

Adult onset epilepsies

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Not all seizures occurring during adult life are due to epilepsy. Many are acute symptomatic seizures which must be recognised to avoid inappropriate antiepileptic drug (AED) treatment. Acute symptomatic seizures can complicate any acute encephalopathy caused by drugs (particularly alcohol, cocaine, antidepressant overdose) or metabolic disturbance (uraemia, hepatic encephalopathy, etc). They are almost exclusively generalised tonic-clonic seizures that may sometimes be preceded by myoclonus. As seizures of this type rarely present for the first time over the age of 30 years as part of an epilepsy syndrome, one should always have a high index of suspicion about such seizures. Also, acute symptomatic seizures can occur in association with acute cerebral insults such as head injury, stroke, and encephalitis; while their occurrence increases the risk of post-traumatic epilepsy the two are not inevitably linked (see below).

Seizure types in adult epilepsies

Epilepsy may develop in adults for a number of reasons. In the early part of adult life it is common to see a number of patients presenting with idiopathic generalised epilepsies, particularly juvenile myoclonic epilepsy and epilepsy with awakening tonic-clonic seizures. Such epilepsies will be characterised by a high probability of generalised spike and wave in the EEG, and patients will be neurologically normal and not require further investigation.

Most other patients presenting with epilepsy in adult life will have a form of partial epilepsy. This may be overtly declared by the presence of an aura to seizures that clearly identifies the localised onset. However, patients will be seen in whom the focal onset does not result in significant symptoms that can be recalled subsequently by the patient, or witnessed by observers. This is particularly the case for seizures that occur during sleep. All seizures occurring during sleep which commence during adult life must be regarded as being of focal onset unless proven otherwise.

While the onset of a partial epilepsy during adult life is more commonly associated with the identification of an underlying neurological disorder than is the case with epilepsies developing in childhood, it must be recognised that over 50% of patients with adult onset epilepsy have no aetiology that can be determined by the investigative means currently available, although this proportion is decreasing as advances in magnetic resonance imaging occur. A number of aetiological groups of adult onset epilepsies will be considered here in more detail.

Causes of adult-onset epilepsy

Post-traumatic epilepsy

The incidence of post-traumatic epilepsy varies depending on the population studied. The best available information on the risk of epilepsy following head injury comes from the community-based survey summarised in Table 1. This would indicate that mild injuries (e.g.

injuries not complicated by skull fracture and with a post-traumatic amnesia of less than 30 minutes) do not carry a significantly increased risk of the development of epilepsy, but that more severe injuries probably do. However, a more recent population-based study from Denmark suggests that even mild head injuries (loss of consciousness for less than 30 minutes, post-traumatic amnesia for less than 24 hours, confusion/disorientation, or focal, transient neurological deficit) may be associated with an increased risk¹. Different definitions of a 'mild' head injury are the most likely explanation for the discrepancy between these studies.

A number of factors influence the risk of epilepsy:

Missile injuries. Several series have looked at the incidence of epilepsy following missile injuries to the head. The best estimate of the risk of epilepsy for such injuries overall would seem to be 50%. A number of factors further influence this risk, and these are summarised in Table 2.

Non-penetrating head injuries. This form of head injury has been widely studied but largely in patients admitted to neurosurgical units. It must be remembered that these represent a selected population of head-injured patients.

If seizures are going to complicate a head injury they tend to do so shortly after injury. Around 75% of patients will have their first post-traumatic seizure within a year of injury, whether this is a missile or blunt injury. Whilst the risk of developing seizures decreases with the passage of time there are no good grounds for differentiating between seizures that occur in the first week and later seizures, as far as their significance is concerned. One exception is that seizures occurring immediately after impact do not carry an adverse prognosis for recurrent seizures.

Jennett defined early seizures as those occurring within seven days of injury². A total of 25% of patients with early seizures had late epilepsy, compared to 3% of patients developing late epilepsy in the absence of early seizures. When other factors contributing to the risk of late post-traumatic epilepsy were excluded, i.e. depressed fracture or haematoma, late epilepsy occurred in only 1.2% in the absence of early seizures, but in 51% of patients in whom early seizures occurred.

The other factors which clearly contribute to the risk of late epilepsy are the presence of an acute intracranial haematoma (31% risk) and depressed skull fracture (15% risk). In patients without these features longer periods of post-traumatic amnesia increase the risk of epilepsy.

The risk of epilepsy shortly after traumatic brain injury is high, but how long this high risk lasts is unknown. In a large population-based study in Denmark, it was found that the risk of epilepsy was increased after a mild brain injury (RR 2.22, 95% CI 2.07–2.38), severe brain injury (7.40, 6.16–8.89), and skull fracture (2.17, 1.73–2.71). The risk continued to be increased more than 10 years later in each group. Interestingly, patients with a family history of epilepsy had a notably high risk of epilepsy after mild (5.75, 4.56–7.27) and severe brain injury (10.09, 4.20–24.26). It appears therefore that even mild head injuries, particularly in susceptible individuals, are associated with a greater long-term risk of developing epilepsy compared to the general population¹.

