PAPER

*J R Coll Physicians Edinb* 2006; **36**:326–331


# Epilepsy

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**ABSTRACT** Epilepsy is common and has a variety of causes. This article discusses the aetiology of the epilepsies, particularly the genetic causes, and provides up-to-date information on how the condition should be diagnosed, classified, and treated. Some guidance is provided about tailoring the choice of drug treatment according to classification, and the best approach to treatment during pregnancy. Recent data from the UK Epilepsy and Pregnancy register are included. The management of patients with particularly severe and intractable epilepsies is discussed as well as the latest guidelines on the management of status epilepticus. The approach to treatment has to be modified for certain groups of patients, including teenagers and those with learning difficulties. A good service can be provided only if structures are in place to ensure that all patients have rapid and responsive access to advice and information.

**KEYWORDS** Epilepsy, diagnosis, treatment, causes

**LIST OF ABBREVIATIONS** Anti-epileptic drug (AED), electrocardiogram (ECG), electroencephalogram (EEG), International League Against Epilepsy (ILAE), learning disability (LD), sudden unexpected death in epilepsy (SUDEP)

**DECLARATION OF INTERESTS** No conflict of interests declared.

***Published online*** ***June 2006***

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## DEFINITION

An epileptic seizure is an abnormal paroxysmal, synchronised discharge of cerebral neurones sufficient to cause disturbances of movement, sensation, or experience apparent to the patient, the observer, or both. Epilepsy is a chronic brain disorder in which spontaneous recurrent seizures occur. Single seizures, or those with an immediate precipitating cause (e.g. alcohol, eclampsia), are not epilepsy. Syncope causes anoxic seizures which may be confused with epileptic seizures.

Epilepsy is common, with a prevalence of 0·5–1% in the developed world and an incidence of 70–80/100,000 per year. The figures are higher in the developing world, where risk factors such as cerebral infections and infestations are greater.

## AETIOLOGY AND CLASSIFICATION

Epilepsy has a wide variety of causes. It is more helpful to think in terms of 'the epilepsies' rather than 'epilepsy'.

The simplest way to classify the epilepsies is to divide them into generalised epilepsies and localisation-related (focal) epilepsies. Beyond this, there is a complex sub-classification put together by the ILAE.

In the main, the generalised epilepsies have a genetic basis, are relatively benign, and respond to medication (see Table 1, Table 2, and Table 3). They are often termed 'idiopathic'. They are not normally amenable to surgical treatments.

The focal epilepsies are occasionally genetic in origin but are usually due to a variety of acquired structural causes.

In a majority of cases, the structural cause is not identifiable and these epilepsies are termed *cryptogenic*. The severe epilepsies are mainly in this group and may, in certain cases, benefit from surgical interventions.

The archaic terms 'Grand Mal' or 'Petit Mal' should no longer be used.

### *Genetic epilepsies*

Recent years have seen significant improvements in our understanding of the genetic basis of some of the epilepsies. Genetic epilepsies are usually polygenic in origin, but may result from somatic or mitochondrial gene mutations or chromosomal abnormalities (see Table 4). Even when the abnormality is at the level of a single gene, there can be wide phenotypic variation, with individuals carrying a mutation ranging from asymptomatic to having very severe epilepsy, and some having migraine or ataxia rather than epilepsy. What is clear is that no single chromosome or gene is responsible for epilepsy, and the pathophysiology is complex.

Many of the single gene mutations cause abnormalities of ion channel function in the cell membrane; the so-called 'channelopathies'. However, genes exert their influence far more widely than at the ion channel. Neurodevelopmental abnormalities such as neuromigrational disorders, tuberous sclerosis, vascular malformations, and some tumours have a strong genetic basis, and these will cause

**TABLE 1** Aetiologically based classification of epilepsy.

| Symptomatic epilepsy | Identified structural cause |
|---|---|
| Cryptogenic | Structural cause likely but not identified. |
| Idiopathic | Cause not known and structural cause clinically unlikely. |
| Genomic | Specific genetic mutation identified. |

**TABLE 2** Classification of seizures.

| | |
|---|---|
| Focal | Focal sensory, focal motor, other focal seizure types. Secondary generalisation. |
| Generalised | Absence, myoclonic, clonic, tonic, tonic/clonic, atonic and other generalised seizure types. |

**TABLE 3** Causes of epilepsy.

Genetic disorders.

