# Part II – Neurological Disorders

## CHAPTER 4
## EPILEPSY

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NEUROLOGY IN AFRICA

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# *CHAPTER 4*

## EPILEPSY

**Introduction**

Epilepsy is a predisposition to recurrent unprovoked seizures. Seizures are caused by attacks of sudden, excessive, abnormal electrical discharges arising mainly from the neurones in the cortex of the brain. The site, spread and pattern of electrical discharges determine the clinical features of epilepsy. The seizures may range from a brief awareness of sensation lasting only seconds to a sudden loss of consciousness associated with involuntary stiffening and jerking body movements. The latter is termed **generalized tonic-clonic epilepsy** and historically was called **grand mal**. Epilepsy is the most common community based major neurological disorder and the individual case history and description of the seizure are crucial to the diagnosis of epilepsy. This chapter outlines the main epilepsy syndromes, their classification, causes, clinical presentation diagnosis and management. The student should aim for an overall understanding of epilepsy and in particular its burden, diagnosis, management and treatment.

### EPILEPSY SYNDROMES

Epilepsy is classified according to cause and clinical seizure type. **Idiopathic** epilepsy (60-70%) occurs where no known cause is found or suspected and many of these are most likely genetic in origin. **Symptomatic** epilepsy (30-40%) occurs when there is an underlying structural abnormality in the cerebral cortex such as a scar or tumour or another condition predisposing to seizures. Seizures in epilepsy may be classified according to their clinical presentation and their site of electrical origin in the brain (Table 4.1). If seizures arise focally from one site within the brain these are termed as the **partial onset seizures**. These can present with motor, sensory, autonomic and psychological symptoms. If the electrical discharge remains focal and consciousness is fully retained, these are classified as **simple partial seizures**. If the electric discharge arises focally and consciousness is altered, these are classified as **complex partial seizures**. If the electrical discharge arises focally and spreads to involve the rest of the entire cerebral cortex, this results in a **generalized tonic-clonic seizure**. These are classified as **secondary generalized tonic-clonic seizures (grand mal)** and are the most common type of seizure disorder **(70%)**. Seizures may also arise from electrical discharges deep within the brain spreading equally rapidly to all parts of the cortex at the same time. These are termed as **generalized onset seizures (30%)**. These include **"absence" seizures** (**petit mal) myoclonic seizures, tonic-clonic seizures (grand mal)** and **atonic seizures**. Epilepsy may also be described as active or inactive, controlled or uncontrolled depending on the degree of remission and response to treatment.

## CLASSIFICATION

**Table 4.1** Classification of Seizures

| Category | Seizure type | Consciousness |
|---|---|---|
| **Partial onset seizures** *(70%)* | simple partial<br>complex partial<br>secondary generalized tonic–clonic | not impaired<br>impaired<br>loss of consciousness |
| **Generalized onset seizures** (30%) | absence<br>myoclonic<br>primary generalized tonic-clonic | impaired<br>not clinically impaired<br>loss of consciousness |

## EPIDEMIOLOGY

Epilepsy is defined as the tendency to have recurrent seizures. It affects 0.4 to 0.6% of the world's population at any point in time, with a larger proportion of the general population (3-5%) having one or two non-recurrent isolated seizures throughout their life which do not develop into epilepsy. The global burden of epilepsy is estimated to be >50 millions of whom 80% live in low or middle income countries. Estimates of the frequency in Africa vary widely and studies from there have in the past suggested that active epilepsy is 2-3 times higher than in high income countries with a median frequency of 15/1000 (1.5%). However methodological difficulties make it difficult to compare most studies. A recent multicentre study from five sites in East Africa which reproduces strict methodology suggests a median frequency there of <0.5% which is similar to other parts of the world. The criteria used to diagnose active epilepsy were 2 or more unprovoked seizures during the previous 12 month period. There are two peak age groups when epilepsy occurs, the first one is in childhood and adolescence during which both birth related and genetic causes are typically found and the second peak occurs in older adults (>65 years) when there is usually an underlying structural cause in the brain.

## AETIOLOGY

The aetiology is unknown or idiopathic in about two thirds of cases of epilepsy in Africa. This may in part be a function of under investigation due to lack of resources. Epilepsy has many causes and it is likely that genetic and historical causes account for a significant proportion of these. The main causes and their estimated frequencies in Africa are presented in Table 4.2. Genetic predisposition and brain injury are both known risk factors for epilepsy. Genetic factors are indicated by a positive family history of epilepsy. The underlying mechanisms of epilepsy are not known but a chronic pathological process as a result of tissue injury or some other common mechanisms seems likely in many cases. Pre and perinatal brain injuries arise largely as a result of hypoxia and hypoglycaemia because of intrauterine infections e.g. toxoplasmosis, rubella, HIV etc and because of poor obstetric care. Febrile convulsions (FC) as an infant or young child are a significant risk factor for scarring in the temporal lobe and epilepsy in later life.

A history of previous CNS infection is a major risk factor for epilepsy in Africa. This is particularly the case for infants, children and younger adults. The main infections are meningitis, cerebral malaria, neurocysticercosis, encephalitis and brain abscess. Malaria is the most common cause of acute symptomatic seizures in children in malaria endemic parts of Africa. HIV is the most common cause in young adults. However it is important to remember that single seizures or

those occurring during a febrile illness are not classified as epilepsy. Helminthic infections are an important cause of epilepsy in parts of Africa, in particular where free-range pig rearing is practised resulting in neurocysticercosis. Traumatic head injury mainly as a result of road traffic accidents and falls are increasingly a cause of epilepsy in young adults. Brain tumours and cerebrovascular disease account for a proportion of epilepsy mainly affecting adults.

