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First seizures in adults

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- Endometriosis (*BMJ* 2014;348:g1752)
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A seizure is a clinical manifestation of presumed or proved abnormal electrical activity in the brain. A first seizure can range from a fleeting subjective experience such as déjà vu or a twitch (myoclonic jerk) through to a tonic-clonic convulsion. Some seizure manifestations overlap with normal phenomena. A single seizure may be provoked (with an acute precipitant that may or may not recur) or unprovoked (idiopathic or of unknown cause). Epilepsy is defined as more than one seizure.

This article focuses on the diagnosis of first seizures and differentiation from their "mimics" in adults. The diagnosis is correct in only two thirds of cases or less and relies almost exclusively on the clinical history.[1-9] Information for patients, particularly regarding risks of recurrence, investigation and treatment, driving, and mortality, will be discussed.

This review uses older seizure terminology,[10 11] as this is better understood by most readers and succinctly conveys important clinical concepts. Where the revised terminology differs, this is noted in the text and the supplementary table.[12]

How common are first seizures?

Few data about the frequency of minor (non-convulsive) first seizures exist. Many minor first seizures are unrecognised. The recorded incidence of first seizure (provoked and unprovoked) in Europe is approximately 70 per 100 000 per year,[13 14] with twice that incidence in poorer countries.[15-17] Febrile seizures are the "first seizure" with the highest worldwide incidence (50 per 100 000 per year), usually occurring in the first three years of life.[18]

The cumulative lifetime incidence of single seizures and recurrent epileptic seizures (including febrile seizures) is estimated as 5-10%.[19 20] The prevalence of epilepsy is between 0.5% and 1% of the population.[20] Epileptic seizures are responsible for 1% of hospital admissions and 3% of emergency department attendances.[21]

First seizures are not always declared in epidemiological questionnaires,[22 23] because of social stigma, fears about losing the driving licence, and concerns about employment.[24 25] Few epidemiological studies of provoked seizures have been done, as episodes are often indexed under their provocation (for example, alcohol withdrawal or head injury) rather than seizure and may not reach neurological attention.[26]

Transient loss of consciousness is the most commonly recorded and studied presentation of "first seizure." In 2005-06 100 000 hospital attendances in the United Kingdom were for transient loss of consciousness.[27] The table summarises the causes of transient loss of consciousness from several descriptive studies. These include epileptic seizure, syncope, and non-epileptic attack disorder.

Diagnosing a first seizure: how do people present?

In addition to the patient's history, an eyewitness account is very important and should be sought whenever possible. The patient's and eyewitness's histories are not only critical for diagnosis of the event. The "first seizure" may be a major event after other missed minor epileptic events, so that the diagnosis is epilepsy rather than a single seizure.[8 9] Clinically, clarifying whether the first seizure occurred with or without loss of awareness or consciousness is useful.

Seizures without loss of consciousness

The brief duration and a clear description of the experience define these seizures, which patients often do not recognise as important. If patients present, it is often to primary care. Early recognition allows for correct management and may change the diagnosis from a single seizure to epilepsy.

Myoclonus

Myoclonus is a sudden irregular jerk caused by involuntary muscle activity, involving the trunk or one or more limbs. Many causes of myoclonus exist—it may be physiological or pathological. In primary care, it is important to be aware of hypnic myoclonus (physiological) and acute causes related to drugs and to refer other patients with myoclonus (including seizures). Myoclonus in the awake state usually requires specialist assessment. Hypnic (night time) myoclonus is the most common form of myoclonus, experienced as a jolt, which may be dramatic and awaken the person, on drifting into sleep. Most of us have experienced

SUMMARY POINTS

First seizures range from a brief subjective experience (aura) to a major tonic-clonic seizure

Up to 10% of people living to 80 years of age have one or more seizures; half of these are febrile convulsions

In 85% of patients, the diagnosis comes from the history; blood tests, electrocardiography, electroencephalography, and sometimes magnetic resonance imaging are important for classification and risk prediction

50% of patients with an apparent "first seizure" have had other minor seizures, so their diagnosis is epilepsy

Low risk patients with first seizures have no neurological deficits, normal magnetic resonance imaging and electroencephalography, and a 35% risk of recurrence at five years; they are not usually offered treatment

