Chapter 9
Resective Surgery for Patients with Epilepsy and Intellectual Disabilities

A. Nicolson

Introduction

Epilepsy is common in patients with intellectual disabilities (ID), and is often refractory to medical treatment. In one long-term study 70% of patients with an intelligence quoitent (IQ) less than 70 continued to have more than one seizure per year, compared to only 25% of those with borderline (IQ 71-85) or average (IQ > 85) intelligence.[1] Such patients are therefore among those whose potentially could benefit most from epilepsy surgery.

When considering the possibility of epilepsy surgery one needs to consider the risks to the patient of ongoing refractory epilepsy. There is the ongoing risk of injury during seizures, and patients with ID and refractory epilepsy are among the highest at risk of sudden death (SUDEP).[2] Added to this are the major psychosocial and cognitive impacts that refractory epilepsy has upon the individual, and so surgical treatment deserves serious consideration in this population. Of course there will be individuals who have clear multiple seizure foci or symptomatic generalized epilepsy who will not be candidates for resective surgery, but many patients with ID and epilepsy may have surgically treatable lesions.

However, it has been a traditionally held view that a low IQ is a relative contraindication to surgery,[3–5] as the ID may represent a global brain dysfunction, with multiple seizure foci. Also of concern in patients with ID is the risk to cognitive functioning in patients with an already limited cognitive reserve. However, until recently this widely held belief has gone unchallenged, and as a consequence there are likely to be many patients who may benefit from surgery who are denied the appropriate evaluation. This is particularly crucial in children with ID and epilepsy whose global development will be adversely affected by ongoing seizure activity, and who may have the most to gain from early assessment for resective surgery.

V.P. Prasher, M.P. Kerr (eds.) *Epilepsy and Intellectual Disabilities*,
DOI: 10.1007/978-1-84800-259-3_9, © Springer Science + Business Media, LLC 2008

Should a Low IQ Be a Contraindication to Epilepsy Surgery?

The first major multicenter study to examine this issue analyzed data retrospectively from over 1,000 adults who had undergone temporal lobe resective surgery in eight centers in the United States[6] and had full pre- and postoperative neuropsychological assessments. Only 24 patients (2.3%) had an IQ less than 70, highlighting the tendency for such patients to not receive resective surgical treatment. This study did show a relationship between preoperative IQ and seizure outcome, but the effect was modest. Indeed the remission rate in those with an IQ less than 70 was 54.2%, and was 73.2% for those with a borderline IQ level. This emphasizes that although a lower IQ may predict a slightly worse outcome in some, there are a significant proportion of patients who can derive great benefit. The poorest outcome in this study was in those with a low IQ who had a structural lesion other than hippocampal sclerosis.

Several other small studies have also addressed this issue of preoperative IQ level and outcome following surgery. In 16 adults with an IQ less than 85, Gleissner and colleagues[7] found a remission rate of 64%, with no deterioration in neuropsychological function and some positive socioeconomic outcomes. The main predictor of a poor outcome was a left-sided lesion, which is likely to be because the surgery in the dominant hemisphere was more restricted.

The same group examined 285 consecutive children who underwent resective epilepsy surgery, and examined the outcome in relation to IQ level.[8] Twenty-one patients (7.4%) had an IQ less than 70, with 24 (8.4%) of below average level (IQ 71-85). There was no significant difference between these groups and those with an average IQ in terms of seizure outcome one year after surgery, with 67% seizure free in the low IQ group, 77% of those with a borderline IQ, and 78% in the group with average intelligence. No change was found in neuropsychological testing, other than an improvement in executive functioning of those with a low IQ. Attention improved and behavioral problems were less marked postoperatively in all groups.

Bjornaes and colleagues[9] found a remission rate of 48% in 31 patients with an IQ less than 70 who underwent resective surgery. Remission was more likely in those with temporal compared with extratemporal epilepsy (52% versus 38%), but the main factor predictive of outcome was the duration of epilepsy. In those with epilepsy for less than 12 years, 80% were seizure free. This raises the crucial issue of timing of epilepsy surgery in general, but in particular in this group with ID. It is well known that chronic refractory epilepsy has a negative neuropsychological and psychosocial effect, and it may be that rather than excluding patients with ID from the option of curative treatment, we should be more aggressive at an earlier stage.

There is a significantly higher rate of psychiatric problems in patients with epilepsy than the general population, particularly in those with drug-refractory partial epilepsy. A mood disorder is very common in such patients, and depending on the definition used, may occur in up to 75% of patients[10]; anxiety has been reported in over 40%[11] of individuals with refractory epilepsy. Suicide rates may be up to 25 times more common in patients with temporal lobe epilepsy compared with people without epilepsy.[12] It has been recognized that psychiatric symptoms may worsen

or appear de novo following epilepsy surgery, and so surgery is often undertaken with extreme caution or refused on the grounds of pre-existing psychiatric problems. This issue may be of particular relevance to the ID population with epilepsy where behavioral problems and other psychiatric symptoms may coexist. Many clinicians may have reservations about epilepsy surgery in a patient with ID for the reasons already stated, and if they have psychiatric symptoms in addition, the patient is often rejected for surgery.