Structural disorders of the central nervous system including:
- Congenital malformations of cortical development;
- Traumatic brain injury;
- Tumours;
- Infections and infestations;
- Cerebrovascular disease and intracranial vascular malformations; and
- Inflammatory disorders (uncommon).

**TABLE 4** Genetic basis of some epilepsies.

**Single gene disorders (1% of epilepsy)**
Benign familial neonatal convulsions (chromosome 20).
Autosomal dominant nocturnal frontal lobe epilepsy (chromosome 15 or 20).
Generalised epilepsy with febrile seizures (chromosome 2 or 19).
Tuberous sclerosis (chromosome 9 or 11).
Many other rare conditions.

**Chromosomal disorders**
Trisomy and deletion of 4p and 13.
Monosomy of 9p.
Down's syndrome (5–10%).
Kleinfelter syndrome (5%).

**Multigenic disorders**
Primary generalised epilepsies:
- Childhood absence epilepsies;
- Juvenile absence epilepsy;
- Juvenile myoclonic epilepsy.

Primary partial epilepsies:
- Benign rolandic epilepsy.

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epilepsy through differing cellular mechanisms. Many epilepsies are caused by external factors such as trauma, infection, and chronic intoxication. Individual vulnerability to these factors is, to some extent, genetically determined, as may be the responsiveness to treatment.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of epilepsy can be difficult and may take time. It is based on a history, from the patient and witnesses, which should include detailed accounts of the clinical manifestations (semiology) of attacks, the context in which they occur, any temporal patterns (duration and spacing of attacks, diurnal variation, or clustering), precipitants, warnings, family history, past medical history and social history. The patient and witness should be encouraged to report what happens before, during and after an attack. A past history of febrile convulsions, non-febrile childhood seizures, head injury or brain infection may be relevant and should be sought. Social factors such as alcohol and illicit drug use are also important. A sleep history will reveal nocturnal convulsions that may otherwise be missed.

The differential diagnosis of epilepsy is wide (see Table 5), and diagnosis is sometimes crucially dependent upon minor details in the history.

If doubt remains on first taking the history, or if a witness account is missing, the patient should be encouraged to keep a diary of attacks and efforts should be made to obtain a witness account. A home video recording may help, though it is often difficult to capture the start of the attack with this. It is unwise to make a snap diagnosis at first consultation, far better to accept uncertainty, gather more information, and wait for events to become clearer. Once a diagnosis of epilepsy is made, it can be difficult to undo, especially if patients have had to give up driving or work, and have become dependent on benefits. Video-telemetry has a role, if seizures continue, and there is real doubt about the nature of the attacks.

In most patients, it is possible to decide whether the epilepsy is primary generalised or focal, and it is helpful to do so since this will guide the choice of medication. Nocturnal seizures are more likely to be focal than primary generalised, whereas seizures occurring on wakening, originating in the teenage years, and exacerbated by alcohol or sleep deprivation, are most likely to be primary generalised. Myoclonic jerks suggest juvenile myoclonic epilepsy. Childhood absence epilepsy produces multiple blank spells in children, but occasional blank spells in adults are usually associated with focal epilepsies.

## INVESTIGATIONS

All patients with suspected epilepsy should have a 12-lead ECG (looking for evidence of an alternative explanation for attacks such as heart block or arrhythmias, including the prolonged QT syndrome), and routine blood tests to exclude a metabolic cause. Serum prolactin measurements are rarely helpful.

