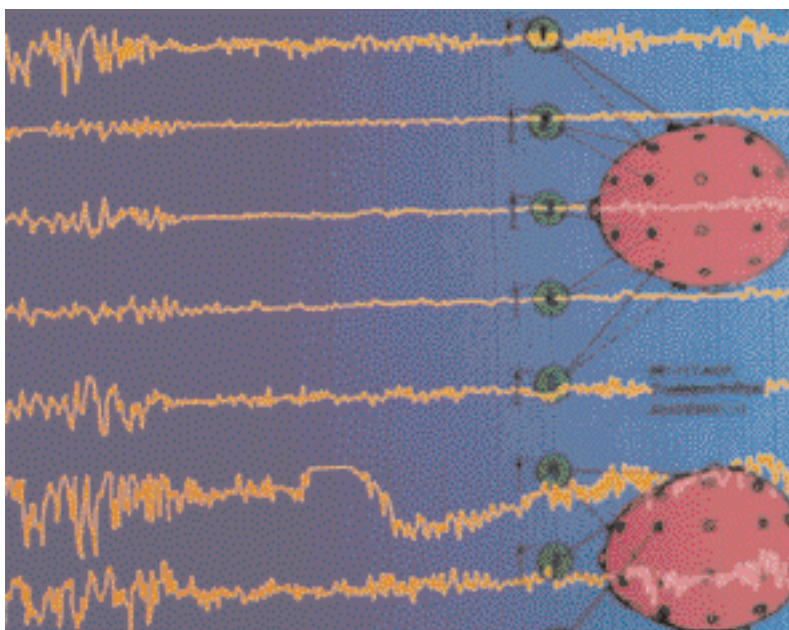


# Epilepsy

## — the aetiology and pathogenesis

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EEG of an epileptic seizure – orange traces show electrical activity in the brain picked up by electrodes placed on different parts of the patient's head

*Epilepsy is one of the most common neurological conditions. In the first article in this month's special feature the authors discuss the classification of seizures, the cellular and genetic basis of epilepsy and some of the known causes of the condition*

**E**pilepsy is the tendency to experience seizures — intermittent, usually unprovoked and stereotyped episodes that result from abnormal electrical discharge of neurons of the cerebral cortex. Seizures can manifest themselves as a motor or sensory disorder, or as altered behaviour, consciousness or emotion. That epilepsy is so variable a disorder reflects the fact that, due to the specialised function of different cortical regions, any individual's symptoms will depend on the area(s) of the brain that experiences abnormal electrical activity.

Furthermore, although epilepsy frequently occurs in isolation, it may be associated with a large number of other conditions. It is also one of the most frequently encountered neurological conditions. Clear descriptions of seizures can be found dating from antiquity (epilepsy is derived from the Greek for “to seize”), and past decades have seen an

explosion of knowledge about the fundamental basis of the condition.

### — EPIDEMIOLOGY

**B**oth seizures and epilepsy are common.<sup>1</sup> Series of epidemiological studies agree that an individual's lifetime risk of a seizure is 2-3 per cent and the prevalence of active epilepsy in economically advantaged countries is 400-600/100,000. The annual incidence of epilepsy is 40-70/100,000 in Europe and North America and, when considered by age, is highest in children (approximately half of all first seizures occur in those under 20 years old). Developing countries show approximately twice the incidence of epilepsy as that in developed countries. This is explained by a higher rate of cerebral parasites and by poorer medical care.

### — CLASSIFICATION

**A**s knowledge of epilepsy has increased, a succession of attempts has been made to codify the various forms of seizures and epileptic syndromes. This approach has

sought to establish uniform terminology, so facilitating communication and further research and allowing targeted treatment of particular variants and conditions. Such classification is evolving constantly and, unfortunately, the process has inherent potential to generate both complex terminology and over-simplification. The International League Against Epilepsy (ILAE) has developed the system of classification that has been most widely accepted, particularly by those with an interest in the field. The ILAE has classified both seizures (the manifestation of the neurological disorder) and syndromes (the disorder itself) (Panels 1 and 2).