Table 1. Head injury.

	Risk of epilepsy			
	Number of patients	1 year (%)	5 years (%)risk	Relative vs expected risk
Severe injuries (brain contusion, intracranial haematoma or PTA > 24 hours)	195	7.1	11.5	29
Moderate injuries (skull fracture or PTA >30 mins)	92	0.7	1.6	4.0
Mild injuries (no fractures PTA <30 mins)	1640	0.1	0.6	1.5 (95%CI 0.6–3.3)
Expected rates			0.4	

PTA = post-traumatic amnesia

Table 2. Factors influencing risk of epilepsy after missile injuries.

Frontal injury
Persistent hemiparesis
Surgical removal of metal
Complicating infection
- abscess
- fungal infection

There seems no doubt that the prognosis for post-traumatic epilepsy is considerably worse than for epilepsy for which no cause is found. Caveness reported a remission rate of approximately 50%³. Jennett's series reported a remission rate of 25%, but one-third of patients continued to have frequent seizures. There is some evidence that the later the onset of epilepsy following head injury the less likely is remission. Furthermore, seizures appearing to arise from the temporal lobes seem to have a worse prognosis than those arising elsewhere.

There is little evidence to suggest that early AED therapy has a significant effect in preventing the development of later epilepsy. This may either be because AEDs do not influence the natural history of this form of epilepsy, or because head-injured patients show a marked tendency to be non-compliant with prophylactic therapy.

Post-operative epilepsy

The overall incidence of post-operative seizures in a five-year period following supratentorial craniotomy is approximately 17%. The incidence may vary from as low as 3% to as high as 92% depending on the condition for which craniotomy is carried out.

A total of 20% of patients undergoing surgery for intracranial aneurysms will develop post-operative seizures. The risks are low for aneurysms of the internal carotid (7.5%) but high for aneurysms of the anterior communicating (21%) and middle cerebral artery (38%). Surgery for arteriovenous malformations (AVMs) and spontaneous intracerebral haematomas carries a 50% and 20% risk of *de novo* epilepsy, respectively. A considerable portion of this risk seems to be directly attributable to surgery, as the risk of epilepsy associated with aneurysms managed conservatively was approximately 8% in 261 patients and an approximately 20% risk over 20 years for AVMs managed conservatively.

The incidence of epilepsy following surgery for supratentorial abscess is extremely high, and virtually all patients develop seizures if followed up for a sufficiently long period of time. The risk of seizures complicating insertion of an indwelling ventricular shunt is about 24%.

The risk of tumour surgery causing epilepsy is more difficult to identify, particularly for progressive tumours such as gliomas. Seizures may develop *de novo* following surgery for meningioma in 22% of cases, though approximately 40% of meningioma patients who had pre-operative seizures do not have further seizures post-operatively. Once again there is a clear relationship between time of surgery and the development of seizures. Approximately 70% who have seizures will have done so by one year and 90% by two years post-operatively. To date there is no evidence that early prophylactic treatment with AEDs significantly reduces the risk of post-operative seizures.

Tumour epilepsies

Tumours remain a relatively rare cause of epilepsy but the incidence of tumour epilepsy is clearly age related. In one series tumours were detected in 16% of patients developing epilepsy over the age of 20, and in 22% of patients developing partial epilepsy over this age. The diagnosis of tumour-based epilepsies is usually straightforward and indicated by the presence of developing focal neurological signs and symptoms, a focal EEG abnormality and by neuroimaging. In patients with benign tumours who present only with epilepsy diagnosis is difficult and management even more problematic.

There is no doubt that the more benign the tumour the more likely it is to present with a history of epilepsy (Table 3). The siting of the tumour also appears to influence the likelihood of a presentation of epilepsy (Table 4). The likelihood of finding a neoplastic basis for epilepsy beginning in adult life is influenced by partial seizure type (Table 5).

Table 3. Incidence of seizures due to different tumours.

Tumour types	Percentage presenting with seizures
Astrocytoma	70
Oligodendroglioma	92
Malignant glioma	37
Meningioma	67
Metastasis	47
Pituitary adenoma	9

Table 4. Incidence of seizures due to tumours at different sites.

Site	Percentage with fits
Frontal	53
Parietal	68
Temporal	48
Occipital	32
Third ventricle	32
Thalamic	8
Pituitary region	8

Table 5. Types of partial seizures and tumour aetiology.

