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REVIEW

Surgery for frontal lobe epilepsy

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INTRODUCTION

Frontal lobe epilepsy makes up between 20 and 30% of all partial epilepsies and is the biggest subgroup of the extratemporal lobe epilepsies. Of the patients who undergo surgery for epilepsy up to 18% have a frontal lobe focus. The aetiology of frontal lobe epilepsy is varied, clinical semiology is diverse and seizures are often frequent, disabling and refractory to treatment. Imaging and EEG findings are often non-localising therefore patients who undergo surgical evaluation for frontal lobe epilepsy require extensive and often-invasive diagnostic investigations[1–7].

FRONTAL LOBE SYNDROME

The importance of the frontal lobes to human behaviour has been known at least since the case of Phineus P. Gage was described in 1868[8]. Phineus Gage, a construction worker survived a severe frontal lobe injury but his personality and behaviour was so altered that friends and acquaintances said ‘he was no longer Gage’. The local physician Harlow reported that ‘the equilibrium of balance . . . between his intellectual faculties and animal propensities seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity, (which was not previously his custom . . .)’.

Another well-known case, that of K.M. was described in the late 1930s. K.M. also suffered bilateral frontal lobe damage that gave rise to changes in behaviour and in addition, epilepsy. To control his epilepsy both anterior frontal poles were excised and K.M. was rendered almost seizure free. Psychology assessments carried out fifteen months later found an absence of the classic behaviour associated with frontal lobe damage and it was theorised that the improvement was due to a decrease in subclinical electrical discharges. The psychologist concluded that ‘no brain is better than a bad brain’ and the case was used to argue against the importance of frontal lobes to adult intelligence[9].

It was not until 1962 that newer cognitive tests included the Wisconsin Card Sorting Test and Word Fluency tasks revealed that K.M. did indeed have deficits consistent with frontal lobe damage and confirmed a link between the frontal lobes, intelligence and behaviour[10].

However this was unknown in the early 1940s when a Portuguese neurologist Moniz influenced by Penfield and others popularised what he termed a prefrontal leucotomy as a treatment for ‘nervous diseases’[8]. The surgery, which destroyed large sections of the frontal lobe, was rarely monitored by comprehensive psychological testing, and later it was found that almost 50% suffered from prolonged catatonic symptoms and mutism. The then Director of the New York Psychiatric Institute at Columbia University wrote ‘The patients’ become rather childlike . . . (and) . . . act as dull as blazes . . . . I think . . . (lobotomies) should stop before we have demented too large a section of the population’[11].

The term ‘frontal lobe syndrome’ is now used to describe the global changes in personality and cognition associated with frontal lobe injury but it has rarely been described in non-lesional epilepsy[12].

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FRONTAL LOBE FUNCTIONS

The frontal lobes are essential not only to motor function and articulation of speech, but the organisation of action, from initiation of speech and movement, to abstract planning, reasoning and the creation of ideas. Control of impulses, behaviour and working memory may be lost when frontal lobes are damaged. Where traditionally the left hemisphere was thought to deal with linguistic information while the right hemisphere relates to visual spatial processes, frontal lobe specialisation is now known to be more variable and complex. The extensive size of frontal lobes, the highly variable nature and location of frontal lobe functions, the rapid propagation of many frontal lobe seizures and the location of epileptogenic regions makes scientific assessment and prediction of deficits difficult. Frontal lobe seizures that rapidly become bilateral may cause bilateral deficits, or a focus in one hemisphere may result in dysfunction in the other. It may be that frontal lobe seizures involve diffuse regions and produce deficits that affect regions differently. Underlying pathology or disturbance during different epochs of development may also give rise to different levels of neuropsychological dysfunction[10, 13–15].