The ILAE seizure classification<sup>2</sup> relies on observation, both clinical and electroencephalographic (EEG, the recording of cortical electrical activity), rather than the underlying pathophysiology or anatomy. Seizures are classified as to whether at their onset the abnormal neuronal discharge is confined to one area (partial seizure) or involves the whole cortex (generalised seizure). This distinction is crucial because focal seizures are thought to result from

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## Panel 1: ILAE classification of epileptic seizures<sup>2</sup>

### I Partial seizures

A — Simple partial seizures (consciousness preserved)

1. With motor, sensory or somatosensory symptoms (eg, movements, tingling or visualising flashing lights)
2. With autonomic symptoms or signs (eg, flushing, sweating)
3. With psychic symptoms (eg, déjà vu, structured hallucinations)

B — Complex partial seizures (impaired consciousness)

1. Delayed impairment of consciousness
2. Immediate impairment of consciousness

C — Partial seizures (simple or complex) evolving into generalised seizures

### II Generalised seizures

- A — Absence seizures
- B — Myoclonic seizures
- C — Clonic seizures
- D — Tonic seizures
- E — Atonic seizures
- F — Tonic-clonic seizures

III Unclassified seizures due to incomplete information, or those that do not fit the above categories

entirely distinct mechanisms to primary generalised epilepsy (see below). The classification is then further refined on the basis of the seizure characteristics — for partial seizures, whether consciousness is impaired or not, or whether subsequent (or “secondary”) generalisation occurs, ie, the seizure spreads from the initial site to involve the entire cortex.

By contrast, the ILAE classification of epileptic syndromes<sup>3</sup> makes use of details of the seizure type plus the associated anatomy and aetiology, together with clinical and EEG features of those affected (the age at onset, any family history, a characteristic pattern of discharges, etc). This method considers the assembly of symptoms, signs and associated information as a whole (ie, as a syndrome). Initially, the site of seizure onset is considered (ie, focal/partial or generalised; other categories exist where the onset is uncertain or when seizures are associated with certain situations). Sub-classification is then made on the basis of the aetiology of the seizure as symptomatic (if a distinct cause is identified), cryptogenic (where an under-

lying cause, such as, say, a temporal lobe lesion, can be assumed but not confirmed) or idiopathic (where no underlying cause can be suggested).

Syndromic classification works well when the characteristics of a particular form of epilepsy are specific and easily differentiated from others. With our current knowledge, however, many variants can only be described imprecisely. As a consequence, some syndromes almost certainly represent a large number of different conditions, each with their own distinct aetiology. The syndromic classification also lumps together focal/partial seizures with those that undergo secondary generalisation, again stressing the crucial distinction between that group and primary generalised epilepsy.

Although the ILAE classification of epileptic syndromes has its drawbacks, and to the non-specialist may appear to generate a list of arcane conditions, closer examination reveals that four broad groups of epileptic syndromes exist and that some general comments can be made about each of them. Idiopathic partial epilepsies begin in childhood and are usually benign. Symptomatic partial epilepsies may present at any age, but certain conditions are associated with particular age groups. Idiopathic generalised

epilepsies usually have their onset between childhood and early adult life in otherwise neurologically healthy individuals; they respond well to anticonvulsant medication. By contrast, symptomatic generalised epilepsies typically manifest in infants or young children with neurodevelopmental problems and often are resistant to anti-epileptic drugs even in combination.

Seizure and syndromic classification play an important role in the selection of anticonvulsant medication.

## MECHANISMS OF EPILEPSY

Briefly, neuronal discharge involves the generation across a cellular membrane of a difference in electrical potential (voltage or, more simply, charge — dictated by the number of positive and negative ions present). Neurons exhibit a resting potential between discharges, with the interior of the cell maintained as more negative by the active export of sodium ions. Discharge — the generation of a more positive action potential — involves a complex interwoven process by which ions (sodium, potassium, magnesium, calcium and chloride) flow across membranes under the influence of both inhibitory and excitatory modulators

## Panel 2: ILAE classification of epilepsies and syndromes<sup>3</sup>

### 1 Location related (focal or partial) epilepsies

- 1.1 Idiopathic (with age-related onset)
  - Benign epilepsy of childhood with centrottemporal spikes
  - Childhood epilepsy with occipital paroxysms
  - Primary reading epilepsy
- 1.2 Symptomatic
  - Epilepsy partialis continua
  - Syndromes characterised by seizures with specific modes of presentation
- 1.3 Cryptogenic

### 2 Generalised epilepsies

- 2.1 Idiopathic (with age-related onset)
  - Benign neonatal familial convulsions
  - Benign neonatal convulsions
  - Benign myoclonic epilepsy in infancy
  - Childhood absence epilepsy
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy
  - Epilepsy with generalised seizures on waking
  - Seizures precipitated by specific modes of activation (reading, reflexes)
  - Other idiopathic generalised epilepsies not defined above
- 2.2 Symptomatic
  - 2.2.1 Non-specific aetiology
    - Early myoclonic encephalopathy
    - Early infantile epileptic encephalopathy with suppression burst