	Number of patients with partial seizures	Percentage identified as having tumour
Simple motor seizures	1211	21
Somatosensory seizures	98	56
Other simple sensory seizures	148	24
Complex partial seizures	228	13

After MAUGUIERRE and COURJON, 1978⁴

Cerebrovascular epilepsy

Cerebrovascular disease is an important contributor to new cases of epilepsy developing over the age of 60 and is largely responsible for the increased age-related incidence at this time of life. A number of studies would suggest that between 5 and 10% of patients with a clinical history of stroke due to occlusive vascular disease will develop epilepsy. However, covert cerebrovascular disease may be much more common on the CT scans of patients with late-onset epilepsy when compared with age-matched controls⁵. The Oxford Community Stroke Study found that 2.8% of patients had a seizure before their first stroke. A total of 2.1% had a seizure within 24 hours of the stroke and 7.1% had seizures subsequently. Actuarial analysis estimated that the one-year cumulative risk of a post-stroke seizure was 4.1% after cerebral infarction, 18.2% after primary intracerebral haemorrhage and 27.8% after subarachnoid haemorrhage.

Epilepsy also complicates cerebral aneurysms whether or not they have bled or been operated upon (see above). AVMs are also a cause of epilepsy in earlier life. Epilepsy is present in approximately 20–25% of patients presenting with AVMs and the risk of developing *de novo* epilepsy in AVM is approximately 1% per annum. Haemorrhage and surgical treatment appear to be the major factors that increase this risk.

Autoimmune epilepsy

Seizures are a common presenting symptom in autoimmune neurologic disorders, particularly in limbic encephalitis or multifocal paraneoplastic disorders^{6–9}. Autoantibodies recognised with paraneoplastic limbic encephalitis include antineuronal nuclear antibody type 1, collapsin response-mediator protein 5 (CRMP-5), and Ma2. Voltage-gated potassium channel (VGKC) complex and glutamic acid de-carboxylase 65 (GAD65) antibodies, often nonparaneoplastic in aetiology, have been reported in patients with limbic encephalitis and idiopathic epilepsy with AED-resistant seizures^{10,11}. Newly identified autoantibody specificities that strongly correlate with clinical seizures include N-methyl-D-aspartate (NMDA), γ -aminobutyric acid B^{12,13} and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors¹⁴.

It is clear that the clinical spectrum of auto-immune epilepsy is still unknown. In a series of patients with epilepsy, VGKC complex antibodies were detected in 10%; NMDA receptor antibodies, in 7% of newly diagnosed patients; and GAD65 antibodies, in 1.6–1.7%¹⁵. It is conceivable that only patients with the most severe presentations in this heterogeneous group are being identified.

Accumulating data support an autoimmune basis in patients with AED-resistant seizures, including those lacking a typical ‘limbic encephalitis’ phenotype. Identification of an immune basis is important because adjunctive immunotherapy may slow, halt, or even reverse the epileptogenic process in these patients. In a cohort study, autoimmune antibodies were detected in 14% of patients with epilepsy¹⁶. This study, along with several case reports and series, suggested a potential benefit of immunotherapy in improving seizure control.

Recurrent seizures are the early and predominant clinical manifestation in patients with an autoimmune aetiology. An autoimmune cause is identified most readily in patients who present with the full syndrome of limbic encephalitis, characterised by subacute memory impairment with mood disturbance and temporal lobe seizures. The diagnosis of autoimmune limbic encephalitis is aided by detection of neural autoantibodies with radiological or pathological evidence of mesial temporal lobe inflammation and in some cases a history of neoplasia in the preceding five years¹⁷.

In addition to the presence of neural antibodies, clinical features suggestive of autoimmune epilepsy include:

- Acute to subacute onset, with seizures occurring every three months or less
- Multiple types of seizures or faciobrachial dystonic seizures
- Resistance to anti-seizure medication
- Personal or family history of autoimmunity
- History of recent or past neoplasia
- Viral prodrome
- Evidence of CNS inflammation.

When autoimmune epilepsy is suspected on clinical grounds, CSF evaluation and comprehensive screening for neural autoantibodies are indicated. If autoimmune epilepsy is suspected, a trial of immunotherapy – intravenous steroids or intravenous immunoglobulin, (IVIg) – is justifiable in the absence of other treatment options and may serve as additional evidence for an autoimmune aetiology when a favourable seizure response is observed^{18,19}.

Questions remaining unanswered include the natural history of autoimmune epilepsy, the selection criteria for patients with epilepsy most likely to benefit from an autoimmune evaluation, the timing for immunotherapy trial, and optimal duration of long-term immunotherapy maintenance.

Epilepsy after cerebral infection

The risk of epilepsy after viral encephalitis has been estimated to be 10–25%, and 3–10% after bacterial meningitis, particularly if a fixed neurological deficit has been acquired²⁰. Uncomplicated viral meningitis has not been associated with an increased risk of seizures.

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Further reading

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