High risk patients with first seizures have neurological deficit, magnetic resonance imaging and/or electroencephalography abnormalities, and a 70% risk of recurrence at five years; they are offered treatment

SOURCES AND SELECTION CRITERIA

I consulted my personal archive of references and searched Medline and the Cochrane Collaboration and Clinical Evidence databases, using "seizure", "first seizure", and specific topics. I also consulted the National Institute for Health and Care Excellence's guidelines. I carefully examined randomised controlled trials, systematic reviews, and meta-analyses. Ranges of results are used in preference to averages, because pooling results from methodologically diverse studies is not accurate

Causes of transient loss of consciousness. Values are numbers (percentages)

Cause	Eagle, 1985—?syncope; emergency department*	Day et al, 1982—first episode (LOC); emergency department†	Angus-Leppan, 2008—first and recurrent episode (LOC); neurology clinic‡	Angus-Leppan, 2013; emergency department§
Syncope—all	—	—	40 (25)	—
Syncope—vasovagal	64 (35)	57 (29)	—	30 (35)
Syncope—orthostatic	16 (10)	7 (3)	—	—
Syncope—cardiac	15 (9)	17 (9)	—	10 (12)
Epilepsy	2 (1)	58 (29)	68 (43)	20 (23)
Non-epileptic attack disorder	3 (1)	14 (7)	19 (12)	10 (11)
Other	7 (5)	20 (10)	11 (7)	—
Unknown	69 (39)	25 (13)	20 (13)	16 (19)
Total	176	198	158	86

LOC=loss of consciousness.
*Patients with first and recurrent events.[90]
†Patients with first events only.[1]
‡Patients with first and recurrent events.[4]
§Patients with first events only (unpublished).

this at least once, and patients can be reassured that this is a normal phenomenon.

Aura (simple partial subjective seizure)

Epileptic auras are brief (seconds only) and should be distinguished from migraine auras, which usually last several minutes. They can be autonomic, usually a rising epigastric sensation, lasting seconds. Psychic epileptic auras such as déjà vu are often unpleasant and out of the realm of any normal experience, sometimes intensely so; they may involve distortions of time or a feeling of separation or depersonalisation. Déjà vu (already seen) and jamais vu (never seen) refer to a false impression that a present experience is familiar. An aura is designated as a "focal seizure without impairment of consciousness or awareness involving subjective sensory or psychic phenomena only" in the revised classification.[12]

Simple partial motor seizure

These are clonic (regular shaking), tonic (stiffening), or dystonic (spasm), usually in a distal limb, and are usually brief (lasting seconds). Rigors can be mistaken for a first seizure, particularly in children.[30] A simple partial motor seizure is designated as a "focal motor seizure without impairment of consciousness or awareness" in the revised classification.[12]

Seizures with loss of consciousness

Absences

Previously referred to as "petit mal," these last seconds or less, with disruption of awareness, activity, and sometimes learning. They may happen many times a day. A motionless stare, sometimes with eyelid fluttering, may be observed. They start in childhood but continue into adulthood in 7-80% of cases. They are more likely to persist to adulthood if onset is in later childhood or in adolescence, if they are difficult to treat, and if they are associated with other types of seizures.[31]

Complex partial seizure

Some impairment of awareness, consciousness, and/or memory of the event occurs during a complex partial seizure.[10] These sometimes evolve from an aura (simple partial seizure). They may be a motionless stare or automatisms (automatic involuntary movements) such as lip smacking, fiddling, and rubbing or pseudo-purposeful movements. Episodes last for seconds to minutes, and communication is usually impaired. These are designated as "focal seizures with impairment of consciousness or awareness" in the revised terminology.[12]

Tonic-clonic seizure (convulsion)

Tonic-clonic seizures may have no warning (if generalised from onset) or may start with an aura (if focal with secondary generalisation) before consciousness is lost. Often an initial cry is followed by a loss of tone and a fall, then a phase of tonic rigidity followed by regular rhythmic shaking in all limbs, trunk, and face, lateral tongue biting, and cyanosis. Eyes are usually open.[33 34] The usual duration is 1-2 minutes, and postictal confusion (a period usually longer than 10 minutes characterised by disorientation, poor concentration, poor short term memory, and decreased verbal and interactive skills) occurs.[10]

Differential diagnosis of transient loss of consciousness

Up to 35% of people will experience at least one episode of transient loss of consciousness by the age of 60 years.[35] The differentiation of tonic-clonic seizures from syncope and non-epileptic attack disorder is discussed below. This may be difficult, particularly if no eyewitness account is available. No single clinical feature or investigation is pathognomonic.