CLASSIFICATION

It was in the late 19th century that Hughlings Jackson first related focal clonic activity or the ‘Jacksonian march’ to lesions in the motor cortex of the frontal lobe[16]. This was done by analysing seizure activity according to the anatomical location of structural pathology at post mortem. Focal motor activity became a recognised symptom of frontal lobe lesions in the precentral area, and was the basis for lateralising and localising lesions in surgical patients. Penfield and Jasper[17] were to further classify frontal lobe epilepsy according to seizure type but it was not until the mid 1980s with intensive video monitoring that a specific type of frontal lobe complex partial seizure was recognised. Subsequently further compartmentalisation of the frontal lobe epilepsies took place, which was formalised by The International League against Epilepsy classification. This essentially empirical system identifies seven anatomical and clinically distinct areas of seizure generation within the frontal lobes and classifies frontal lobe seizures according to localisation of seizure onset[18]. There are distinct problems associated with this classification system. Frontal lobe lesions frequently cross the anatomical boundaries and cerebral function involves complex integrated neural pathways that are not restricted to anatomic boundaries. Large studies show seizure semiology is not easily related to a particular region of the frontal lobe and therefore not easily categorised. As well some frontal lobe seizure semiology is seen in temporal lobe epilepsy while seizures that are clinically apparent as frontal lobe seizures may have interictal EEG abnormalities in the temporal lobe. In the same patient there can be a spectrum of symptoms that reflect seizure spread as opposed to the site of seizure onset[3–5, 7, 19, 20]. The ILAE classification also predates MRI and the discovery of a frontal lobe genetic epilepsy.

More recently it has become popular to describe three categories of frontal lobe semiology that relate to specific frontal lobe regions. These are focal motor seizures, supplementary motor seizures and complex partial seizures, but as many of the features of frontal lobe complex partial seizures overlap with features of focal motor and supplementary motor seizures, this classification system also has limitations[20–22].

Focal motor seizures arise from the precentral cortex and are characterised by unilateral focal clonic motor activity, contralateral version of the head and preservation of consciousness. Speech arrest, blinking and tonic posturing are common features and indicate spread of the electrical discharge to the supplementary motor area (SMA).

Supplementary motor seizures involve unilateral or bilateral tonic posturing and vocalisation or speech arrest. They are usually nocturnal and brief but tend to cluster and many seizures may occur in one night.

Frontal lobe complex partial semiology typically involves staring, or absence like seizures, bilateral tonic or repetitive arm movements, vocalisation, unconscious adversion and sometimes-bizarre bimanual–bipedal movements. Consciousness is often retained well into the seizure and post-ictal recovery is rapid.

The frontal lobe is also thought to cause startle provoked seizures which are generally refractory to treatment. Consciousness may be preserved during the attack and seizure onset is within seconds of the stimulus. The ictal behaviour typically involves brief asymmetric tonic posturing, which may evolve into clonic motor activity[23, 24].

SIMPLE PARTIAL SEIZURES

Simple partial seizures (or auras) commonly occur with frontal lobe supplementary and complex partial seizures. They include somatosensory symptoms such as tingling or pins and needles and cephalic sensations which are often described as ‘electrical sensations in the head’ or a ‘discharge’ in the body. Visual hallucinations or illusions involving brightness or blurred vision, white circles or a ‘persistence of images’ might occur or patients may describe an inability to recognise objects.

Autonomic changes such as pallor, flushing, cyanosis, apnea, bradycardia and taccycardia are frequent manifestations of frontal lobe epilepsy, while viscerosensory signs such as abdominal or throat constriction and difficulty breathing, are also common.

About 25% of FL patients experience psychic phenomena such as fear, terror, excitation, and euphoria while some patients experience obsessive imposing thoughts or describe being 'forced' to look at an object[5, 20–22].