**Table 4.2** Main causes of epilepsy in Africa & their estimated frequency

| Cause | % of total | (range) |
|---|---|---|
| **genetic** | 40 | (6-60) |
| **pre & perinatal** | 20 | (1-36) |
| **infections & febrile convulsions** | 20 | (10-26) |
| **cerebrovascular disease** | 10 | (1-42) |
| **head injury** | 5 | (5-10) |
| **brain tumour** | 5 | (1-10) |

*Ref Preux & Druet-Cabanac Lancet Neurol 2005; 4: 21-31*

### Key points

- active epilepsy affects at least 0.5% of the population in Africa
- peak age groups affected are young children, teenagers & older adults
- cause is unknown in up to two thirds of cases
- genetic factors may account for a sizable proportion
- pre & perinatal brain injury & infections are main causes in young persons
- stroke, head injury and tumour are main causes in older age groups

## COMMON FORMS OF SEIZURES

### Generalized tonic-clonic seizure (GTCS)

This is the most common form of epilepsy in adults. Typically it involves consecutive clinical phases including tonic-clonic limb movements, loss of consciousness, frothing from the mouth, tongue biting, incontinence and post ictal confusion. If the origin of the seizure is focal as in secondary or **partial onset epilepsy** an aura may be present at the onset. In contrast there is no aura in **primary** or **generalized onset epilepsy.**

### Aura phase

The clinical type of aura depends on the site of origin of the seizure. This phase typically lasts a few seconds or less and consists of a brief recurring stereotyped episode. The episode is characterized by an awareness of a familiar, typically epigastric feeling or the hallucination of a smell, taste but rarely hearing, usually coupled with automatisms if the origin is in the temporal lobe. If the origin is the parietal lobe, the episode is sensory, if in the frontal lobe it is motor and if in the occipital lobe it is visual. The aura phase of a partial onset GTCS may be forgotten because of retrograde amnesia.

### Tonic phase

The tonic-clonic phase starts suddenly with loss of consciousness; the patient may make a loud noise or a cry and fall to the ground. There is a brief stiffening and extension of the body due to sustained tonic muscle contraction lasting about 10 seconds but which can last a minute.

During this tonic phase breathing stops and cyanosis may be recognised by observers. Urinary incontinence and less frequently faecal incontinence may occur at the end of this stage.

**Clonic phase**

The tonic phase is followed by the clonic phase characterized by repeated generalized convulsive muscle spasms. These are violent, sharp, rhythmical, powerful, jerky movements involving the limbs, head, jaw and trunk. The eyes roll back, the tongue may be bitten and frothing from the mouth may occur due to excess salivation as the result of excessive autonomic activity. This phase typically lasts a minute or two but may be more prolonged. The patient remains unconscious.

**Coma phase**

When the jerking has stopped normal breathing pattern returns but is shallow, the limbs are now flaccid and the patient remains unconscious and cannot be roused. The duration of unconsciousness ranges typically from about 5-20 minutes and reflects the extent and duration of the seizure. Then there is a gradual return of consciousness.

**Post-ictal phase**

On recovery of consciousness there may be confusion accompanied by a headache, drowsiness and typically sleepiness for a variable period sometimes lasting for up to several hours. Over the following days, there is usually some muscle stiffness and soreness and evidence of any injury sustained during the attack. Patients have retrograde amnesia for the seizure but may sometimes remember the aura phase before loss of consciousness.

### Diagnostic features of a GTCS

- witnessed convulsion
- loss of consciousness
- tonic-clonic limb movements
- incontinence
- tongue biting
- postictal confusion

**Absence seizures**

This is the most common form of primary generalized onset epilepsy. It affects mainly children usually <10 yrs, (4-12 yrs) and is more common in girls. An attack occurs without warning. Usually parents or teachers note that the child suddenly stops what he or she is doing for a few seconds but does not fall down or convulse. The eyes remain open staring blankly ahead with occasionally blinking or eyelid fluttering. There is no response to an outside stimulus during the attack which ends as suddenly as it starts, usually with the child resuming activities unaware of what has happened. The attacks are brief lasting, typically between 5-15 seconds and can reoccur several times daily. The EEG shows a characteristic 3 per sec symmetrical slow and spike wave discharges. Both attacks and EEG changes can be provoked by hyperventilation. The attacks respond well to treatment with low dose sodium valproate or ethosuximide. Children usually grow out of these attacks in their late teens but some few may develop into generalized onset TCS.

### Diagnostic features of absence seizures

- mainly a childhood disorder & more common in girls
- stereotyped recurring episodes of loss of awareness or absences
- child goes blank, switches off for few seconds, stares ahead & may blink
- unresponsive during attack but does not convulse or fall down

**Myoclonic seizures**

These are another form of primary generalized onset seizures which are characterized by sudden, brief involuntary jerky limb movements lasting a few seconds. These seizures typically occur in young teenagers in the mornings after waking, with consciousness being preserved. Simple myoclonic jerks, which are generally benign, must be distinguished from **juvenile myoclonic epilepsy (JME). JME** consists of the triad of myoclonic jerks on waking occurring in all patients, generalized onset TCS in >90% of patients and typical day time absences in about one-third of patients. Absences may sometimes be an early feature, they begin in childhood and early teens and myoclonic jerks follow usually at around the age of 14-15 years. GTCS usually appears a few months after the onset of myoclonic jerks typically occurring shortly after waking. Occasionally JME may start or become clinically identified in adult life as 'adult myoclonic epilepsy'. The EEG in JME shows typical polyspikes and slow wave discharges and may show photosensitivity. Treatment with low dose sodium valproate is usually very successful.