However, some reports have suggested that the psychiatric status of epilepsy patients is either not influenced, or may even improve, following epilepsy surgery[13,14] and that even patients with chronic psychosis may have a successful outcome.[15] The evidence for the psychiatric outcome in patients with ID is limited, but one of the studies examining the seizure outcome in patients with different IQ scores commented on an overall improvement in behavioral problems in patients with ID.[8]

A study of 226 consecutive patients who underwent epilepsy surgery at a single center showed a favorable psychiatric outcome overall[16] but did not specifically examine patients with ID. There was a high proportion (34.5%) of some psychiatric disturbance preoperatively, with psychosis in 16%. In 22 patients (28%) the psychiatric symptoms resolved post surgery; the main symptom was postictal psychosis, which suggests that this may be a factor favoring surgery. Thirty-nine patients (50%) had a persistence of psychiatric symptoms postoperatively, and the symptoms appeared de novo in 17 (22%). In many of those patients with new-onset psychiatric symptoms there were detectable personality traits presurgery that would predispose to psychiatric problems, which has been reported previously.[17] De novo postsurgery psychosis has been reported to be more common in nondominant resections[18,19] and some tumors such as gangliogliomas,[20] but this has not been confirmed in other studies.[16] Major depressive episodes may occur following epilepsy surgery, but these are usually transitory and in individuals with a history of a milder mood disorder.[17]

Despite concerns over performing surgery in patients with ID, recent evidence, albeit from small studies, suggests that a low IQ should not itself be an exclusion factor for resective epilepsy surgery. There may be a trend for patients who have more severe ID to have a slightly worse outcome, but still a significant proportion derive great benefit, with no evidence of worsening cognitive performance or behavior. However, further studies on this issue are required in larger numbers to confirm these findings and also to examine whether patients with a more severe ID may also benefit from resective surgery, as the data for the group with an IQ less than 50 are very limited. It seems intuitive that if surgery is to be considered, it should be undertaken as early as possible, rather than waiting for years of chronic drug-refractory epilepsy and the consequential negative impact that this has, particularly on a child's development. This will require a fundamental shift in thinking outside of specialist centers, as currently many such patients may be managed in the community or by psychiatrists with an interest in ID and may never have access to neurological and specialist epilepsy services.

Special Consideration for Presurgical Evaluation in People with LD

The main role of epilepsy surgery is to achieve seizure freedom, or a significant reduction in seizure frequency, without producing adverse cognitive or psychological effects. It has been proposed that epilepsy surgery should be considered in anyone "in whom the seizure represents the sole or predominant factor preventing a normal quality of life."[21] This may not be the case in individuals with ID, as achieving a "normal" quality of life may not be possible, and the goals of epilepsy surgery need to be carefully considered.

The investigative process in patients with ID may be even more complicated than in those with normal intelligence. Vital to accurate seizure localization is the correlation between clinical features, imaging, and electroencephalograms (EEG). Patients with ID may not be as able as those with a higher IQ to give a detailed account of their seizure symptomatology, magnetic resonance imaging (MRI) may be difficult without a general anesthetic, and neuropsychological testing needs to take the low IQ into account.

Neuropsychological Assessment

There are several aims of the preoperative neuropsychological assessment in all patients in an epilepsy surgery program. It gives us information about the cerebral organization of an individual's verbal and visuospatial skills and determines any evidence for areas of brain dysfunction which could be relevant to the seizure focus. It also examines the postoperative risk to memory and language skills. An essential part of the assessment, in addition to these principal functions, is to evaluate the potential psychosocial consequences of surgery to that individual. This includes the identification of any psychiatric comorbidity and the evaluation of the patient's (and family's or caregiver's) expectations about surgery. How a patient copes with epilepsy and his or her preoperative support network are relevant when identifying the possible psychosocial consequences of successful surgery. Patients are more likely to perceive the surgery as a success if their goals have been realistic and practical before surgery.[22] The change from having frequent seizures that negatively impact social lives, employment, driving, and relationships to being seizure free after surgery is a major life event that can be difficult to adjust to.[23] The goals from surgery for patients with ID may vary considerably from those without such a disability. However, this may be difficult to ascertain easily, and specific counseling about this issue is essential for the patient and family or caregivers.

These factors are applicable to any candidates for epilepsy surgery, but special consideration may be required for individuals with ID. The neuropsychological assessment tools are not specific to individuals with ID, and it is not known whether they provide as accurate a picture of overall cognitive functioning as in people with average

intelligence. The actual neuropsychological tests used vary widely between centers — there is no uniform approach,[24] and there is no specific protocol for patients with ID. This is also particularly relevant to children with ID, who provide their own unique challenges. It is likely that at different ages during childhood certain neuropsychological methods may be most beneficial or alternatively difficult to interpret.