All patients with a firm or suspected clinical diagnosis of epilepsy require brain imaging or EEG, or both. Those



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**TABLE 5** Differential diagnosis of epilepsy.

| | |
|---|---|
| Syncope | Panic attacks |
| Non-epileptic attack disorder | Drop attacks |
| Migraine | Narcolepsy |
| Daydreaming | Transient global amnesia |
| Vertigo | Movement disorder |

with a probable primary generalised epilepsy should have an EEG first, and no further investigations are required if the EEG confirms typical features. An EEG cannot exclude epilepsy, and should not be used to diagnose the condition, but it may help classify the epilepsy type once a clinical diagnosis has been made, or to provide additional diagnostic evidence where epilepsy is likely.

All other patients need brain imaging (i.e. suspected focal onset epilepsy or those with possible primary generalised epilepsy but an unremarkable EEG). Magnetic resonance imaging is the ideal choice where available.

More detailed investigations (e.g. sleep-deprived EEG, video-telemetry, functional imaging) may be required in selected cases.

## APPROACHES TO TREATMENT

Drugs are the mainstay of treatment, but should not be prescribed until the diagnosis is secure. Underlying structural or metabolic causes should be treated as appropriate. Patients whose seizures are infrequent and do not interfere with life may prefer not to take medication.

Table 6 shows the most commonly used drugs. If the epilepsy is unclassifiable, a broad-spectrum drug such as sodium valproate should be chosen. Carbamazepine may exacerbate myoclonic jerks and absences.

Monotherapy should be the aim, starting with a low dose and increasing slowly until either the seizures remit, or adverse effects emerge. A single drug should be increased to the maximum tolerated level before abandoning it for another. The routine measurement of serum levels is necessary only for phenobarbital and phenytoin.

If a patient fails to respond to two or three successive drugs in therapeutic doses, and with adequate compliance, he may have drug-resistant epilepsy, or the diagnosis may be incorrect. In this case, combinations of two drugs may be tried. Sodium valproate and lamotrigine work well in combination, but evidence for the effectiveness of other specific combinations is lacking. Polypharmacy tends to be counterproductive, sometimes producing exacerbations in seizures and worsening side effects. Surgery may be appropriate in some cases (see next section).

It is important that precipitating factors such as alcohol, sleep deprivation, and, for some patients, photosensitive triggers, be minimised. Some drugs, such as antidepressants, may exacerbate seizures, and should be used with care.

**TABLE 6** Drugs used in epilepsy.

| Primary generalised epilepsies | Focal epilepsies |
|---|---|
| **Most commonly used drugs** | |
| Sodium valproate | Carbamazepine |
| Lamotrigine | Lamotrigine |
| Phenytoin (in the developing world) | Sodium valproate |
| | Phenobarbital and phenytoin (in the developing world) |
| **New anti-epileptic drugs** | |
| Levetiracetam | Levetiracetam |
| Topiramate | Topiramate |
| | Gabapentin |
| | Oxcarbazepine |
| | Tiagabine |
| | Pregabalin |
| | Zonisamide |

Alternative therapies, such as acupuncture, cannot replace drug treatment, but may have a role in reducing stress and improving wellbeing. This in turn may reduce seizure frequency.

## SPECIAL SITUATIONS

### *Severe intractable epilepsy and epilepsy surgery*

Twenty per cent of patients fail to respond to medication. In these cases, the diagnosis or treatment may be incorrect and should be reviewed. Non-epileptic attack disorder should be considered, particularly where seizures are frequent and prolonged, and where intellectual function is normal between seizures (video-telemetry is the investigation of choice here). Non-neurological, especially cardiac, investigations may be required.

Some patients have genuinely drug-resistant epilepsy and surgery is indicated in a minority of these. This should take place in a specialist centre where close liaison between neurologist, psychiatrist, psychologist, neurophysiologist, neuroradiologist, and neurosurgeon allows adequate workup and aftercare. Investigations such as video-telemetry, standard EEG, invasive EEG techniques, sodium amytal testing, and imaging are used to pinpoint the focus of seizures and establish whether epileptogenic lesions can be safely removed. A few patients with catastrophic seizures will benefit from palliative procedures such as vagal nerve stimulation, corpus callosotomy, subpial resection, or hemispherectomy.