### Diagnostic features of juvenile myoclonic epilepsy

- simple myoclonic jerks are benign and may not need treatment
- JME consists of morning myoclonic jerks, daytime absences & GTCS on waking

**Partial onset seizures**

If the site of electrical discharge is restricted to a focal area of the cortex in one cerebral hemisphere, then the patient will have partial onset seizures. The main causes include infections, infarcts, head injuries, tumours and hippocampal sclerosis, the latter due to frequent febrile convulsions in childhood. The clinical features depend on the site of the cortical focus and thus may be sensory or motor and involve alteration in consciousness. If there is no accompanying alteration of consciousness, then it is classified as a simple partial motor or sensory seizure. If there is alteration or clouding of consciousness, then it is a complex partial seizure. If the electrical spread becomes generalized, then it is classified as a secondary GTCS. Any patient presenting with new partial onset seizure disorder should be investigated with a brain scan to exclude a focal underlying cause.

**Temporal Lobe epilepsy (TLE)**

Complex partial seizures arise mainly in the temporal or frontal lobes. Temporal lobe epilepsy (TLE) is the commonest type of complex partial seizure disorder. The temporal lobe structures, particularly the hippocampus, are susceptible to injury during febrile convulsions, which may result in mesial temporal sclerosis (Fig. 4.6) and later TLE. The clinical features reflect the functions of the temporal lobe which include memory, speech, taste and smell. Seizures present as stereotyped episodes characterised by subjective experiences and movements. The subjective experiences include blank spells or absences, a sense of fear or déjà vu (an indescribably familiar

feeling "that I have had this before"), or an inexplicable sensation rising up in the abdomen or chest. They may also include memories rushing back and hallucinations of smell, taste, hearing or images. To an observer the patient may appear confused and exhibit repeated stereotyped movements or automatisms including chewing and lip smacking. The attack typically lasts seconds to minutes depending on the extent and cause of the lesion. Attacks can be still more complex and if the electrical activity spreads to the rest of the brain then a GTCS may occur.

### Diagnostic features of TLE

- stereotyped episodes lasting seconds
- déjà vu, depersonalization, rising sensation in epigastrium
- hallucination of mainly taste or smell
- movements, automatisms: lip smacking, chewing
- confusion and altered emotion
- may develop into a GTCS

**Motor seizures (Jacksonian epilepsy)**

This is a partial onset motor seizure disorder which occurs as a result of a focal lesion in the frontal lobe in or near the motor cortex. The convulsive movement begins typically in the corner of the mouth or in the index finger or big toe and then spreads slowly proximally to involve the leg, face, and hand (Jacksonian march) on the side of the body opposite the lesion. There may also be clonic movements of the head and eyes to the side opposite the lesion. The attack may develop into a secondary GTCS, and may infrequently result in a temporary limb paralysis (Todd's paralysis).

### Diagnostic features of focal motor seizures

- clonic movements begin focally in the corner of mouth or finger or toe
- spreads slowly to involve face, hand, arm, foot & leg on the same side
- may develop into a secondary GTCS
- may result in a temporary limb paralysis

**Febrile convulsions**

Febrile convulsions are seizures in children which typically occur between the ages of 3 months and 5 years as a result of fever from any cause. They are mostly GTCS in type and are a known risk factor for epilepsy in later life, and in particular TLE. They can cause damage to the temporal lobe that subsequently causes epilepsy. The scarring is mainly in the mesial temporal lobe and can be seen on MRI. The worldwide risk of epilepsy after childhood febrile convulsions is estimated to be 2-5%. In Africa this risk increases to around 10%, particularly after a history of repeated convulsions in malaria. Convulsions complicating malaria are one of the most common reasons for children presenting to clinics and hospitals in Africa. Convulsions occurring in uncomplicated malaria tend to be brief and non recurrent, whereas those occurring with complicated and cerebral malaria are more prolonged, multiple and recurrent, and carry a higher subsequent risk of epilepsy.

**Clinical diagnosis**

The diagnosis of epilepsy is mainly clinical. Epilepsy is difficult to diagnose and there is both under and over diagnosis of the condition. The first principle of diagnosis is to obtain a clear history from the patient and an eye-witnessed account of the episode. This involves the

context in which the attack occurs, the details of the minutes or seconds leading up to and what happened during and after the attack. An attack of a GTCS is diagnostic if it includes a description of the convulsion, incontinence, tongue biting (Fig. 4.1) and post ictal confusion. All of these may not be present in any one patient. The description may alternatively be that of the typical vacant episodes of absence seizures or the aura of a partial onset seizure or of any another type of seizure disorder. If a patient cannot describe what happened, very often it is necessary to interview and record an eye-witnessed account or review a video of the attack if available.

The history from the patient or family should include current illnesses and specific questions concerning known risk factors for seizures including perinatal injury, febrile convulsions, infection, head injury, alcohol consumption and drugs. A detailed family history is helpful particularly in suspected cases of primary generalized seizures. There should be a thorough general and neurological examination. Look for evidence of seizures including tongue biting, scars and evidence of injuries. Patients who have had a single non recurrent seizure are not considered to have epilepsy, they should however be investigated to exclude an underlying cause e.g. toxoplasmosis in HIV, a vascular cause or tumour. The differential diagnosis of epilepsy includes any cause of syncope or loss of consciousness including, pseudoseizures, hypoglycaemia, hyperventilation and transient ischaemic attacks (Chapters 5 & 9). The main differences between epileptic and or non epileptic attacks (pseudoseizures) are summarised below in Table 4.3.