The intracarotid amytal, or Wada, test is established as a method of examining laterality of language functioning and predicting those at risk of postoperative amnesia. As with standard neuropsychological testing, the procedure varies between centers, and some feel it is not a necessary investigation when baseline neuropsychometry provides clear evidence for lateralization.[25] When the test is performed, the sodium amytal is injected into a single carotid artery to provide anesthesia of one hemisphere, enabling the neuropsychologist to test the memory and language abilities of the contralateral hemisisphere. Whether the Wada test is valid, or requires modification, in patients with ID is not known, and some do not perform this test in individuals with an IQ below 75.[24] It may be that in the future other methods will replace the role of the Wada test, in particular functional MRI (fMRI) (Figure 9.1AD) and magnetoencephalography (MEG), but any protocols developed in these technologies may need to be adapted for people with ID.

Seizure Recordings

Seizure recordings are routinely required in the presurgical evaluation process, and even in the most clear-cut cases it is valuable in confirming seizure semiology. In patients with ID, obtaining seizure recordings may be more problematic, and measures such as allowing caregivers to stay with the patient may be required. Reducing medication on the day of admission may help to shorten the length of hospital stay. Often in cases associated with ID the seizure focus cannot be reliably determined with scalp EEG recordings and routine MRI, and so invasive depth or subdural strips/grids are required (Figure 9.2). Such procedures may be more difficult for patients with ID to tolerate, and if any intraoperative mapping is required, this may be very difficult.

Consent

At every stage during the presurgical evaluation process it is essential that every effort is made to ensure that informed consent is given. This may be difficult in patients with ID, and although in this situation a legal guardian will have to provide assent it is of paramount importance that professionals experienced in dealing with such patients and their families undergo detailed discussions about the aims, risks, and expectations from investigations or procedures.

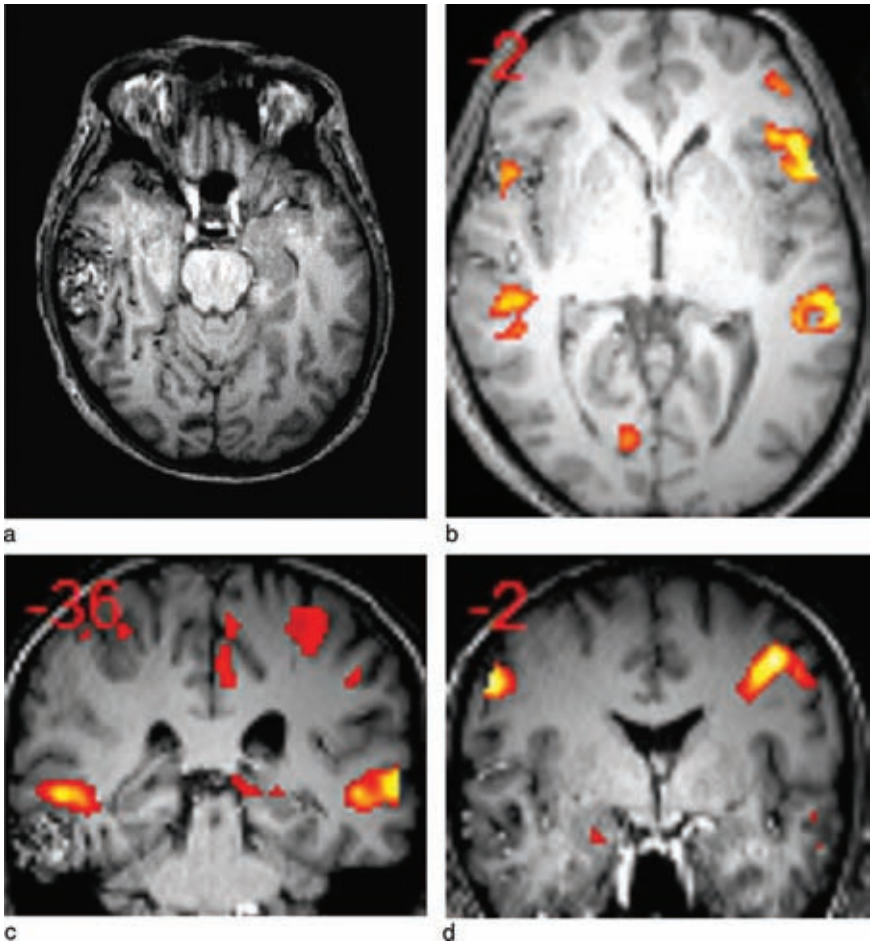

Fig. 9.1 Functional MRI (fMRI). A 45-year-old left-handed man presented with a single tonic-clonic seizure; MRI revealed a right temporal lobe arteriovenous malformation (AVM) (A). During the evaluation process for surgical excision of the AVM he underwent fMRI for language localization. This was carried out with three different language paradigms. The verb generation paradigm demonstrated bilateral Broca's and Wernicke area activation, with the Wernicke's area just superior to the nidus of the AVM on the right (B-D)

Pathologies Associated with ID That May Benefit from Resective Surgery

Focal Cortical Dysplasia

Focal cortical dysplasia (FCD) was first described over 30 years ago,[26] and while our abilities to detect it have improved significantly with new imaging techniques, uncertainties about FCD remain.