Postictal confusion,[7 34 36] cyanosis,[36] lateral tongue biting,[36] preceding déjà vu or jamais vu,[36] confirmed unresponsiveness,[36] head or eye turning to one side,[7 36] and rhythmic limb shaking or unusual (dystonic) posturing are strong seizure markers.[34 36] Seizure is five times more likely than syncope if the patient has postictal confusion characterised by disorientation ($P<0.001$).[7] Patients themselves are poor judges of their own postictal confusion, and the eyewitness account is crucial for this information.[7] Incontinence and injury do not discriminate between seizure, syncope, and non-epileptic attack disorder.[7]

Syncope

Transient loss of consciousness is much more commonly caused by syncope, particularly reflex (vasovagal) syncope, than by seizure. Many cases will not reach medical

attention. Prodromal blurred vision, sweating, dizziness, dyspnoea, nausea, or palpitations,[7 36 37] precipitation by prolonged sitting or standing,[36] and pallor during the episode are common.[34] If movements occur, they are usually brief, often myoclonic jerks. However, syncope can sometimes be convulsive with tonic-clonic movements, owing to cerebral hypoxia, particularly if the patient is not able to assume the horizontal position.[38] Eyes are usually open in both syncope and epileptic seizures but not in non-epileptic attacks.[33 38 39] Nausea or sweating before the event make seizure much less likely than syncope.[7] Cardiac syncope may be an apparently bland event, with no prodrome, brief loss of consciousness, and pallor, sweatiness, or clamminess, followed by rapid recovery. Cyanosis strongly suggests cardiac rather than reflex syncope.[7] Cardiac syncope due to arrhythmia or structural abnormality of the heart doubles the standardised mortality ratio and needs urgent investigation.[37]

Non-epileptic attack disorder

These are episodes resembling seizures but caused by psychological or psychiatric illness. They are also called non-epileptic seizures, dissociative seizures, or psychogenic non-epileptic seizures and were previously called pseudoseizures or hysterical seizures (but they are not seizures). Sometimes the term "non-epileptic attack" is misused for any event that is not epilepsy (including syncope, psychiatric or psychological events, and migraine)

Non-epileptic attack disorder occurs in about 12-18% of people with transient loss of consciousness,[40] can be difficult to diagnose and manage, and presents in many forms. A successful outcome is more likely when the diagnosis is made early.[41] Key features are prolonged apparent loss of consciousness with normal colour or oxygen saturation on room air, fluctuating motor activity, asynchronous movements, pelvic thrusting, side to side head or body movements, ictal crying, some responsiveness such as resistance to eye opening, memory recall, and rapid post-event recovery. If the event is one of prolonged shaking and apparent loss of consciousness (more than 10 minutes) and the patient retains normal colour, the event is almost never an epileptic seizure.

Who is most at risk?

Worldwide, social deprivation is closely associated with first seizures and epilepsy.[48] Young people and older people are at the highest risk for first seizure (as well as for epilepsy).[18 49] The frequency and cause of first seizures also vary in different economic and geographical settings.

Provoked seizures in early life are usually febrile convulsions,[50] caused by viral infection in 80%, with 8% due to meningitis (viral or bacterial).[51] Unprovoked remote symptomatic seizures in children are more commonly due to prenatal than postnatal factors.[13] An unprovoked idiopathic (presumed genetic) first seizure occurs in childhood or teenage years, commonly with a family history of idiopathic epilepsy.[52]

Worldwide, in adults, infections such as acute meningitis, encephalitis, malaria, HIV related disease, and cysticercosis are common causes of first seizures.[53] Provoked seizures due to intoxication and withdrawal from alcohol are also frequent.[13 54] In later life, vascular disease becomes the most common cause.[55] Brain tumours, including metastases, are responsible for about 4% of first seizures.[13] Paradoxically, lower grade primary tumours are more likely to present with a seizure than are higher grade ones.[56]

How should first seizure be managed?