- Other symptomatic generalised epilepsies not defined above
- 2.2.2 Specific syndromes/aetiologies
  - Cerebral malformations
  - Inborn errors of metabolism
- 2.3 Cryptogenic
  - West's syndrome
  - Lennox-Gastaut syndrome
  - Epilepsy with myoclonic-astatic seizures
  - Epilepsy with myoclonic absences

### 3 Syndromes undetermined as to whether focal or generalised

- 3.1 With both generalised and focal seizures
  - Neonatal seizures
  - Severe myoclonic epilepsy in infancy
  - Epilepsy with continuous spike waves during slow-wave sleep
  - Acquired epileptic aphasia
  - Other undetermined generalised epilepsies not defined above
- 3.2 Without unequivocal generalised or focal features

### 4 Special syndromes

- 4.1 Situation-related seizures
  - Febrile convulsions
  - Isolated seizures/status epilepticus
  - Seizures occurring only with acute metabolic or toxic event (alcohol, eclampsia, etc)
  - Reflex epilepsy

and the voltage over the neuron's membrane. Afterwards, the cell must regenerate its resting potential difference before it can discharge again.

It is disturbance of this basic physiological mechanism that leads to seizure generation. But at present much remains to be understood of the details of epileptogenesis and no overall explanation yet exists.<sup>4</sup> It does however appear that focal and generalised seizures arise by different mechanisms and so we will consider them separately.

**Focal epileptogenesis** Crucial to the abnormal discharge of neurons is their intermittent but sustained depolarisation — the paroxysmal depolarisation shift (PDS). Generation of a PDS is made more likely by any of three situations, occurring either alone or in combination. First, the excitatory neurotransmitters aspartate and glutamate may be present in excess, relative to the inhibitory gamma-aminobutyric acid (GABA). Secondly, the voltage-gated ion channels of neuronal membranes may be abnormal, favouring the conductance of sodium and calcium to that of potassium, so making the interior of the neuron more positive. Finally, an imbalance may exist between other neuromodulators: dopamine favours neuronal stability but acetylcholine (ACh) enhances depolarisation. Genetic studies have revealed abnormalities in ion channels, GABA and ACh receptors (see below).

For a focal seizure to be generated, neighbouring neurons must be recruited to the same synchronised pattern of discharge. Spontaneous but asynchronous activity ("burst firing") has been demonstrated in certain neurons of the cortex and hippocampus, but how synchronisation occurs remains uncertain. The mechanism by which focal discharges are propagated to other neurons — a chain reaction — is also incompletely understood. It is, however, apparent that propagation demands intact excitatory cortico-cortical connections and a failure of inhibitory regulation.

**Generalised epileptogenesis** Generalised seizures differ from the localisation-related epilepsies. Instead of propagation from one area, generalised seizures involve the entire cortex simultaneously. The basis of this is an abnormality of the looped connection between the thalamus and the cortex. A disturbance of this leads to the development of a generalised discharge (the so-called "spike and wave" phenomenon seen on EEG). While hyperexcitation causes neurons to discharge spontaneously (spikes), this alternates with their heightened inhibition and hyperpolarisation (waves).

In humans it appears that the primary abnormality is hyper-excitability of the cortex. This may follow either a metabolic disturbance (genetically determined, subse-

**Table 1: Monogenic causes of epilepsy (from reference 5)**

Syndrome	Gene and protein	Locus
<b>(a) Autosomal dominant (AD) inheritance</b>		
AD nocturnal frontal lobe epilepsy	<i>CHRNA4</i> , nicotinic ACh receptor subunit	20q13
	<i>CHRN2</i> , nicotinic ACh receptor subunit	1p21
Benign familial neonatal convulsions	<i>KCNQ2</i> , potassium channel subunit	20q13
	<i>KCNQ3</i> , potassium channel subunit	8q24
Generalised epilepsy with febrile seizures plus	<i>SCN1A</i> , sodium channel subunit	2q24
	<i>SCN1B</i> , sodium channel subunit	19q13
	<i>GABRG2</i> , GABA <sub>A</sub> receptor subunit	5q31-33
Juvenile myoclonic epilepsy	<i>GABRA1</i> , GABA <sub>A</sub> receptor subunit	5q34
AD partial epilepsy with auditory features	<i>LG11</i> , leucine-rich, glioma-inactivated 1 (unknown function, not an ion channel)	10q24
<b>(b) Sporadically occurring</b>		
Severe myoclonic epilepsy of infancy	<i>SCN1A</i> , sodium channel subunit	2q24
<b>(c) Uncertain association — only found in some patients</b>		
Febrile and afebrile seizures	<i>SCN2A</i> , sodium channel subunit	2q23-24
Episodic ataxia type 1 with partial epilepsy	<i>KCNA1</i> , potassium channel subunit	12p13
Episodic ataxia type 2 with spike wave epilepsy	<i>CACNA1A</i> , calcium channel subunit	19p13
Juvenile myoclonic epilepsy	<i>CACNB4</i> , calcium channel subunit	2q22-23