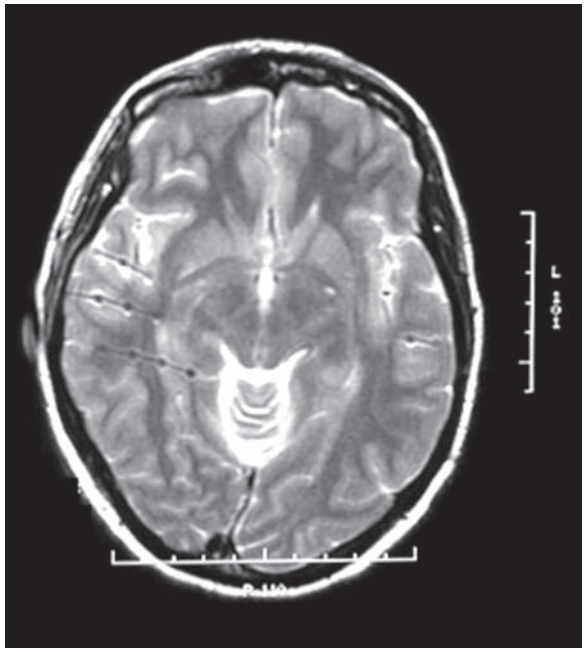

Fig. 9.2 Depth electrodes. A 25-year-old man had complex partial seizures preceded by a stereotyped olfactory aura. MRI was normal, and ictal scalp EEG recordings had suggested that the seizures had a right temporal onset. This was confirmed with depth electrode recordings, with three electrodes placed in the right temporal lobe and one in the left temporal lobe

Focal cortical dysplasia is commonly associated with severe drug-resistant epilepsy, including epilepsia partialis continua; therefore, evaluation for potential surgery is increasingly important. Focal cortical dysplasia is frequently associated with a degree of ID, and many cases that were previously termed cryptogenic may now have FCD identified with high-resolution MRI, although even the most sophisticated MRI will not currently identify all cases of FCD and therefore the true prevalence of FCD is not known. Surgery offers some hope to patients with FCD, as antiepileptic drugs (AEDs) will often fail to achieve remission.

Several surgical series have been published on the outcome of patients undergoing surgery for FCD, with reported remission rates mostly around 40–50%[27–34] but with some studies showing rates as high as 70–90%.[35–40] As with any reports of data from surgical series one needs to take into account different methodologies when interpreting the data, such as patient numbers, selection criteria, and length of follow-up in particular. We know from studies of surgical outcome in patients with hippocampal sclerosis that late relapses can occur,[41] and a lengthy follow-up is needed to accurately predict prognosis. One such study reported a 10-year follow-up of patients who underwent surgery for malformations of cortical development (MCD), 31 of whom had FCD.[30] In the group overall, the remission rate remained stable between 2 years and 10 years, suggesting that patients with MCD who initially do well following epilepsy surgery are likely to have a favorable long-term outcome. However, in another

study of 49 patients with FCD the proportion of patients with a favorable postoperative seizure outcome following surgery dropped from 84% to 70% over the 10 years of follow-up, and most of this change was observed during the first 3 years.[34]

Several studies have identified factors that may predict outcome from surgery, with completeness of resection commonly identified.[30,33,42] As with other pathologies, outcome has also been dependent on the location of the lesion, with extratemporal FCD having a poorer surgical outcome.[29,43] Attempts have been made to examine whether the histological subtype of FCD influences outcome, with varying results. Cortical dysplasia can be classified in order of cytological disruption as "mild malformation of cortical development" (mMCD) or FCD type 1a (isolated architectural abnormalities); 1b (with additional immature or giant neurons); 2a (with additional dysmorphic neurons); and 2b (with additional balloon cells) (Figure 9.3).[44]
This is a pathological classification system, and we do not currently know how this correlates with clinical features and severity of the epilepsy or outcome following surgery. It is clear, however, that the patients with FCD are a heterogenous group. One study