Following a first seizure of any kind, all patients should be referred to a specialist for investigation. In the UK, patients with a first seizure see a wide range of health professionals including paramedical officers, emergency department nurses and doctors, primary care doctors, neurologists, other physicians, and specialist nurses, or none at all in at least 25% of cases.[48] If a tonic-clonic seizure is witnessed then stabilisation, removal of surrounding dangers, and examination for acute factors (including blood glucose, metabolic disturbance, sepsis, toxins and withdrawal states, acute stroke, and brain injury) are the starting points. If the tonic-clonic seizure lasts longer than two minutes, benzodiazepines (such as rectal diazepam, buccal midazolam, or intravenous lorazepam) are usually given as rescue medication. Admission is needed if the seizure recurs or continues, an underlying cause requiring acute treatment exists, level of consciousness is reduced, a neurological deficit is present, or social support for discharge is inadequate.[57] A provoked (acute symptomatic) first seizure with a trigger may need urgent treatment (such as for infection, encephalitis, metabolic disturbance, toxicity, haemorrhage). Remote or progressive symptomatic causes (such as chronic cerebrovascular disease or brain tumour) may also need treatment. A single seizure without loss of consciousness does not usually need any first aid.

Why is investigation after first seizure important?

When the history has not clarified whether the event was a seizure, the investigations are unlikely to do so. Retaking the history from the patient and from eyewitnesses is often more useful. Clinical assessment contributes more than 85% of the diagnostic yield in transient loss of consciousness.[1 4] Warning patients that investigations are unlikely to change the clinical diagnosis and may all be normal, even with a firm diagnosis of an epileptic seizure, is important.[4]

After a first seizure, further seizures (that is, epilepsy) occur in between 6% and 82% of patients.[18 58] Averaging these figures does not allow prediction of the risk for an individual. Thorough clinical assessment and investigations help to establish the type of seizure, cause, and recurrence risk. Provoked seizures are more common in people with an underlying genetic or other tendency to epilepsy,[52] and a single trigger (such as alcohol) should not be assumed to be the only cause.

What investigations are needed after first seizure in acute setting?

The most important initial tests in the acute setting are blood glucose measurement (for hypoglycaemia or hyperglycaemia) and electrocardiography. Electroencephalography is mandatory in anyone with loss of consciousness, as syncope of any cardiac cause may present as a secondary hypoxic seizure, and potentially fatal arrhythmias,

particularly long QT syndromes (Brugada syndrome), will otherwise be missed.[59] Cardiac disease is the most common cause of non-traumatic sudden death in young people, sometimes preceded by potentially treatable cardiac syncope.[60]

Other blood tests will exclude hyponatraemia or hypernatremia, hypocalcaemia or hypercalcaemia, hypothyroidism, uraemia, liver failure, anaemia (which can trigger syncope), leucocytosis (suggesting infection, although mild leucocytosis can occur after a seizure), and eosinophilia (a clue to parasitosis, an important cause of a first seizure in many parts of the world).[48] Although the yield of blood tests is low,[1 4 59] they are needed to determine whether the seizure is provoked.[50]

What investigations will be done at early specialist follow-up?

Early specialist assessment by a neurologist can reduce investigations, improve diagnostic accuracy, and save time for the patient.[4 61] If, for example, the neurologist revises the diagnosis from seizure to reflex syncope, no further investigations are needed beyond the blood tests and electrocardiography.

Electroencephalography is useful in suspected first seizure for predicting recurrence and in classification of the seizure (idiopathic generalised or focal). Yield is highest in the first 24 hours after the seizure.[9] Relevant abnormalities (spikes and/or slow waves)[59 62] are found in 8-50% of cases.[59]

Is brain imaging needed in all first seizure patients?