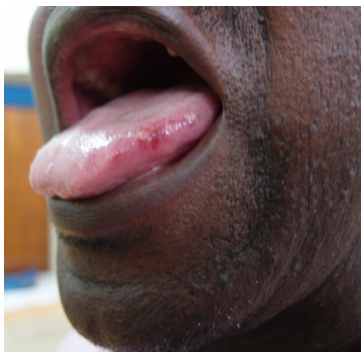


**Figure 4.1** Tongue biting

## Key points

- obtain a clear history from the patient
- get an eye witnessed account of the episodes
- check past & family for any risk factors for epilepsy
- do a general & neurological examination
- look for stigmata of seizure/epilepsy

**Pseudoseizures** (non epileptic dissociative attacks)

Some patients have unexplained GTCS like episodes of loss of consciousness either consciously or subconsciously. The diagnosis should be suspected if there are atypical episodes of loss of consciousness occurring in a teenager or young adult, often female, lasting longer than 5 minutes. These episodes resemble seizures and are considered to be psychogenic or non epileptic in origin and are a major cause of misdiagnosis of epilepsy. There are no absolute criteria to distinguish between pseudoseizures and epileptic attacks clinically (Table 4.3). The attacks can mimic a GTCS and can occur in association with known epilepsy. In high income countries as many as one third of patients with known epilepsy may suffer from a non epileptic attack at some time. During a typical attack there is no tonic phase, there may be shouting and coordinated limb movements particularly involving hyperextension of the back, pelvic thrusting and repeated side to side head turning. There is no post-ictal confusion phase and the patient typically reports no awareness during the attack or memory of the episode afterwards. The

vital signs and neurological reflexes remain normal during the episode. Definitive assessment of a suspected case requires simultaneous co-registration of both the clinical attack and an EEG using telemetry. Management includes reassurance and in particular the avoidance of unnecessary antiepileptic medications. A psychiatric opinion may be helpful in persistent cases.

**Table 4.3** Differences between epileptic and non epileptic attacks

| Clinical features | Epileptic | Non epileptic |
|---|---|---|
| **Sex** | any sex | females > males |
| **Age group** | any | teenagers/young adults |
| **Duration** | minutes | prolonged |
| **Vital signs**<br>**Tonic/post ictal phases** | abnormal<br>present | normal<br>absent |
| **Body movements** | repetitive | stereotyped |
| **Plantar response** | may be up going | normal |
| **EEG** | abnormal | normal |

## INVESTIGATIONS

The diagnosis of epilepsy is primarily based on a clinical description of the seizures. The main aim of investigations is to confirm or exclude the diagnosis, to establish a cause and to classify the type of epilepsy. Routine investigations including full blood count, serum glucose, renal and liver function tests are rarely helpful in screening for causes of epilepsy. However other screening tests should include HIV and other possible local causes of seizures in sub Saharan Africa (SSA) including cysticercosis. Electroencephalography (EEG) and brain imaging are the main methods of investigation of epilepsy.

### Electroencephalography

The EEG is extremely useful in the diagnosis and classification of epilepsy. It is particularly useful if recorded during an epileptic attack, where the finding of epileptiform activity (spikes and sharp waves) confirms the clinical diagnosis. However the majority of EEGs are recorded interictally (between the attacks) when the EEG may be normal (Fig. 4.2). Only about 50% of persons with proven epilepsy have an abnormal first interictal EEG. This percentage can be increased to around 85% with repeated EEG testing, using provocation tests (hyperventilation and flashing lights) and by doing sleep recordings. The finding of a normal interictal EEG therefore does not exclude the diagnosis of epilepsy. By the same token more than 10% of normal persons may have non-specific EEG abnormalities and approximately 1% may have epileptiform paroxysmal activity without clinical seizures. The prevalence of these abnormalities is higher in children, with about 2-4% having functional spike discharges. The EEG is particularly useful in children and young adults where a diagnosis of either primary or secondary seizure disorder is suspected. This is especially true for absence seizures when the characteristic symmetric 3 per second spike and wave pattern is seen in all leads (Fig. 4.3). In partial onset seizures the EEG frequently reveals sharp wave abnormalities originating focally from one area of the brain (Fig. 4.4). In generalized seizures the EEG shows electrical discharges in all leads (Fig. 4.5).