### *Sudden unexpected death in epilepsy*

Patients with epilepsy have a mortality rate 2–3 times greater than that of the population at large. Of these

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**TABLE 7** Treatment of status epilepticus in hospital.

| | |
|---|---|
| **Immediate measures** | Secure airway.<br>Give oxygen.<br>Assess cardiac and respiratory function.<br>Secure IV access.<br>Give lorazepam 4 mg IV or diazepam 10 mg IV.<br>Repeat after 10 mins if no response. |
| **In hospital** | Take blood for electrolytes, LFT, calcium, glucose, clotting, AED levels and storage for later analysis.<br>Measure blood gases.<br>Establish aetiology.<br>Give thiamine or 50% glucose solution if indicated. |
| **Within 30 minutes** | In patients with established epilepsy: give usual AED orally, NG or IV.<br><br>In patients with new-onset epilepsy or if seizures continue:<br>fosphenytoin (18 mg/kg phenytoin equivalent), up to 150 mg/min with ECG monitoring or phenytoin 18 mg/kg, 50 mg/min with ECG or phenobarbital 15 mg/kg IV, 100 mg/min. |
| **Longer than 30 minutes** | ITU may be necessary.<br>Anaesthetise with EEG monitoring.<br>Midazolam, phenobarbital, propofol, or thiopentone most commonly used. |
| **Non-convulsive status** | Augment or reinstate usual AEDs.<br>Consider lorazepam or diazepam IV. |

deaths, 40% are directly related to the epilepsy. Causes include death due to the underlying disease in symptomatic epilepsy, sudden unexpected death, status epilepticus, suicide, treatment, and accidents due to seizures. Sudden unexpected death in epilepsy accounts for 8–17% of these deaths, and is more likely to occur in those with severe drug-resistant seizures. The overall risk of SUDEP is 1/1,000 rising to 1/100–300 in severe drug-resistant epilepsy.

### *Status epilepticus and other emergencies*

Convulsive status epilepticus is a medical emergency. It is defined as a single seizure (or series of seizures without recovery) lasting 30 minutes or more. In individuals known to have epilepsy, warning signs are common in the hours and days leading up to the emergency and should be heeded, since early treatment with benzodiazepines can abort the crisis. Status-prone patients should have protocols in place so that carers know how to act when seizures are more than usually prolonged. Rectal diazepam or buccal midazolam should be used before an ambulance is called. A protocol for treating status epilepticus in hospital is given in Table 7.

**TABLE 8** Mothers with epilepsy: rates of fetal malformation.

| | |
|---|---|
| No AED | 3·5%** |
| Monotherapy | 3·7%** |
| Polytherapy | 6·0%** |
| Total | 4·2%** |
| **Fetal malformation rate associated with individual drugs** | |
| Background rate | 1·2% |
| Carbamazepine | 2·2% * |
| Lamotrigine | 3·2% * |
| Sodium valproate | 6·2% * |
| Phenytoin | 3·7% ** |
| Gabapentin | 3·2% ** |

* narrow confidence intervals
** wide confidence intervals

In adults, apparent status epilepticus is due to non-epileptic attack disorder in up to 50% of cases. This possibility should always be borne in mind, especially in cognitively intact individuals who present with recurrent status. An EEG or, ideally, video-EEG monitoring, should be performed as soon as possible in patients with status epilepticus.

## EPILEPSY, FERTILITY, AND PREGNANCY

Fertility may be reduced in patients with epilepsy for social as well as medical reasons. Enzyme-inducing drugs (e.g. carbamazepine, phenytoin) may reduce the efficacy of combined oral contraceptives.

Pregnancies should be planned. Patients should start taking folic acid, 5 mg per day, prior to conception and continue at least until the end of the first trimester. Anticonvulsant polypharmacy and high peak doses should be avoided. Women on carbamazepine require oral vitamin K in the third trimester of pregnancy to minimise the risk of haemorrhagic disease of the newborn and all women on AEDs should have intramuscular vitamin K in the delivery room.
Breast-feeding should be encouraged. Women who have convulsive seizures will need to breast feed in a safe position, such as on the floor with cushions, and should be supervised when bathing the baby.