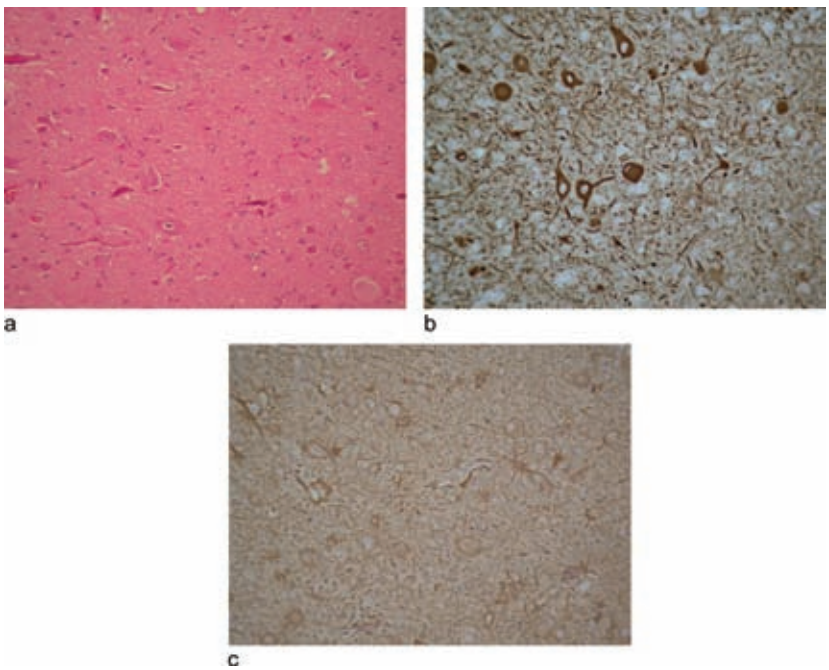

Fig. 9.3 Histological slide of focal cortical dysplasia. Photomicrograph depicting an abnormal cluster of dysplastic neurons with irregular profiles closely admixed with large, binucleated astroglial cells exhibiting pale pink cytoplasm (A). When stained with neurofilament protein this shows the perikaryion of the neurons and their axons embedded in a disorganised neuropil background (B). On the slide stained with GFAP (Glial Fibrillary Acidic Protein) stroglial cells are highlighted in close apposition to the neurons (which remain unstained) (C). A subpopulation of cells exhibiting co-localisation of reactivity with both Neurofilament protein and GFAP, suggestive of a dysplastic nature of divergent phenotype

that examined whether the histological subtype of FCD influenced surgical outcome found a trend towards better results in those patients with a less severe histological subtype (mMCD or FCD type 1a),[32] but this study has relatively small numbers with limited follow-up. Others have found the reverse situation, with outcome better in FCD 2[39] or no correlation.[34] This issue clearly needs evaluation in larger studies with longer follow-up data, which would allow us to further our understanding of the clinicopathological correlate in FCD and ultimately enable us to identify presurgery those candidates who are likely to have the most favorable outcome. With a condition such as FCD, this will only be possible with multicenter collaboration.

Focal cortical dysplasia can coexist as "dual pathology" with other pathologies which are also known to cause epilepsy, such as hippocampal sclerosis (HS) and dysembryoplastic neuroepithelial tumors (DNT). Certain dual pathologies have an unfavorable outcome following epilepsy surgery, for example HS with periventricular nodular heterotopia,[45] but some small studies suggest that if both pathologies are readily identifiable presurgery and considered resectable then the outcome is favorable. A study of 28 patients with temporal lobe epilepsy associated with FCD found no difference in the outcome between those patients with FCD only and those with additional HS.[35] In a study of patients with DNT who underwent surgical resection, an associated cortical dysplasia was identified in over 80% of patients.[46] This finding emphasizes that in tumors such as DNT a focal resection may not be sufficient to achieve remission, and in many the surrounding tissue may be dysplastic and "epileptogenic." Other authors have also reported that in cases of temporal lobe dual pathology the outcome is good if the lesions are resected in addition to the mesial temporal structures.[47,48]

In the past decade the identification of FCD has been revolutionized by advances in MRI techniques in particular, but still this may not identify FCD in up to 30% of patients.[49] Characteristic findings on MRI are an abnormal gyral pattern, increased cortical thickness, poor grey-white matter differentiation, and increased subcortical signal on T2-weighted and FLAIR images.[50] Detailed presurgical evaluation is necessary to identify the epileptogenic zone, and this is a particular challenge in those patients with normal MRIs. As imaging techniques improve, it seems likely that more patients with FCD will be able to be identified and become surgical candidates. Currently, as a routine in the presurgical evaluation process these patients should undergo high-resolution MRI and scalp video-EEG telemetry. In some patients this will be sufficient to identify the FCD, but in others techniques such as intracranial EEG recordings, positron emission tomography (PET), or ictal single-photon emission computed tomography (SPECT)[51] will be required. Ictal SPECT identifies the epileptogenic zone as a an area of hyperperfusion based on cerebral metabolic and perfusion coupling,[52] and an early injection can reduce the risk of identifying a postictal hypoperfused area. SPECT coregistered to MRI (SISCOM) (Figure 9.4) may identify a localized region of cerebral perfusion concordant with the epileptogenic zone[53] and improve the localizing value of ictal SPECT. Patients are most likely to have a favorable seizure outcome if the focal cortical resection includes the region of peri-ictal blood flow change.[53,54] Ictal SPECT and SISCOM may be particularly useful in patients with FCD which is not identifiable on standard MR imaging.

