the various brain areas:
 - There is a difference in the epileptogenicity of the various brain areas. For example, the temporal lobe has the lowest threshold for the development of epileptic focal activity while the parietal lobe has the highest threshold.

Spatial distribution of focal epileptic activity includes:

1. Centromidtemporal (sylvian, rolandic) spike discharge of childhood.
2. Occipital sharp activity of childhood.
3. Centro-parietal sharp activity of childhood.
4. Anterior temporal sharp activity.
5. Frontal sharp activity.

- Centromidtemporal spike discharge of childhood

The site of the discharge appear to be the perisylvian area (the posterior frontal, the anterior temporal and the central electrodes). The discharge is maximum in the lower rolandic or the motor strip areas of the face, and upper limb. The discharge has an age specific character, being seen only in children and adolescents between the ages of 4-16 years.

The discharge consists of high voltage, repetitive, multiphasic spike and sharp wave activity, usually followed by an after coming high voltage slow wave with a duration of 200-300 msec. This discharge pattern is very prominent and frequently occurs in clusters, and in serial trains. It could be unilateral or bilateral, or may shift from one side to another. This discharge is marked enhanced during non REM sleep.

About 60% of children with this discharge pattern has seizures. The seizures have been termed the benign rolandic epilepsy of childhood.

However this discharge pattern can be seen as an incidental finding in the EEG of asymptomatic children who do not have seizures.

This discharge pattern is seen with increased frequency in a symptomatic first degree relatives of patients with benign rolandic epilepsy of childhood and it appears to be the expression of a dominant genetic trait (genetic EEG trait), which is not necessarily associated with any clinical seizure disorders. Its occurrence in non-epileptic children should suggest a genetic predisposition rather than an epileptic disease entity. The genes locus responsible for this genetic EEG trait has not yet been mapped to a particular chromosome.

- **The occipital sharp activity of childhood.**

Occurs mainly between the ages of 2-5 years. This discharge pattern has the same characteristics of the centromidtemporal discharge pattern and is seen in patients with benign occipital epilepsy of childhood.

This discharge pattern is also the expression of a genetic trait, and is not necessarily associated with any seizure disorder. In fact only 50% of children with this discharge pattern has seizure disorder.

- **The centroparietal sharp activity of childhood.**

A part from being maximum in the centroparietal region, this discharge pattern has the same criteria of the centromidtemporal and occipital sharp activity of childhood. This discharge pattern pattern is seen between the ages of 4-10 years.

- **Anterior temporal sharp activity:**

This discharge pattern is seen mainly in the adult age usually after the age of 16 years. It has a maximum activity in the anterior temporal region. As the sharp activity is derived mainly from the medial (mesial) temporal structures (The hippocampus and amygdala), so it usually has much lower voltage compared with the more superficial centro-mid temporal discharge pattern. Because of its lower voltage, the spike activity may be drowned in the ongoing EEG activity, so that visual inspection of the EEG may fail to detect it, and the EEG is occasionally read as within normal. This discharge pattern is markedly enhanced by non REM sleep.

About 90% of patients with this discharge pattern has clinical seizure disorders consist in of he various manifestations of complex partial seizures of temporal lobe epilepsy.

- **Frontal lobe harp activity.**

About 90% of patients with this discharge pattern have clinical seizure disorders. This discharge pattern is often secondary to an overt underlying pathology such as trauma, tumour, vascular lesion, scarring, or residual encephalitic changes. This discharge pattern can occur in any age and is not characteristic of the childhood period.

To sum up, most of the focal epileptic discharge in the childhood period is relates to the functional benign focal epilepsies. Apart from the site of the discharge (centro-midtemporal, centro-parietal or occipital), the discharge pattern of benign focal epilepsies share common characteristics, being composed of high voltage, repetitive, spike, sharp waves often occurring in clusters, and commonly followed by slow waves. This discharge pattern is enhanced by non REM sleep. It represents a genetic trait and is not necessarily associated with clinical seizure disorders. Anterior temporal spiking characteristic of temporal lobe epilepsy occurs much less commonly in the childhood period.