COMPARISON WITH TEMPORAL LOBE SEIZURES

Frontal lobe seizures are generally thought to be brief, involve motor phenomena and cluster in sleep. However they may also mimic the vacant stare typically associated with temporal lobe or absence seizures, and while some studies show frontal lobe epilepsy to be primarily nocturnal, others found only a third of patients have mainly nocturnal seizures. Seizures may be brief but there is little overall difference in the duration between temporal and frontal lobe complex partial seizures. Laskowitz showed frontal complex partial seizures lasted an average of 1 minute, almost twice the previously reported frontal lobe seizure duration, while the average duration of temporal lobe seizures is between 30 seconds and 2 minutes[5]. The frequency of temporal lobe seizures ranges from less than one, to up to 30 a month, and they also may cluster and arise from sleep. The distinguishing features of temporal lobe seizures are the presence of epigastric auras and hand automatisms[32], which are rarely seen during frontal lobe seizures, and longer post-ictal periods of drowsiness or confusion[25–27].

STATUS EPILEPTICUS

Status epilepticus (SE) is common in frontal lobe epilepsy. Whereas about 10% of all patients with refractory epilepsy experience an episode of SE, around 25% of patients with FLE have at least one episode, and in 50% there is no previous history of epilepsy[28, 29]. The episodes may present as generalised tonic clonic SE, non-convulsive SE (NCSE) or focal clonic SE.

Symptoms of NCSE include hypomania and disinhibition, aggression, perseveration and fluctuating unresponsiveness, staring, head turning or eye deviation, and automatisms such as picking at clothes. The subtlety of these symptoms commonly leads to a delay in diagnosis and long episodes, which contribute to increased morbidity and mortality rates[30, 31].

Partial motor status epilepticus is a further occasionally malignant manifestation of frontal lobe SE that may warrant aggressive treatment. Seizures are either focal motor or epilepsia partialis continua with a frequency of between 40 per day to almost continuous seizure activity. The underlying pathology is often focal cortical dysplasia[32, 33].

ELECTROENCEPHALOGRAM

An important aspect of frontal lobe epilepsy is to understand the limitations of the EEG. As only a small portion of the total cortical surface is accessible by scalp electrodes the ictal activity remote from the surface of the brain may not be detected. Frontal lobe neuronal networks and pathways also account for rapid regional, extrafrontal or bilateral seizure spread so that interictal EEG spikes when they are present are often non-localizing and widespread. Discharges may be falsely localised to the frontotemporal region or the temporal lobe, they may falsely lateralise the focus, or the focus may give rise to generalised bursts of spike and wave activity[5, 19, 20, 35–37]. Only when the interictal scalp EEG shows consistent unilateral interictal spikes does it usually correctly lateralise the abnormal hemisphere and it will only localise the seizure focus in about one third of patients with ictal EEG changes.

Where EEG findings and seizure semiology are convergent with the site of a single MRI identified lesion in non-eloquent cortex, surgery may proceed, however chronic intracranial EEG recording is necessary to define the extent of the epileptogenic zone in the majority of patients with frontal lobe epilepsy.

In the event of the proposed resection being near eloquent cortex, electrical stimulation studies are carried out to map and identify the margins of eloquent cortex in relation to the epileptogenic zone, either during intracranial monitoring or immediately prior to the surgical resection[38–40].

VIDEO-EEG

Video-electroencephalogram (VEEG) monitoring is well-recognised as an essential investigation for epilepsy surgery. It enables seizure semiology to be more closely scrutinised for lateralising and localising features and, correlated with ictal EEG discharges, can provide greater localising information. Where lateralisation and localisation of the seizure focus remains uncertain VEEG is an essential step in deciding on placement of invasive intracranial electrodes.

However seizures of considerable diversity can originate within an identical area of the frontal lobe, while

resection of an area can cause complete cessation of seizures that differ considerably in their semiology. Thus, the clinical semiology remains a working hypothesis of localisation but is not used in isolation to reach a decision about the operation site. Only focal motor activity and unilateral post-ictal paresis, which is contralateral to the epileptogenic zone, always provides reliable lateralising evidence. Other lateralising features include unilateral upper limb dystonia and ictal and post-ictal vocalisation. Speech or non-speech sounds such as groaning or shouting during seizures occur in about 50% of patients with frontal lobe epilepsy and are more common in patients with left-sided foci and dorsolateral localisation, than in patients with right-sided foci[34, 35, 41].