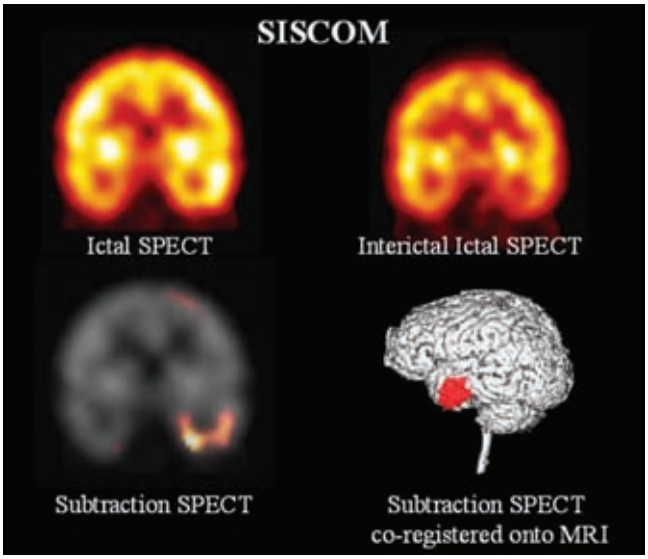

Fig. 9.4 Ictal SPECT coregistered to MRI (SISCOM). SISCOM in a patient with right temporal lobe epilepsy. Routine MRI was normal. Note that the right side of the brain is on the right side of the figure

Our knowledge of FCD has advanced significantly in recent years, but the major challenges of being able to identify all patients with FCD preoperatively and to verify whether there are subgroups of patients who are most likely to respond well to surgery remain.

Other Malformations of Cortical Development

Schizencephaly is a malformation of cortical development (MCD) that consists of congenital clefts in the cerebral mantle extending from the pial surface to the lateral ventricles and lined by cortical gray matter.[55] It may have a variable clinical presentation ranging from little or no deficit to severe developmental delay, hemiplegia, and epilepsy, which often will be refractory to AED treatment. The structural changes may be unilateral or bilateral, and when unilateral surgery may be considered. However, data on the outcome of surgery in patients with schizencephaly are limited,[56–58] and the evaluation process is likely to be complex. Even when the cleft is unilateral it may be multilobar, the structural abnormality may be distant from the epileptogenic zone, and the dysplastic cortex may be essential for language and motor functions.[59] Invasive EEG recordings are required in such patients, but SISCOM may provide useful data to guide electrode placement and/or cortical resection.[60] In the reported cases the surgical strategy has varied and includes temporal lobectomy, excision of the dysplastic cortex, and resection of cortex distant

from the cleft. Polymicrogyria is an MCD characterized by an increase in the number and decrease in the size of gyri; it may be generalized or localized. It has a widely varying clinical presentation which depends upon the distribution of the dysplastic cortex and the presence of any other underlying abnormality. In some patients with refractory epilepsy a focal potentially resectable region may be identifiable.[61]

MRI has improved our recognition of uncommon MCDs such as schizencephaly and polymicrogyria. The majority of these patients are managed medically, but surgery may be an option for some with unilateral dysplastic cortex.

Dysembryoplastic Neuroepithelial Tumor (DNT)

Dysembryoplastic neuroepithelial tumors are benign glioneuronal tumors frequently associated with refractory epilepsy in children and young adults.[62] They have characteristic findings on imaging with a mixed signal lesion on MRI which is based in the cortex but may involve the white matter, often with overlying skull abnormalities indicating a chronic lesion.[63] They typically have a disorganized arrangement of neuronal and glial elements without cytological atypia and frequent association of foci of dysplastic cortical disorganization. Cortical dysplasia is frequently associated with DNTs,[63–71] which need careful evaluation preoperatively, as a high proportion of associated "MRI-invisible" cortical dysplasia has been reported.[46] For optimum surgical outcome, this needs to be identified presurgically by invasive methods (intracranial EEG recordings and/or electrocorticography) to ensure resection of the entire epileptogenic zone,[72,73] but in some patients functional imaging such as SISCOM may provide a noninvasive alternative.[74]

Intellectual disability may occur in around 40% of cases with DNT,[75] but the presence of LD may imply a more widespread cortical dysfunction. DNTs are often surgically resectable, with studies generally showing a favorable outcome in terms of seizure control,[62,63,66,67,76–80] but the outcome is less certain in patients with ID.

Tuberous Sclerosis

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with variable expression and a high spontaneous mutation rate, which is characterized by multiple hamartomas in the skin, retina, heart, kidney, and brain. It is associated with epilepsy in up to 90% of cases, which is usually of early onset and refractory to medical treatment in up to 30%.[81] The central nervous system involvement in TSC also gives rise to focal neurological deficits and developmental and intellectual delay. There is evidence that achieving early seizure control may have a positive impact on cognitive development and social adjustment.[82] Traditionally, epilepsy surgery has not been considered an option for TSC patients, as imaging often reveals multiple tubers and therefore potentially multiple epileptogenic zones.

However, in certain cases surgery may be a realistic option, particularly for those patients with stereotyped seizures that suggest an origin from a single tuber.