- **Benign focal epilepsies.**

Benign focal epilepsies are an age specific epileptic disorders that are encountered almost exclusively in children who have neither history nor evidence of brain damage.

Benign focal epilepsies resemble in many ways primary generalized epilepsies because of the following:

1. **The fits is the disease being not secondary to any structural brain lesions.**
2. **Neurological examination is free.**
3. **Intact mentality of the patients.**
4. **Strong genetic background.**
5. **Very good prognosis, and most patients outgrow their disease even without medical treatment.**

Benign focal epilepsies, being focal, in the tradition sense, is paradoxical. They are unequivocally focal, both clinically and in the EEG, however they are not secondary to any structural brain lesion and they also have a good prognosis. In general benign focal epilepsies of childhood is the most common cause of focal epilepsies in the childhood periods.

The best studied and the most frequent of benign focal epilepsies is the centro-mid temporal subtype, the benign occipital epilepsies is the second most frequent subtype.

- **Benign focal epilepsy with centro-mid temporal discharge.**

The source of disturbance in the seizure type lies in the lower rolandic cortex representing the face and the oropharynx. The seizure frequency in this disorder is very low occurring mostly at night especially during the first 1/3 of the night in 80% of cases. Past history of febrile convulsions is present in some patients with this seizure type.

The seizure usually takes the form of hemifocal convulsion that may spread to involve the upper limb. The seizures, especially the nocturnal ones often become generalized. The partial onset is occasionally missed and the seizure is described as grand mal fits.

Other form of focal onset include:

1. Somatosensory onset with unilateral paraesthesia involving the tongue and the lips.
2. Speech arrest, anarthia.
3. Drooling of saliva.

- **EEG of Benign focal epilepsy with centro-mid temporal discharge. (NFE)**

The EEG shows the characteristic discharge pattern of high voltage, repetitive spikes/sharp waves that occur in clusters and serial trains and often followed by high voltage slow waves. The discharge is prominent in the central and temporal electrodes and becomes prominent in non REM sleep specially during stage II. The intensity of the spiking is not related to the frequency or the duration of the clinical seizures. Generalized SWD is occasionally seen in patient with centro-mid temporal epilepsy, however it is usually not accompanied by clinical absence.

- **Genetics of BFE with centro-mid temporal discharge.**

The discharge pattern of the BFE with centro-mid temporal epilepsy is the expression of a single dominant gene with an age dependent penetrance that has the following characteristic.

1. **Low penetrance below the age of 4 years.**
2. **The penetrance rise to 50% between 4-16 years.**
3. **It becomes very low after the age of 16 years.**

In fact the discharge pattern of BFE with centro mid temporal should be regarded as genetic EEG trait as the number who bear this EEG trait but otherwise clinically free exceeds those who have clinical seizure disorder. Those who are seizure free represent a group of a symptomatic gene carrier who have high propensity to seizure.

In general the genetic profile of BFE with centro-mid temporal discharge is very close to that of type I primary generalized epilepsies as both are inherited by a single dominant gene that has a low penetrance before the age of 3.5-4 years and a low penetrance after the age of 16 years, from the EEG point of view, both discharge pattern could be found in either of them. This raised the question as to whether BFE with centro-mid temporal discharge and absence seizures are genetically linked.

References

1. Metwally, MYM: Textbook of neurimaging, A CD-ROM publication, (Metwally, MYM editor) WEB-CD agency for electronic publishing, version 10.1a January 2009

**The author,
Professor Yasser Metwally
Professor of clinical neurology, Ain Shams university, Cairo, Egypt.
www.yassermetwally.com**

- ◆ **A new version of this publication is uploaded in my web site every month**
- ◆ **Follow the following link to download the current version:
<http://brainmapping.yassermetwally.com/map.pdf>**

© Yasser Metwally, all rights reserved