NEUROIMAGING

MRI is the structural imaging method of choice in epilepsy. Approximately 50% of patients with frontal lobe epilepsy are MRI positive and there is a high correlation between an MRI identified lesion and the location of the epileptogenic zone[42–44]. This finding has influenced the diagnostic evaluation of patients such that there is now a bias towards lesional rather than non-lesional surgery. The presence of a lesion also influences the placement of intracranial electrodes. Three-dimensional MRI surface rendered images may further increase the yield of imaged abnormalities and enhance surgical outcomes[45].

In MRI negative patients and patients where clinical and neurological findings fail to lateralise the epileptogenic zone, functional neuroimaging has a very important role. Abnormal neuronal activity at the site of the seizure focus is associated with changes in regional cerebral blood flow and regional cerebral glucose metabolism which can be measured with ^{99m}Tc HMPAO SPECT and (FDG)-PET. These findings provide physiological information not often available from anatomical modalities. The diagnostic sensitivity of ictal SPECT is greater in frontal than in temporal lobe epilepsy with up to 91% of patients with FLE showing a unilateral frontal hyperperfusion. However the disadvantage of ictal SPECT is that it must be performed as an inpatient during video-EEG monitoring, the patient must have a seizure, and it requires specially trained staff to identify the onset of that seizure and to time the injection of the radiopharmaceutical accordingly.

The advantage of [^{18}F]fluorodeoxyglucose (FDG) PET is being an interictal it can be preformed as an outpatient. A finding of unilateral hypometabolism almost always localises the ictal onset zone although most studies show PET to be less sensitive to frontal lobe epilepsy than SPECT studies[46–48].

PSYCHIATRIC AND PSYCHOLOGICAL FACTORS

People with refractory epilepsy comprise a vulnerable group with sometimes significant psychiatric problems which are regarded as endemic to that group. The suicide risk is fourfold that of the normal population and depressive disorders are reported in about 40% of patients who attend tertiary epilepsy centres[49]. The process of undergoing presurgical work-up may further exacerbate psychiatric and psychological morbidity. Some procedures are invasive and the patient's hospital stay is frequently uncomfortable, stressful and lacks privacy. Patients may experience uncertainty and concerns about diagnostic and prognostic outcomes, dislocation from family and friends and economic worries, and require substantial support to enable them to cope with the surgical process. Interventions that enhance coping, in particular epilepsy nurse specialist support and information about tests, results and their implications may significantly decrease anxiety and depression levels in many patients[50].

All presurgical patients have a neuropsychiatric assessment and any psychiatric illness is treated prior to surgery. Neuropsychology tests are also carried out to identify or confirm deficits specific to frontal lobe pathology, to provide presurgical baseline measures, and to predict potential cognitive morbidity following surgical resection of the frontal lobe[51, 52]. Neuropsychiatric and neuropsychology findings also influence the selection of patients for surgery.

SURGERY

Epilepsy surgery involves the disconnection or removal of the epileptogenic zone from the cerebral cortex. In recent studies of frontal lobe surgical outcomes, up to 70% of patients are rendered seizure free. This is a significant improvement on earlier outcomes and has been credited to advances in both functional and structural neuroimaging[1, 36, 53–57].

Patients who undergo presurgical work-up must be compliant, have a reliable diagnosis of epilepsy and pharmacoresistant seizures that are sufficiently disabling to warrant invasive intervention. Routine investigations include a neurological examination, a detailed history and description of ictal signs and symptoms, a MRI, interictal EEG, video telemetry, neuropsychology and psychiatric assessments.

The most effective and commonly performed procedure for frontal lobe epilepsy involves resection of the epileptogenic zone. Multiple subpial transection (MST) is occasionally carried out where the epileptogenic zone is in an area of eloquent cortex. It is generally associated with less favourable outcomes although

this may be because many patients who undergo this procedure have progressive neurological disease or neurodegenerative disorders[58, 59].