The presurgical assessment of a patient with TSC offers some unique challenges. Magnetic resonance imaging will often reveal multiple tubers in TSC and does not identify the origin of the seizures,[83] and interictal EEG may show multiple abnormalities or be nonlocalizing.[84–86] On MRI, FLAIR sequences, or even diffusion-weighted imaging,[87] may be optimal to detect tubers. Computerized tomography can be useful to identify calcification, one study suggesting that such tubers may be more likely to be epileptogenic.[88] In some cases with TSC the epileptogenic tuber will be relatively easy to identify with concordance between MRI, interictal, and ictal EEG. However, in many cases invasive EEG recordings with depth electrodes and/or subdural grids will be necessary. Functional imaging such as ictal SPECT can aid localization with hyperperfusion anterior to the epileptogenic tuber.[89] FDG-PET scans may reveal multiple hypometabolic regions corresponding anatomically to the tubers, and will not differentiate between those with or without epileptogenic potential.[90–92] Other radioactive ligands such as C-alpha-methyl-tryptophan (CAMT), a marker of serotonin synthesis, may be more promising in this regard, as this has been shown to have a significantly greater uptake in epileptogenic tubers.[93,94] FDG-PET coregistration with MRI and diffusion tensor imaging may provide additional information to PET alone.[95]

At present, such functional imaging techniques, and more recently SISCOM, are useful tools to aid localization, but in practice invasive EEG recordings are usually required and this information can assist with the placement of such electrodes. Invasive monitoring can also identify adjacent functional cortex to guide resection. MEG is a technique that selectively measures tangential sources (e.g., sources on a sulcus) rather than the radial sources also detected by EEG. MEG can be combined with EEG recordings simultaneously and then visualized by plotting the equivalent current dipole on the patient's MRI brain scan with volume reconstruction.

Experience in localizing the epileptogenic zone with MEG is limited in TSC, but some provisional studies have suggested that it may have a role,[96,97] and in combination with PET and ictal SPECT could provide a three-dimensional map of the relation of the epileptic activity to the adjacent structural and functional anatomy.

Several small series of cases of surgically treated TSC have been reported, with a remission rate between 10% and 78% (Table 9.1).

The best outcome is for:

1. Patients with a single seizure type or single tuber
2. Patients with multiple tubers and one large calcified tuber, with concordant interictal EEG abnormalities related to it
3. Patients with concordant investigationsAlthough the evaluation process is more complicated and potentially higher risk, patients who do not fall into these good prognostic groups should not be denied appropriate investigation. There are reports of successful outcomes in cases requiring multistage investigation and surgery, even for bilateral seizure foci.[111,112]

The multifocal nature of TSC means that when undergoing resective surgery special consideration needs to be given to the possibility of further epileptogenic

Table 9.1 Selected series of resective surgery for tuberous sclerosis patients (modified from Romanelli and colleagues.[98]

Author	No. of Patients	Remission Rate (%)	Follow-up (months)
Bebin[99]	9	67	38
Avellino[100]	8	55	35
Baumgartner[101]	4	0	30
Guerreiro[102]	12	58	120
Acharya[103]	9	78	1 mon-14 yrs
Neville[104]	6	67	60
Koh[88]	13	69	48
Thiele[105]	21	33	50
Karenfort[106]	8	38	42
Vigliano[107]	4	75	24
Sinclair[108]	4	78	60
Jarrar[109]	21	42	60
Lachhwani[110]	17	65	25

tubers developing, and patients need to be counseled accordingly. One study found that in this patient group the remission rate fell from 59% (13 of 21) to 42% after five years,[109] but larger systematic long-term studies are required to see whether this phenomenon is more common in TSC patients than others with a different underlying pathology such as FCD or hippocampal sclerosis.

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is a form of symptomatic generalized epilepsy that is characterized by a peak age of onset between two and six years of age, multiple seizure types, a characteristic EEG abnormality, and often severe ID. Approximately one third of children will have had West syndrome in the first year of life. Symptomatic cases may be caused by focal, multifocal, or diffuse cerebral abnormalities, which could be congenital or acquired.

As LGS is a generalized epilepsy syndrome, it typically is not amenable to resective surgery. However, atypical LGS may be related to a focal lesion, and if such a lesion is identified on MRI, it may be possible to identify a resectable epileptogenic zone and provide a good seizure outcome.[113,114]

Hemispherectomy

The technique of hemispherectomy was first used to treat refractory epilepsy in Toronto in 1938.[115] After the technique was utilized in a number of cases,[116] it became apparent that there was a significant associated mortality and morbidity,

and in particular a high risk of the development of superficial siderosis, due to hemorrhage into the fluid-filled cavity left by the removal of the hemisphere. The hemispherectomy only became an accepted treatment for refractory epilepsy caused by diffuse hemispheric syndromes when the technique was modified by Rasmussen.[117,118]

Hemispherectomy is indicated as a treatment for refractory partial seizures secondary to a diffuse hemispheric abnormality. Presurgical evaluation is required to ensure that seizures originate solely from the affected hemisphere, and that the contralateral hemisphere is normal. Magnetic resonance imaging can determine whether there is any structural abnormality, and functional techniques such as PET, SPECT (showing interictal hypoperfusion and ictal hyperperfusion from the affected hemisphere), fMRI, and MEG can evaluate the functions of the hemispheres in terms of motor, sensory, and language functions. Further localization may be performed with intracranial recordings with subdural strips or grids, which provide intraoperative mapping of eloquent cortex.