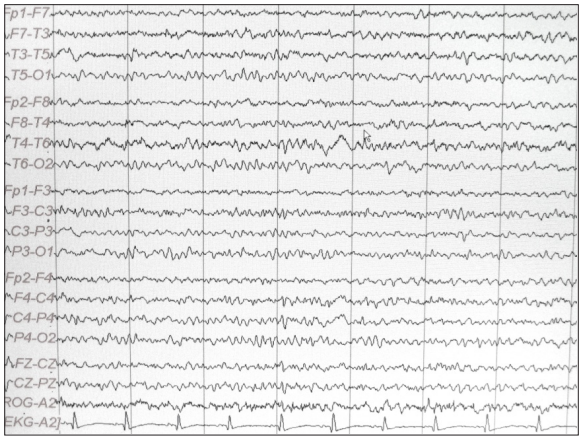



**Figure 4.2** EEG normal

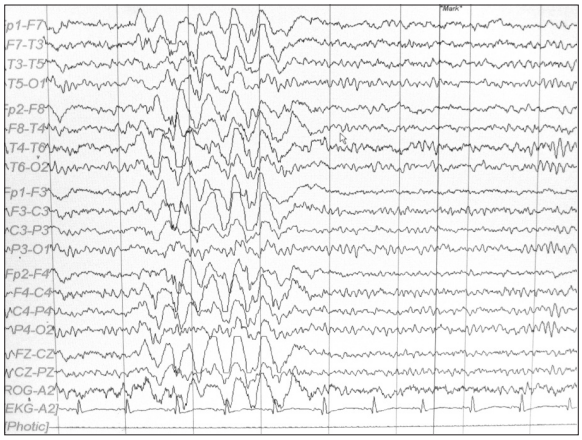



**Figure 4.3** EEG absence seizure. Three per second spike & wave.

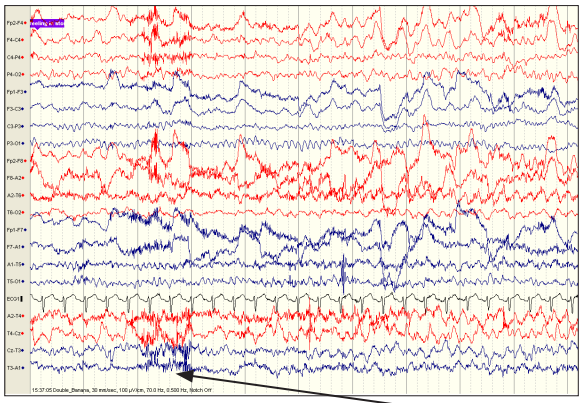


**Figure 4.4** EEG focal seizure. Unilateral right sided electrical discharge.

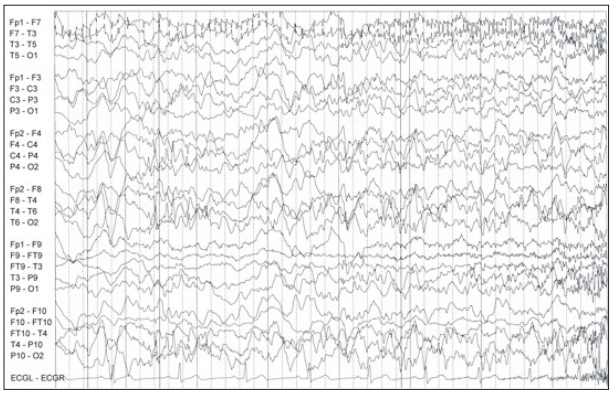



**Figure 4.5** EEG generalized seizure. Bilateral electrical discharge.

## Brain imaging

Brain imaging with CT or MRI is helpful when a focal cause of epilepsy is suspected, particularly in partial onset epilepsies. This is even more so the case in epilepsies of later age onset, 25 yrs or greater because of their likely focal onset. Brain imaging is expected to be normal in most generalized onset epilepsies which occur in a mainly younger age group e.g. teenagers. MRI scanning is more sensitive than CT, and may be necessary to show the underlying lesion e.g. mesial temporal sclerosis (Figure 4.6) in some partial onset seizure disorders.

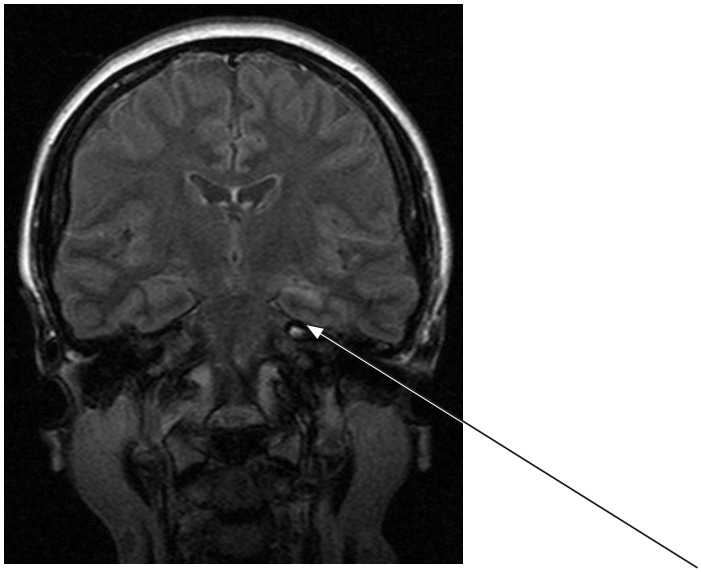


**Figure 4.6** MRI T1. Mesial temporal sclerosis. Sclerosis & contracted hippocampus (left).

### Key points

- aim is to confirm the clinical diagnosis, find the cause & classify epilepsy
- EEG & imaging are indicated in recent new onset seizure disorders
- EEG may be normal initially & need repeating with provocation testing & sleep
- EEG can distinguish between partial & generalized onset seizure disorders
- brain imaging is mostly indicated in new onset partial seizure disorders in adults

## MANAGEMENT OF EPILEPSY

### General advice

Remember that epilepsy has a bad name and has been falsely attributed to witchcraft, spirits, and demonic possession and to contagion in Africa. The sudden unpredictable attacks, the need to take medications every day for years and their side effects and obvious restrictions on social life and occupation make patients feel stigmatized. It is important therefore to listen to patient's and family's anxieties and to explain the nature of epilepsy and its management. Antiepileptic drugs (AED) are usually advised when two or more unprovoked seizures have occurred within the previous 12 months. Patients may require medication for years and sometimes for life, and all the AEDs have side effects. It is important to explain that about two thirds of patients with epilepsy suppress their attacks completely by using a single AED in adequate doses and also that young people with primary generalized onset seizure disorders tend to grow out of their epilepsy in their late teens or early twenties.

The patient should be made aware of the potential triggering effect on seizures of fatigue, sleep deprivation, alcohol, infections and also flashing lights if photosensitive. Driving may be legally restricted nationally and some jobs may be off limits including bus, lorry and train drivers, airline pilots, and the armed forces. Some activities are obviously dangerous to the patients with epilepsy and precautions are necessary, these include fishing, boating, swimming, working at heights, near moving machinery and open fires. Remember that most patients in Africa will visit the traditional healer and receive advice and treatment. Patients with epilepsy are most probably safer when they are with other people.