EVALUATION

Reliable surgical outcome measures are needed to improve surgical procedures and inform patients of the potential risks and benefits of surgery. Yet many epilepsy surgical centres fail to identify frontal lobe from extra-temporal lobe outcomes and report only neurological morbidity and seizure frequency as outcome measures. In some retrospective studies patient inclusion criteria, diagnostic investigations and resection techniques changed over time and post-surgical seizure outcomes are described according to different rating scales, which obscure comparisons between them.

Seizure outcomes are usually assessed at between 6 months and 2 years post-surgery but relapse rates may continue to increase more than 5 years after surgery. As well a number of patients have seizures in the post-surgical period that remit after a period of months to years. This phenomenon, called a 'running-down' period may be more common in patients with frontal lobe surgery but the reverse of seizure exacerbation has also been described. Generally seizures beyond the first 2 months after surgery are predictive of a poor outcome and patients with seizures beyond 1 year rarely achieve remission[54, 56, 60–62].

SURGICAL COMPLICATIONS

The size of the resection is a likely factor in the rate of complications. More complications are described in patients with larger resections that extend into the temporal lobes. In one series complications included hemiparesis, aphasia, leg monoparesis, psychosis, a significantly decreased verbal IQ and homonymous field cut.

Frontal lobe resections may also cause transient or permanent changes in personality and affect intelligence. Up to 38% of frontal lobe postsurgical patients have problems with personality and behaviour and of these 10% are rated as severe. Resections of the cingulate gyrus are particularly associated with higher rates of psychopathology[54, 56, 62, 63].

PATHOLOGY AND PREDICTORS OF OUTCOME

The underlying causes of frontal lobe epilepsy are diverse. Neuronal migration disorders and in particular cortical dysplasia have become increasingly recognised as an important cause of frontal lobe epilepsy. Tumours, vascular malformations, ischaemic lesions and gliosis with an antecedent of encephalitis, are also common causes. Discrete tumours include hamartomas, ganglioglioma, epidermoid cyst, low-grade glioma and venous angioma[36, 42–44].

The presence of a single MRI identified abnormality is one of the strongest presurgical predictors of a seizure-free outcome. The predictive value of a lesion on MRI in part relates to the underlying pathology and localisation within the frontal lobe. Focal well-defined lesions correlate with complete resections and more favourable seizure outcomes, while patients with multilobar pathology are unlikely to benefit from a cortical resection. Similarly a post-surgical finding of an incomplete resection on MRI is a strong indicator of an unfavourable outcome.

When relapse rates for frontal lobe surgery are related to pathology, glioma is associated with a high rate of favourable outcomes (75% remained seizure free at 2 year follow-up) as well as vascular lesions, while relapse rates reached 25% in patients with developmental lesions. Patients with unilateral post-traumatic lesions and resulting encephalomalacia or gliosis respond well to surgery although multilobar gliosis had a poor surgical outcome[36, 44, 54, 57, 64–66].

IN SUMMARY

The historical events surrounding Phineus Gage, K.M. and the leucotomy patients underpin our knowledge of frontal lobe functions and surgery for epilepsy. They serve to remind us of the importance of the frontal lobes to cognition, while advancing the concept of an epileptogenic zone that surgically excised, will cause the cessation of seizures. These essentially conflicting notions are still being grappled with today. Seizure activity disrupts cerebral function and is potentially life threatening yet successful surgical outcomes and morbidity both increase in proportion to the extent of resected area of cortex. Frontal lobe functions continue to prove difficult to localise and comprehensive neuropsychology testing today is unable to accurately predict morbidity. The advances in neuroimaging, video-EEG, and neurophysiology, have substantially improved outcomes but many patients' experience invasive, costly, stressful and time consuming investigations and may continue to have seizures after surgery. The continuing challenge is to reduce the costs, the risks and the time taken to investigate patients and make further improvements in post-surgical outcomes. In doing so many diagnostic difficulties and dilemmas faced by the specialist epilepsy team when considering patients for frontal lobe surgery will be resolved.

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