quent to hypoxia or pro-epileptic drugs, etc) or a local structural abnormality (see below). Increasing evidence points to a key role for calcium T channels in generating the cortico-thalamo-cortical oscillation. T channels are found at high density in neurons of the thalamus and are activated by relatively low-voltage discharges (as would come from the cortex) after sustained depolarisation.

## GENETICS OF EPILEPSY

As would be expected for such a clinically and aetiologically diverse group of conditions, the genetics of epilepsy are complex.<sup>5</sup> Rarely, families demonstrate the transmission of the same seizure disorder from one generation to the next as a clear genetic trait. In some such kindreds, mutations of single genes have been identified as the cause, and this knowledge has advanced our understanding of how neuronal dysfunction underlies epilepsy (Table 1[a]). It should be noted that, with one exception, the identified genes encode components of ion channels.

Further examination of the monogenic epilepsies reveals other points of interest. Either partial or generalised seizures may result. More than one gene disorder can produce the same phenotype (the physical expression of genetic variation), as seen in juvenile myoclonic epilepsy (Table 1[a and c]). Moreover, even within the same family, proven carriers of mutations may not develop seizures (ie, genetic penetrance) is not complete) and the clinical features of those

that do frequently vary (implying that other factors — environmental or genetic — beyond the single mutation influence the phenotype).

The idiopathic epilepsies are, by definition, of uncertain cause, although a family history may be apparent. First-degree relatives have their risk of developing epilepsy raised approximately two or three times, but clear generation-to-generation inheritance is rare. Studies of monozygotic twins show that single genes of complete penetrance are not responsible. Instead, the heritability of epilepsy (its genetic component, as opposed to that determined by environmental factors) is estimated as 70 per cent. Closer attention to the particular epileptic syndrome may reveal that relatives in fact suffer from distinctly different seizure disorders but it does appear that when monozygotic twins both develop epilepsy, it is highly likely to be of the same type.

A number of attempts have been made to identify shared genetic variants in large numbers of patients with idiopathic epilepsy (association studies, as opposed to linkage analysis, which seeks a shared chromosomal area in affected members of single families). The most statistically significant results have followed restriction of cases to particular subtypes (eg, juvenile myoclonic epilepsy).

Taken together, these observations suggest an overall mechanism whereby rare genetic variants may cause epilepsy by themselves, but are subject to the influence of other genes or environmental factors. Usually, however, epilepsy is the product of several, if

not many, genes plus the environment. Their interactions determine both an individual's susceptibility to epilepsy, and how the seizures appear.

## — AETIOLOGY

We must stress that a seizure is a symptom and epilepsy merely the tendency to experience seizures. Thus the formal diagnosis of an individual's epileptic syndrome involves examining the possibility that a seizure has resulted from some cerebral (or systemic) abnormality — of any nature and that possibly originated some time beforehand.

As medical knowledge has advanced, an increasing number of conditions have been associated with seizures. From the review of classification above, it is apparent that a crucial difference exists between focal and primary generalised seizures, as the former suggest a localised brain lesion. Neuroimaging techniques have improved enormously in recent decades with CT and now MRI scanning becoming essentially routine investigations. As a consequence, more and more focal abnormalities can be diagnosed. An increased recognition of inborn errors of metabolism means that the relative proportion of epilepsies that can be classified as symptomatic has increased. Despite this, no specific aetiology will be found for the majority of patients currently diagnosed with epilepsy. We will briefly review some of the known causes below.

**Perinatal causes** *Malformations/dysgenesis* — As well as gross abnormalities, it has become apparent that many people with drug-resistant epilepsy have more subtle disorders of brain structure, in particular sclerosis of the mesial temporal lobe. In such cases, neurosurgery may be considered, in which the epileptic focus is excised.