### Key points

- epilepsy is a very stigmatizing disease
- listen to worries of patient & family & explain the nature of epilepsy
- AED treatment is advised if two or more unprovoked seizures occur within the last12 months
- explain the hazards & restrictions & that AED treatment may need to be taken for life
- 60-75% become seizure free on single AED if taken in adequate doses

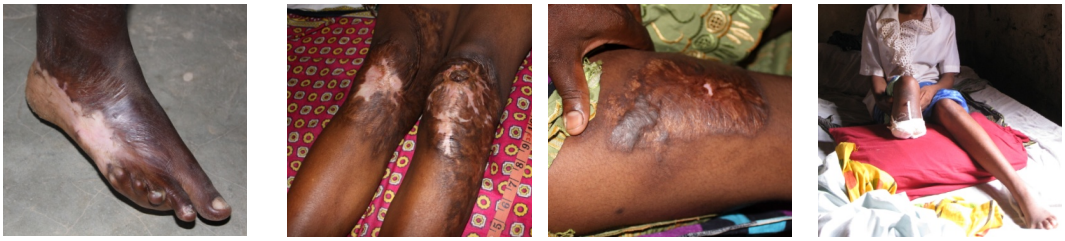
### First aid for seizures

Most tonic-clonic seizures do not require emergency drug treatment. Firstly, avoid injury by removing the patient from any immediate danger e.g. fire, road traffic, water etc. See the scars from burns and scalds in Fig 4.7**.** Do not attempt to force anything between the teeth. Wait until the tonic-clonic phase is over, and then make certain that the airway is clear by extending the neck. Then place the patient on his side in the recovery position to avoid aspiration if he vomits. If the seizure stops and there is a previous history of seizures, then no further medical

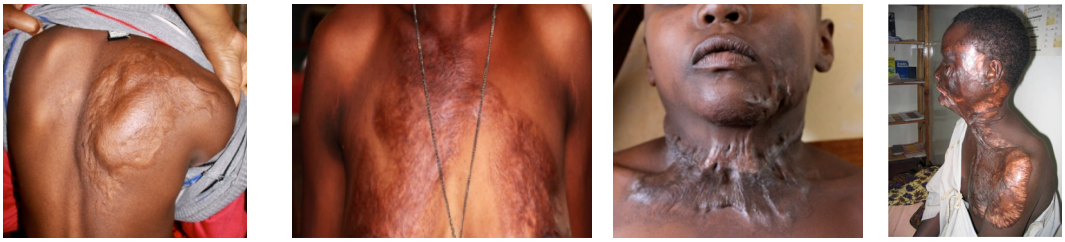
action is required. If the seizure does not cease spontaneously, emergency medical treatment is needed. In children with febrile convulsions, it is important to lower the temperature and treat the underlying cause.

**Upper Limbs**

**Lower Limbs**



**Trunk and face**



**Figures 4. 7** Scars & deformities as a result of burns & scalds

## DRUG TREATMENT

The aim of drug treatment is to make the patient seizure free. The choice of drug is determined mainly by the type of epilepsy. Every effort should be made early on to find the single best drug (monotherapy) available using the smallest dose with the fewest side effects. The main drugs, their indication, dosage and side effects for treatment of epilepsy in Africa are outlined in Table 4.4. Treatment is started at low dose and increased slowly as necessary to an effective maintenance dose, when seizures are controlled or the patient develops intolerable side effects. The single most common reason for failed drug treatment is using insufficiently high doses of medication where necessary. One of the main limiting factors in epilepsy treatment is the side effects of medication. Other reasons for treatment failure include non-compliance due to lack of accessibility and availability of drugs, their cost, and life style including alcohol. However, if seizures still persist despite using an adequate dose of an appropriate single AED, then another first line drug is added withdrawing the first drug only after establishing seizure

control. Treatment is always aimed at making the patient completely seizure-free but this may not be possible in up to one third of patients. Reasons include refractory epilepsy and underlying cause. In these situations when monotherapy is ineffective a group of epilepsy patients will require two and possibly even three drugs in combination (polytherapy). Deaths directly attributed to the AEDs are uncommon (<1:50,000) and are usually caused by early idiosyncratic reactions.

### Key points

- using one drug start slow & aim low
- if seizures are stopped, do not increase the dose any further
- if seizures are not controlled, increase dose as long as no or few side-effects
- if seizures still persist add a second AED
- all drugs prescribed should be available locally

## Drugs

**Phenobarbitone (PHB):** This is indicated for all types of epilepsies and is widely available and used in Africa. WHO recommends it as the first line drug for the treatment of epilepsy in Africa in both children and adults. Phenobarbitone is usually used in previously untreated patients and is particularly useful in status epilepticus because with an adequate loading dose it has a quick effect. It has a long half life and may be used in a single daily dose often taken at night just before sleep. The starting dose for teenagers and adults is usually 60 mg, it can be increased by 30 mg weekly to a usual maximum maintenance dose of either 180 mg once daily or 90 mg twice daily. For children the dose should be calculated by weight at 5 mg/kg. Any reduction in dosage needs to be particularly slow (every 2 weeks) and gradual because of the risk of withdrawal seizures and status epilepticus. The main side effects are sedation, photosensitivity and cognitive/behavioural dysfunction in children. Phenobarbitone is a potent microsomal liver enzyme inducer and decreases the half life of other drugs metabolised in the liver. This becomes particularly relevant clinically with concomitant use of the oral contraceptive pill, where the dose of the pill has to be increased to be effective.