Many guidelines advocate magnetic resonance imaging in all first seizure patients.[59] However, no sound justification exists in idiopathic epilepsy presenting at a young age. For example, in an 18 year old with a single convulsion, previous early morning myoclonic jerks, normal neurological examination, and an electroencephalogram with 3/second spike and wave discharges, the diagnosis of juvenile myoclonic epilepsy (idiopathic) is clear cut. Relevant lesions on magnetic resonance imaging are not found in patients with electroencephalogram proved idiopathic epilepsy. Magnetic resonance imaging can be safely restricted to first seizure patients without clinical or electroencephalographic evidence of idiopathic epilepsy.[65] Overall, magnetic resonance imaging has a yield of 10% in first seizures and is superior in resolution to computed tomography scanning, especially for temporal lobe epilepsy.[59]

Computed tomography scanning is useful for first seizure patients with acute head injury or patients with reduced level of consciousness. It is safer and faster than magnetic resonance imaging for acutely unwell patients,[65] and it may influence acute management in 9-17% of patients.[66]

Is this a first seizure and will it recur?

This is a critical question. The first step is to go back to the history. Up to half of people with a "first seizure" have historical evidence of non-convulsive seizures or nocturnal seizures (bed wetting, tongue biting, blood on the pillow, early morning headache, or "hangover" without alcohol), which suggests that the diagnosis is epilepsy.[8 9 13 67]

Studies with varying methods and follow-up from two to 26 years estimate the risk of recurrence after a first seizure to be between 6% and 82%.[68 69] Maximum recurrence risk is within the first 3-6 months.[8 18] For the individual patient, predictive factors need to be examined. For example, after a febrile convulsion, the risk of developing epilepsy is 6%, reducing over time.[68] Neurological deficits (prenatal injury, neurological deficit, intellectual disability) or relevant magnetic resonance imaging or electroencephalographic abnormalities (spikes, slow waves, or both) are the strongest predictors of recurrence across many studies.[70] For patients with one or both of these factors, the risk of recurrence is 70% over five years.[71] For patients without these factors, recurrence is estimated at 35%.[70 71]

To treat or not to treat?

After a first seizure, the default position is not to give antiepileptic drug treatment. We offer treatment to first seizure patients with a high risk of recurrence, because of known neurological deficit, a magnetic resonance imaging or electroencephalographic abnormality, or individual factors.[72] These include risk of fracture or injury, social isolation, and the need to return to driving as soon as possible.

What follow-up is recommended after first seizure?

Specialist review and investigations are recommended for first seizure patients within four weeks.[65] Unless the diagnosis is revised to syncope, follow-up with results will usually occur after about three months, earlier if abnormalities are found. Further specialist follow-up depends on the estimated risk of recurrence, whether drug treatment has been started, and other individual factors. Many patients with a first seizure and normal investigations will be discharged to primary care, with specialist review if a further event occurs. Patients may remain concerned, even after explanation, when told that they have had a seizure and they cannot drive but their tests are normal and they do not need further specific treatment or specialist follow-up. Primary care physicians have an important role in further explanation, particularly in the significant minority of first seizure patients in whom the diagnosis may trigger depression and anxiety.[76]

What should we advise with regards to driving?

Driving is often a great concern to patients with a first seizure.[77] People with epilepsy have 40% more serious road traffic accidents than do other people.[78] Initial advice to the first seizure patient should be not to drive until medically advised otherwise, whether or not the diagnosis is certain. First seizures should be reported to the Driver and Vehicle Licensing Agency (DVLA) in the UK or the equivalent body internationally.

Driving regulations vary considerably between, and sometimes within, countries. In the UK, decision making is centralised.[79] The regulatory body, the DVLA, gathers information from treating doctors, with the advantage of separating the therapeutic relationship and decision making about driving. New regulations allow some patients with only simple partial seizures to drive. If the first seizure is unprovoked, investigations are normal, and no neurological deficit is present, driving will usually

QUESTIONS FOR FUTURE RESEARCH

What are the recurrence rates of defined seizure types analysed by their cause?

What is the optimal management strategy for first seizure patients, particularly regarding antiepileptic drugs?

When should we treat provoked seizures with antiepileptic drugs?

Are first status epilepticus and multiple seizures a "first seizure" or epilepsy?

What causes sudden unexpected death in epilepsy and what prevents it for first seizure patients?

How can we improve the way we advise first seizure patients on lifestyle and safety?