*Hypoxic-ischaemic encephalopathy* — This is the most frequently encountered cause of seizures in the neonate, and is most common in term or post-term births. Asphyxia causes cerebral white matter infarction and necrosis.

*Cerebral haemorrhage* — Peri- or intra-ventricular bleeding is more common in premature infants.

**Hereditary conditions associated with epilepsy** More than 200 conditions have been associated with seizures that are the result of either single or multiple gene defects. These disorders may produce a structural lesion (such as neurofibromatosis, tuberous sclerosis), a metabolic disorder (eg, Baltic myoclonus — mutation of a protease inhibitor, cystatin B, that causes myoclonic epilepsy) or a complex neurodevelopmental

syndrome in which the mechanism of epilepsy is complex or uncertain (eg, Fragile X syndrome and Angelman's syndrome).

**Infections** A host of congenital infections, both viral and bacterial (for example, rubella, cytomegalovirus infection, syphilis, toxoplasmosis), can cause epilepsy subsequently. In later life, but especially childhood, other conditions become more significant and together account for 2–3 per cent of all cases. The severity of infection and the age at which illness occurs are important in determining whether or not epilepsy will result.

*Bacterial meningitis* — Epilepsy is more likely to develop where there are extremes of age, seizures during the original illness, delayed treatment or severe illness (bacteraemia, coma).

*Intracerebral abscess* — Infections may arise in the brain from either local sites (sinuses, middle ear, after skull fractures) or via the blood (from endocarditis, the lungs or in drug-users). Focal seizures are the most common sequelae.

*Viral encephalitis* — Herpes simplex has a predilection for the temporal lobes but other viruses can also cause direct damage to the brain parenchyma. Presumably as a result of this, the risk for later seizures is higher than with bacterial meningitis.

*HIV infection* — Although recent advances in antiretroviral therapy have greatly improved the outcome for people with HIV infection, those infected carry a greater risk of seizures. HIV can cause a primary encephalitis, lead to secondary infections (especially toxoplasmosis), and increase the risk of cerebral lymphoma, all of which can cause seizures.

*Tuberculosis* — Although the common presentation of central nervous system infection by TB is an insidious meningitis, focal seizures from cerebral tuberculomata may be the first manifestation of the disease. Tuberculomata may develop during treatment and brain scanning should be considered if seizures occur later.

*Neurocysticercosis* — The tapeworm *Taenia solium* is endemic in many parts of the world. Its definitive host is the pig but when cysts are eaten by humans (typically through eating unwashed vegetables contaminated by excrement, rather than meat itself, because cooking kills the cysts) they will develop in multiple organs, including the brain. Cysticercosis is consequently one of the most common causes of epilepsy in developing countries. Early administration of praziquantel can be curative, but later calcification of cysts may continue to act as an

epileptic focus after treatment.

**Head injury** The risk of post-traumatic epilepsy is related to the nature and severity of the cerebral insult: penetrating wounds carry a worse prognosis than closed trauma, and the degree of injury (length of unconsciousness and amnesia, plus any brain damage) correlates with the later risk of seizures. No benefit has been demonstrated for giving anticonvulsants prophylactically.

**Brain tumours** Tumours are a rare cause of epilepsy but frequently present with seizures. The chance that a first seizure is so associated increases with the age of the patient. Tumour-associated seizures are often difficult to treat with antiepileptic medication. Cerebral secondaries from other cancers (notably lung, breast and melanoma) are more common than primary intracerebral tumours (principally malignant gliomas or primary cerebral lymphomas, benign meningiomas).

**Cerebrovascular disease** *Stroke* — Stroke is the commonest cause of epilepsy in the elderly, accounting for around one-third of new seizures in those over 60. Cerebral infarcts are the most common type of stroke (85 per cent) but are less likely than haemorrhages to cause epilepsy.

*Arteriovenous malformations* — Anomalous vascular development leads to direct communication of arterial and venous circulations as a tangle of blood vessels. The malformations have a 1–2 per cent annual risk of haemorrhage and commonly present in this way but may also present with focal epilepsy.

*Venous sinus thrombosis* — This is an uncommon disorder, in which thrombosis occurs in the sinuses that drain venous blood from the brain. It is often idiopathic but favoured by hypercoagulability, pregnancy or sepsis. Epilepsy is a frequent presentation or complication.

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