

Frontal lobe epilepsy

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While frontal lobe epilepsy accounts for only 10–20% of patients in surgical series, the prevalence in non-surgical cohorts is probably higher. Frontal lobe epilepsy (FLE) probably represents 20–30% of partial seizures; calculating the prevalence of FLE in the UK from the National Institutes of Health estimates for the USA gives a figure of about 115,000, of whom 35,000 remain refractory to medical treatment. The International League Against Epilepsy has proposed a classification, compartmentalising different clinical manifestations into anatomical subdivisions of the frontal lobes of which there are many, with diverse functions¹. However, FLE presents some particular diagnostic problems, both in the clinical and the electrographic diagnosis of seizure types. The extensive anatomical connections between subdivisions of the frontal lobe and between the frontal and other lobes blur these categories. Seizures may, for example, spread from temporal to orbitofrontal cortex (or vice versa) within milliseconds, giving substantial overlap between the seizure manifestations documented from these two regions². FLE in general has been less well studied than temporal lobe epilepsy. Some consider that seizure freedom after surgery is the most reliable way of defining a particular localised syndrome and thus various conceptual aspects of FLE remain poorly understood.

Aetiology

In a large series of 250 cases operated on for FLE³:

Head injury	77
Tumour	63
Birth trauma	26
Gliosis (from abscess, haematoma etc)	14
Encephalitis	13
Gunshot	11
Other known	17
Unknown	29

The spectrum is likely to be different for those cases not requiring surgery, e.g. fewer tumours, but post-traumatic epilepsy is commonly frontal. Series with modern neuroimaging data show that tumours, malformations and vascular anomalies are also not infrequently detected. The cause in many cases remains unknown.

Clinical diagnosis

The evolution in time of frontal lobe seizures. The seizures which most of the time occur without warning, are often short and are followed by very rapid recovery. They frequently

occur from sleep, and may occur in clusters of 5–6 or more per night, usually with partial recovery between, but status epilepticus is also common.

Seizure manifestations^{2,4–7,9}. The seizure semiology is dependent on the area of cortex activated during a seizure, and therefore can give important clues as to the presumed epileptogenic zone. However, the area of cortex generating symptoms during seizures need not be identical with the epileptogenic zone, as spread frequently occurs from the area of ictal onset. Understanding the functional anatomy of the frontal lobes allows us to link clinical symptoms during the seizure and areas of cortex activated, and electro-clinical characteristics have been recently summarised^{19–21}. For practical purposes in epileptology the main areas of the frontal lobe are defined by stimulation and lesion studies and include:

The primary motor areas (precentral gyrus); supplementary sensorimotor areas (SSMA) in the mesial aspect, the posterior part of the superior frontal gyrus and in the paracentral lobule; the frontal eye field in the posterior part of the middle frontal gyrus; the frontal language area in the pars opercularis and triangularis in the dominant inferior frontal gyrus; the prefrontal cortex; and the orbitofrontal cortex. Negative motor areas are represented in the posterior inferior frontal gyrus and in the posterior mesial superior frontal gyrus in front of the SSMA proper.

Frontal lobe seizure semiology with predominantly positive motor symptoms can be grouped into three main categories: 1) focal clonic seizures; 2) bilateral asymmetrical tonic seizures; 3) complex motor seizures; 4) other rarer seizure semiologies as listed below.

- 1) Classical, hemiclonic Jacksonian motor seizures are the easiest to localise, invariably involving the contralateral motor strip. Consciousness is usually preserved. There may be a short preceding aura (non-specific or sometimes somatosensory, the latter likely in part due to some overlap of motor and sensory representations in the pericentral region).
- 2) More anteriorly, in the supplementary motor area (SMA) medially and the premotor cortex (PMC) laterally, more complex motor manifestations are recognised: turning of head and eyes and posturing of arms and legs. Classically, SMA seizures cause sudden assumption of a ‘fencing posture’, the contralateral arm being abducted at the shoulder, externally rotated, flexed at the elbow. Though characteristic, these seizures are not pathognomonic of SMA, or even frontal, onset. Motor automatisms may occur, particularly in PMC seizures, although it is not entirely clear whether this is partly due to temporal lobe involvement. The seizure may be preceded by a vague somatosensory aura such as numbness or tingling, more poorly localised than in parietal seizures. Vocalisation at the onset of the seizure is also common. These motor manifestations may be ipsilateral, contralateral or bilateral from a unilateral discharge. Consciousness may be retained. Secondary generalisation may be too rapid for the posturing to be detected.
- 3) Complex motor seizures. Such seizures may arise from frontopolar, anterior cingulate, opercular-insular and orbitofrontal regions. There is usually complex motor activity, usually considered ‘hypermotor’, ‘gestural’ or ‘repetitive’. There may be somatic, experiential or psychic aura, and so these may cause confusion with temporal lobe seizures; there may be an aura including epigastric sensations and olfactory hallucination. Autonomic manifestations are common, e.g. facial flushing and/or pallor, tachycardia, pupillary dilatation and incontinence of urine. Speech arrest may be seen, particularly in dominant hemisphere seizures, and there may be a post-ictal phase of predominantly expressive dysphasia. Spread of the seizure discharge posteriorly may produce PMC and SMA manifestations. Motor automatisms are common.

- 4) Rarer seizure types include: seizures characterised by brief lapses of awareness, which are mainly seen with anterior mesial frontal seizures, frontopolar or orbitofrontal seizures; in addition, akinetic seizures, aphasic seizures or seizures characterised by early head version without loss of awareness.

Spread of seizure discharges may occur very rapidly between the hemispheres, resulting in sudden hypertonia, or less frequently hypotonia, causing drop attacks with severe injury. The seizure may: a) continue in the same phase on the ground, b) progress to a generalised clonic seizure, or c) there may be rapid recovery.