TIPS FOR FIRST CONTACT DOCTOR

After stabilisation of a patient with a first seizure, take a careful history from the patient and eyewitness(es)

Blood tests and electrocardiography are important, especially for hypoglycaemia and arrhythmias

Advise the patient not to drive and not to bath alone; give details of educational resources (see box)

Refer to a specialist for early review (further assessment, tests, and antiepileptic drugs if indicated)

be permitted after six months. Otherwise, driving is usually permitted after 12 months seizure free. Commercial licences are subject to more stringent regulation.[79]

Should we warn all patients about sudden unexpected death in epilepsy?

In the UK, specialists are mandated to discuss sudden unexpected death in epilepsy with all patients with epilepsy,[65] but not for first seizure patients. Only 5% of neurologists discussed sudden unexpected death in epilepsy with all patients; 60% discussed it with some, usually high risk, patients or those who specifically asked about it.[86] The standardised mortality rate after a first seizure is about 2.3,[87] which overlaps with the 2-4 described for epilepsy.[88] If we discuss sudden death with patients with epilepsy, we should also do so with patients with first seizures and those with cardiac syncope. Discussing sudden unexpected death in epilepsy at the first visit is not always appropriate, as there is much to discuss and sometimes a risk of information overload. Content and timing of this discussion must be individualised to prevent a negative psychological effect.[89]

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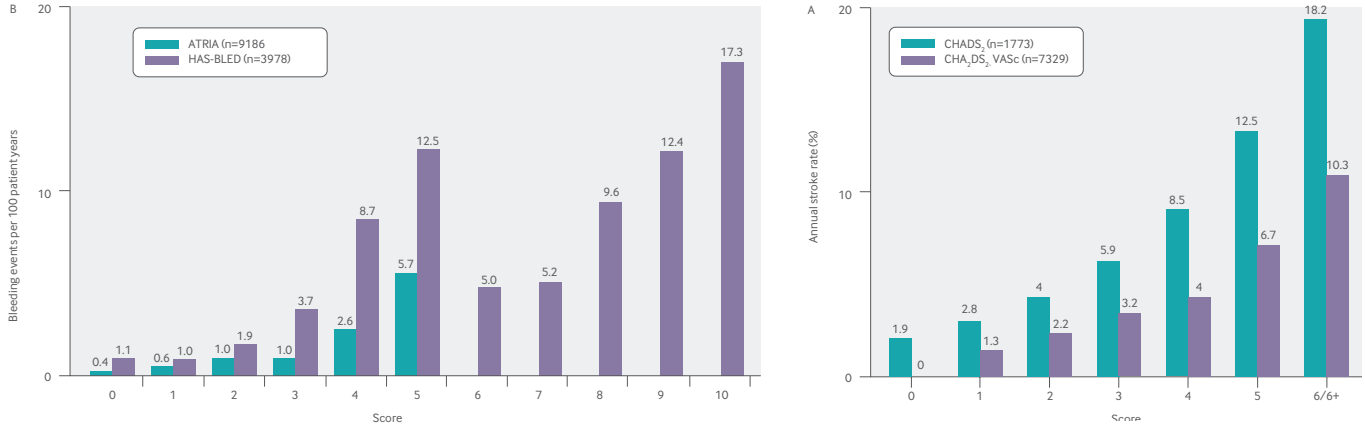
Full version of this article is on bmj.com.

State of the Art reviews: Anticoagulation in atrial fibrillation

This week our State of the Art review is anticoagulation in atrial fibrillation (http://www.bmj.com/content/348/bmj.g2116). Atrial fibrillation is the most common disturbance of cardiac rhythm in adults and carries a lifetime risk of about one in four. It significantly increases the risk of stroke and thromboembolic events and consequently is a major cause of mortality and morbidity.

Long term oral anticoagulation reduces the risk of stroke or systemic embolism in patients with atrial fibrillation. However, the use of anticoagulants is challenging because they significantly increase the risk of bleeding, which can be fatal. The appropriate selection of patients for treatment represents an important clinical dilemma.

The review discusses the rationale for anticoagulation in patients with atrial fibrillation, risk stratification for treatment, available agents and their appropriate use. Special considerations such as treatment in people with renal impairment, planned interruptions and transitions between drugs are also summarised.



Event rates, according to scores on the various risk stratification algorithms, for (A) stroke and (B) bleeding