Table 8 shows figures from the UK epilepsy and pregnancy register presented at the ILAE meeting 2005.

## EPILEPSY IN ADOLESCENTS AND CHILDREN

Children with epilepsy tend to be cared for in hospital paediatric departments. They will transfer to adult services



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at an age when they are seeking independence from adults, may be starting to resent the limitations imposed on them by their epilepsy, and may not wish to take their medication. New issues such as pregnancy, fertility, and sexual matters will need to be discussed with them and they may prefer this to be done without parents present. Decisions about work and higher education need to be taken. The optimal setting for this transition is a specialised teenage clinic. Many may be able to leave hospital services at this stage. Others can be referred on to appropriate specialists, following assessment at the teenage clinic.

## EPILEPSY AND LEARNING DISABILITY

Epilepsy affects up to 60% of patients with LD. Patients may be intimidated in a clinic environment and time must be taken to put them at their ease and allow them to express their feelings. The best setting for consultations is in or near the patient's home. Where patients are living in a group home, it makes more sense for the clinic to come to them rather than vice versa.

Patients may be incapable of speaking for themselves, so must be accompanied in the clinic by someone who knows them well. It is helpful to issue carers with a checklist so that they know to bring the correct information with them to the clinic. All must be aware of new laws surrounding consent in the incapacitated.

Epilepsy may be very severe, and care must be taken to go through drug changes in a systematic and well-documented way. Polypharmacy should be kept to a minimum, and in some instances, where the patient's epilepsy is genuinely drug-resistant, there is a case for withdrawing medication altogether. Learning disabled individuals will often brighten up considerably on reducing their medication, and their fits may improve. Status epilepticus is a risk in this group. Protocols and training need to be in place so that carers know the early warning signs of status epilepticus and know how and when to administer rescue medication and call for help.

## LIFESTYLE ISSUES AND PATIENT ADVICE

The provision of written information and advice for patients is currently very poor. Patients should have access to a named person whom they can contact by telephone or e-mail at times of crisis, and this may be a nurse or field worker. They need information on a range of issues including driving, employment, medication, first aid, sport and leisure, employment, benefits, contraception, pregnancy and fertility. Much of this information is widely available from the different epilepsy charities in leaflet form or online. Clinicians should ensure that patients have access to this information.

## CONCLUSION – HOW TO RUN AN EPILEPSY SERVICE

Epilepsy is common but is usually well controlled with drugs. Although the initial diagnosis should be made by an epilepsy specialist, follow-up is most appropriately carried out in primary care in a setting close to the patient's home. Learning disabled individuals are best followed up in their own homes, if feasible.

Continuing hospital care is required in only about 20% of adult patients. A good service will provide easy access at primary care level for information and support, regular medical review by the GP or practice nurse, and allow easy and immediate communication between primary and secondary care. For those patients who require ongoing hospital attention, a shared care protocol should be in place. Each region should have a tertiary care centre where the most complex patients are managed, and where specialists should have an active role in training.

As we improve our understanding of the epilepsies, the demand on services will grow. We can ensure the best possible care for our patients only if these structures are in place.

### KEYPOINTS

- Epilepsy is the most common of the serious neurological conditions and has a prevalence of 0·5–1% in Britain.
- Although epilepsy has a wide variety of causes, most cases can be classified as either primary generalised or focal, and treatment is decided according to this simple classification.
- The majority of patients achieve good control with a single AED. However, 20–30% of patients have severe drug-resistant epilepsy.
- An EEG cannot exclude a diagnosis of epilepsy. Accurate diagnosis relies on the history.
- Routine measurement of drug levels is required only for phenytoin and phenobarbital.

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3 Scottish Intercollegiate Guidelines Network (SIGN). Guideline 70. *Diagnosis and Management of Epilepsy in Adults, a National Clinical Guideline*. Published April 2003.

4 National Society for Epilepsy. www.epilepsynse.org.uk

5 Epilepsy Toronto. This is a useful website with a very good reading list. http://epilepsytoronto.org/reading.html

6 Epilepsy Scotland. www.epilepsyscotland.org.uk

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|---|---|
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