**Carbamazepine (CBZ):** This is used in all types of epilepsy except in absences and myoclonus. It is the drug of first choice for partial onset epilepsies and is very effective. The starting dose is low at 100 mg twice daily increasing slowly by 200 mg increments every 2 weeks until seizures are controlled. The usual therapeutic dose is between 400-1600 mg daily in divided doses. The maximum dose is 2,400 mg daily. Most people respond to a daily dose of 2-400 mg twice or three times daily. The main side effects are drowsiness, ataxia and dizziness which are dose dependent and decrease with time but may limit the dose. The onset of rash and hypersensitivity allergic reaction usually within the first two weeks of starting treatment requires immediate stopping of the medication. CBZ is the least teratogenic of the main AEDs and has a liver enzyme induction effect similar to phenobarbitone.

**Phenytoin (PHT):** This is used to treat all types of epilepsy except absence seizures. Its advantages are that it can be given once daily as a single dose usually at night. Loading with phenytoin is possible in previously untreated patients and in status epilepticus for a quick effect. The usual loading dose is 900 mg and the usual oral starting dose is 200-300 mg daily. The main disadvantage is that it has a narrow therapeutic range and dose adjustments may produce large changes in plasma concentrations and intoxication. Therefore any increase in

dosage should be by small increments of 25-50 mg every 2 weeks up to a usual maximum dose of 400-450 mg daily. If available, the measurement of drug levels can guide dosage. The main side effects are ataxia, drowsiness and dizziness which are dose dependent. The chronic toxicity effects of hirsutism, gum hypertrophy, facial skin thickening and acne limit its long term usage over years particularly in young persons. Liver enzyme induction occurs similarly to phenobarbitone.

**Sodium valproate (SVP):** This is the drug of first choice for idiopathic and generalized onset epilepsies and is also used in partial onset secondary generalized seizures. The starting dose is 200 mg twice daily increasing by 200-400 mg increments if necessary every 2 weeks up to a maximum of 1.4 gm twice daily. The main side effects are nausea, vomiting, tremor, weight gain, hair loss, polycystic ovary syndrome and teratogenesis all of which are dose dependent. Hepatotoxicity is idiosyncratic and may very rarely be fatal. It displaces phenytoin from plasma protein binding which may lead to phenytoin toxicity.

**Ethosuxamide:** This is indicated for generalized absence seizures only. It is given twice daily and the starting dose is 250 mg daily increasing weekly to a maintenance dose of 750-1500 mg in divided doses. The main side effects are nausea, drowsiness, headache and ataxia. Rare idiosyncratic reactions include lupus like syndrome and blood dyscrasias.

### Newer drugs for epilepsy

These include **lamotrigine, levetiracetam** and **topiramate** amongst many others. They are used in people who have not responded or tolerated standard AEDs. **Levetiracetam** is a particularly useful second line drug in adults with uncontrolled focal epilepsies. Information on these drugs is available in larger textbooks and online.

**Table 4.4** Drug treatment of epilepsy in Africa

| Drug | Main indications | Dosage starting | Dosage maintenance | Main side effects |
|---|---|---|---|---|
| **Phenobarbitone** | all epilepsies | 60 mg/po/daily | 180 mg/daily | **sedation**, ataxia, photosensitivity, **cognitive/ behavioural dysfunction** |
| **Carbamazepine** | partial onset epilepsies | 100 mg/po/bd | 2–800 mg/bd | **ataxia/sedation** (dose dependent), **rash**, allergic reaction |
| **Phenytoin** | partial onset/ secondary generalized seizures | 200–300 mg/ po/nocte | 3–450 mg/daily | **ataxia, drowsiness**, dizziness (dose dependent) hirsutism, **gum hypertrophy, facial skin thickening** and acne |
| **Sodium Valproate** | primary generalized and partial onset epilepsies | 200 mg/po/bd | 400–1400 mg/bd | **nausea**, vomiting, **tremor**, **weight gain**, hair loss, **polycystic ovary syndrome**, hepatotoxicity, teratogenesis (dose dependent), |
| **Ethosuxamide** | absence seizures only | 250 mg/po/od | 250–750 mg/bd | **nausea, drowsiness**, headache, ataxia, **blood dyscrasia** |

### Discontinuing of AEDs

AEDs may be effectively withdrawn in some patients who have been seizure free for 2-5 years. This will largely depend on the type of epilepsy, the implications for recurrence and the side effects of medications. There is an increased risk of recurrence in adults particularly between

1 and 2 years after stopping. This risk is greatest in partial onset seizures which are severe. Children who have been seizure free for 2 years off medication tend to remain so. The final decision to withdraw medication must be made by the patient or family and be carried out slowly over months with gradually decreasing doses because of the risk of provoking seizures by too rapid a withdrawal.

## AEDs AND WOMEN

There are some special precautions when using AEDs in women. Carbamazepine, phenytoin and phenobarbitone are all liver enzyme inducers that decrease blood levels of oestrogen and progesterone. In patients taking these AEDs, the dose of oestrogen in the contraceptive pill needs to be increased from 25mg to at least 50 mg in order to be effective and even then contraceptive efficacy is reduced. Depot preparations are less affected by concomitant AED usage. The use of AEDs in women with epilepsy is associated with increased risk of teratogenicity. Women should be counselled about the risks of taking AEDs before becoming pregnant. The rate of major malformations born to mothers taking **valproate, carbamazepine, phenytoin** or **phenobarbitone** is **4-8%**. This risk increases proportional to number of AEDs and the dosage used. Valproate is the most inclined to cause malformations and these defects include the neural tube defects, anencephaly and spina bifida, hole in the heart, hare lip and cleft palate. In order to decrease this risk the total recommended daily dose of valproate in childbearing women is **<1000 mg**.