Electroencephalography

Inter-ictal EEG recordings are often challenging and it has been reported that up to 40% of patients with FLE do not have inter-ictal epileptiform discharges. The yield of prolonged video EEG recordings and careful review of EEG samples with closely spaced midline electrodes may be of higher yield. Ictal scalp recording of EEG changes in FLE is hampered by the size of the frontal lobes, which means that signals from distant, mesial or deep gyral discharges may be attenuated and undetectable^{8,9}. Where detected, the spatial resolution and discharge localisation is often very poor. As motor manifestations are prominent, often without any aura, ictal scalp EEG recording is often swamped by muscle artifact and thus uninterpretable. Post-ictal EEG suppression may be very short. Localisable ictal EEG changes were found in 30–40% of cases.

Intracranial EEG recordings using subdural grid electrodes and/or depth electrodes may be necessary in lesional cases where exact delineation of extent of epileptogenicity is necessary, in addition to allowing for mapping of eloquent cortex using cortical stimulation. In non-lesional cases invasive EEG can be undertaken if there is a clear hypothesis of the ictal onset zone. However, intracerebral studies suffer from sampling error, only detecting discharges that are very near the electrodes. Without accurate information to guide electrode placement, this too is often unsuccessful.

Imaging

Even in refractory FLE the detection rate of imaging is poorer than in temporal lobe epilepsy (TLE)⁹. Computed tomography identifies abnormalities with localising value in about 20% of cases and magnetic resonance imaging in a further 30–40%. Positron emission tomography frequently shows abnormalities but these are commonly rather non-specific. As magnetic resonance imaging becomes more sensitive, small areas of dysplasia and heterotopia are increasingly detected; their clinical significance remains to be evaluated. The size of the frontal lobes means the location of the lesions responsible for FLE is more variable than for TLE.

Frontal versus non-epileptic seizures

It has been recognised that some seizures previously labelled as non-epileptic are in fact due to FLE. The reasons for the confusion include:

- Motor activity in FLE is frequently bizarre and complex.
- Bilateral motor activity may occur in FLE with partial preservation of awareness.
- The inter-ictal EEG may be normal and the ictal changes obscured by artifact.

There are some differentiating features: epileptic seizures are often stereotyped for an individual, shorter and commonly occur from sleep. Caution should be exercised in diagnosing seizures arising purely from sleep as being non-epileptic. An earlier age of onset

favours an epileptic basis. Non-epileptic seizures show more fluctuation in the level of motor activity. Some qualitative differences in the movements have been suggested but these are less clear-cut¹⁰.

Frontal lobe seizures versus parasomnias

Paroxysmal motor disorders occurring from sleep include not only frontal lobe seizures, but also parasomnias. There are benign, unpleasant or undesirable behavioural or experiential phenomena that occur predominantly or exclusively during sleep. To a reasonable degree parasomnias, such as sleep-walking or sleep tremors, can be distinguished from frontal lobe seizures by clinical inquiry. Events in parasomnias tend to last longer individually, are less likely to occur in clusters in a given night, are more likely to cause complex behaviours, such as wandering outside the bedroom, and tend to be less stereotyped than frontal lobe seizures. Prolonged EEG with videopolysomnography may be required to distinguish parasomnias from frontal lobe seizures. A clinical scale has recently been validated and may obviate the need for prolonged monitoring in some cases¹¹.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

ADNFLE is a distinctive disorder, with autosomal dominant (Mendelian) inheritance¹². A number of families have been described across the world. The seizure pattern is remarkably consistent, with predominantly nocturnal clusters of brief motor seizures, which may be complex or even violent. Though the semiology may vary between members of the same kindred, seizures are stereotyped within a given individual. Consciousness may be retained. Neuroimaging is normal, as may be the inter-ictal and even ictal EEG. Videosomnography differentiates the condition from parasomnias. Mutations in the neuronal nicotinic acetylcholine receptor alpha-4 and beta-2 subunits (CHRNA4 and CHRNB2) have been identified^{12,13}. However, these genes are not mutated in the majority of kindreds, suggesting genetic heterogeneity despite the clinical homogeneity (see also Chapter 5). Carbamazepine is usually effective treatment.

Treatment

The pharmacological treatment of FLE is as for other focal epilepsies. There are no good comparative drug trials specific to FLE. Surgery is less successful than for TLE with complete remission after focal resection in only 20–40%, even in the most highly selected cases³, though some newer reports document better outcomes¹⁴. Seizure freedom rates decline over the years. A recent large series has analysed 70 patients who underwent a frontal lobectomy between 1995 and 2003. A favourable outcome was defined as complete seizure freedom, allowing for auras and seizures restricted to the first post-operative week. The estimated probability of complete seizure freedom was 55.7% at the first postoperative year, 45.1% at three years after surgery, and 30.1% at five years¹⁵. It should be noted that, in addition to patients becoming seizure free, a significant percentage of patients experience an 80% or more reduction in their seizures. Another recently published cohort of frontal lobe surgeries documented 55% seizure freedom rate at seven years after surgery¹⁶. Completeness of resection of a visible lesion remains one of the most important predictors of good outcome. Surgery need not be associated with increased neurological or neuropsychological deficit. Corpus callosum section may be of benefit in patients with drop attacks, who are at risk of major injury. This may prevent secondary generalisation, or at least slow seizure spread, with less devastating collapses¹⁷.

Other treatment options for refractory frontal lobe epilepsies include vagal nerve stimulation, regarded mainly as palliative treatment when focal resective surgery is not possible, and, more experimentally, repetitive transcranial magnetic stimulation (rTMS)¹⁸.

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