Best practice is to use a single drug in the lowest effective dose and to offer folic acid prophylaxis before conception. A dose of **folic acid** of 5 mg daily has been shown to decrease incidence of neural tube defects in women not taking AEDs. Note that this dose is higher than the usual prophylactic dose (0.4mg) prescribed with ferrous sulphate in early normal pregnancy. The dose of AEDs may have to be increased in pregnancy particularly during the third trimester and just before delivery because of an increased risk of seizures which happens in about one quarter of patients. Any dose increase can be reversed 6 weeks after delivery.

Vitamin K is routinely recommended in patients taking enzyme inducing AEDs starting one month before delivery and also to the baby at delivery. Seizures occurring in late pregnancy or in the immediate postpartum period should suggest the possibility of eclampsia. In eclampsia, **magnesium sulphate** is the drug of choice in a dose of 3-4 gm iv stat (max 20 gm daily).

### Key points

- oestrogen dose should be increased to 50 mg in some women on AEDs and the pill
- AEDs increase risk of teratogenesis, SVP is the most teratogenic & CMZ is the least
- folic acid 5mg before conception decreases the risk of neural tube defects
- dose of AEDs may need to be increased in the 3rd trimester
- vitamin K is given to mother & all infants if on enzyme inducing AEDs

## STATUS EPILEPTICUS

Status epilepticus is defined as continuous seizures or two or more repeated attacks of GTCS without recovery of consciousness between attacks or an attack lasting longer than 30 minutes. It is a medical emergency with a mortality rate of 10-20% in Africa. Permanent brain damage can occur as a result of hypoxia and acidosis if repeated or single seizures last longer than 30

minutes. The main risk factors in Africa are a history of epilepsy, current infection, suddenly stopping AEDs in particular phenobarbitone, mental handicap and an underlying structural brain disorder.

### Management

The drug treatment of status is outlined in Table 4.5. General measures include ensuring a clear airway with adequate oxygenation (> 95% oxygen saturation) and ensuring an adequate circulation (pulse & BP) and establishing iv access (Chapter 9). A blood glucose should be checked and if low (<2.5 mmols) treated with 50 ml of 50% glucose. Infections are treated. If there is a history of alcohol abuse or poor nutrition then thiamine 100-250 mg should be given iv slowly. Reasons for failure to respond to emergency treatment include inadequate doses of phenytoin or phenobarbital, failure to continue adequate maintenance therapy and the presence of acidosis or an underlying medical disorder.

**Table 4.5** Drug treatment of status epilepticus

| Stage | Drug/route/rate | Comment |
|---|---|---|
| **early status (0-30 mins)** | **diazepam** 10 mg/iv bolus over 2 minutes<br>***or***<br>**lorazepam** 4 mg (0.1 mg/kg) iv bolus over 2 minutes | if seizures continue after 5 mins either one can be *repeated* just once but may cause respiratory depression |
| **established status (30-60 mins)**<br>*(if seizures continue & patient is not on phenytoin or phenobarbitone)* | **phenytoin** iv n. saline infusion of 15 mg/kg (900-1,000 mg total dose) @ 50 mg/min/iv (in N/S over 20 mins)<br>***or***<br>**phenobarbitone** infusion iv 10 mg/kg/@100 mg/min/ over 7-10 minutes (adult total dose is 700 mg) | if iv is unavailable, give phenytoin via nasogastric tube, *(absorption is excellent)*<br><br>if patient is already on phenytoin or phenobarbitone then use half the usual full loading dose<br><br>if seizures stop continue with *maintenance* oral phenytoin or phenobarbitone |
| **refractory status (>60 mins)**<br>*(if seizures still continue)* | involve anaesthesia & proceed to ventilation,<br>Rx **thiopentone** or **midazolam** or **propofol** | if seizures are stopped for >24 hours; stop ventilation & continue daily maintenance dose of phenytoin or phenobarbitone & reinstate regular AEDs |

## PROGNOSIS

The standardised mortality rate worldwide in patients with epilepsy is 2-3 times higher than in the general population and studies suggest that mortality is much higher in Africa, possibly 5-6 times. Some of this is explained by the underlying cause at diagnosis but most is related to the epilepsy itself, its severity and the lack of diagnosis and treatment in Africa. Risk factors for increased mortality include age group, seizure type, frequency and drug compliance. The main causes of mortality and morbidity due to seizures include accidents, drowning, falls and burns. Status epilepticus and sudden unexpected or unexplained death which occurs in epilepsy **(SUDEP)** may each account for 5-10% of all epilepsy related deaths.

### Driving and epilepsy

Patients with epilepsy must not drive unless their seizures are completely controlled by medication. Generally driving is not allowed until the newly diagnosed and treated seizure patient has been seizure-free for at least three months. When AEDs are discontinued, driving again is forbidden until the patient has been seizure-free for at least three months after the last dose of medication. Legal restrictions on driving with epilepsy vary between countries and should be researched and followed.

## TREATMENT GAP

In Africa the vast majority of people with epilepsy (75-80%) do not receive any or adequate treatment for their disease. This is called the treatment gap. Among the reasons for this are the social stigma, poor medical infrastructure, insufficient supply and cost of and accessibility of AEDs, and the scarcity of well informed or trained medical personnel. There are also higher levels of cognitive impairment among the patients with epilepsy. Future plans for intervention must prioritise and find novel ways to encourage the diagnosis and treatment of epilepsy in the community. This is supported by first raising the level of awareness of epilepsy and ensuring that adequate supplies of the first line AEDs are available with clear guidelines concerning their use. These AEDs should be free or affordable and available at sites which are convenient and accessible to the patient. There is also a need to provide and train health care workers and to involve traditional health care workers and patient's supporters and families in the care of the patient.

### Key points

- epilepsy is the most common major community based neurological disorder
- majority do not receive or get adequate treatment
- reasons include stigma, lack of education, resources, manpower & infrastructure
- there is a great need to improve the care of epilepsy in Africa

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