The ideal timing for hemispherectomy is uncertain. Earlier intervention will reduce the adverse cognitive effects of years of poorly controlled seizures and the sedative effects of AEDs and subsequently improve quality of life. However, it is uncertain whether surgical intervention should be delayed until neurological deficits such as hemiparesis or dysphasia become established, or to perform the procedure as early as possible. Although there is evidence for a better cognitive outcome in cases of Sturge-Weber syndrome (SWS) if hemispherectomy is performed during the first year of life,[119] there is also fMRI evidence that sensory and motor functions may transfer to the contralateral hemisphere at different stages of cerebral maturation[120] and that postponement of surgery until completion of transfer of functions from the diseased to intact hemisphere leads to better fine and motor function.[121] A fine balance clearly is required to consider both of these factors in each individual being considered for hemispherectomy.

One of the major indications for hemispherectomy is Sturge-Weber syndrome (SWS) (Figure 9.5), a neurocutaneous syndrome characterized by a facial capillary angioma (port-wine stain) seen predominantly in the distribution of the first branch of the trigeminal nerve; however, it may be more extensive, with an underlying leptomeningeal angioma that can occasionally be bilateral. The leptomenigeal angioma may be detected by skull X-ray, CT, or MRI. Typically SWS is associated with a moderate to severe ID (a normal IQ occurs in only 25-30%)[122] and refractory epilepsy. Status epilepticus is common, and there may be periods of encephalopathy associated with cognitive and developmental plateau and increased hemiplegia.[123] Although the leptomeningeal angioma may be easily evident on standard imaging, the epileptogenic zone may be more extensive; seizure recordings thus are essential, and intraoperative electrocorticography may be used to guide the extent of resection.[124]

Any other conditions that cause a diffuse unilateral hemispheric disorder and epilepsy may be considered for hemispherectomy, in particular hemimegalencephaly (a neuronal migration disorder resulting in a unilateral enlarged hemisphere), Rasmussen's encephalitis, hemiconvulsion-hemiplegia, and epilepsy (HHE) syndrome, and a spastic hemiplegia caused by perinatal stroke.

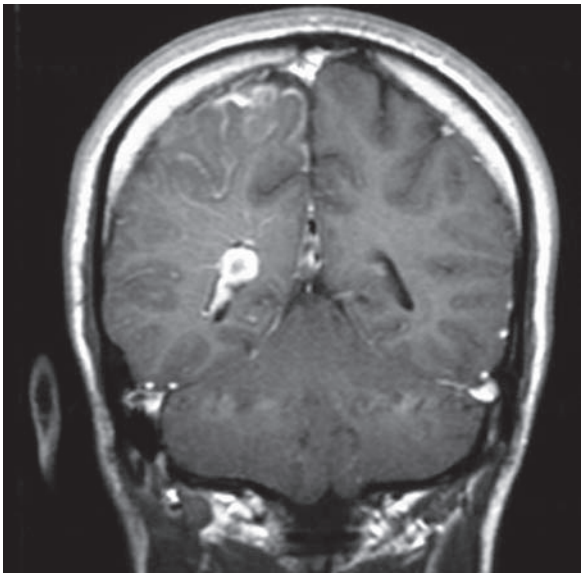

Fig. 9.5 Sturge-Weber syndrome. Post-contrast MRI shows the characteristic features of Sturge-Weber syndrome with abnormal enhancement, suggesting calcification in the cortical veins, together with right hemisphere atrophy

Several small series of the outcome from hemispherectomy have been reported, with generally favorable results. One of the largest series with prolonged follow-up found that 65% of 111 children who underwent hemispherectomy were seizure free, and 89% could walk without assistance. The poorest seizure outcome was found in those with neuronal migration disorders.[125] Another study of 115 patients found the poorest outcome and most complicated surgery in cases of hemimegalencephaly, but not in those with unilateral hemisphere cortical dysplasia, i.e., without the abnormally enlarged hemisphere.[126] Other series have produced remission rates of 52–81%[127–132] with a generally good motor outcome, usually cognitive stability or improvement, and behavioral improvement in many.

Since the earlier anatomical hemispherectomy technique was found to be associated with an unacceptable degree of complications, the technique has evolved to more restricted resections with disconnections. The functional hemispherectomy was first described in 1983 and entails the resection of the parietal and temporal lobes, Rolandic region, and severing the connections with the thalamus and brainstem, hence leaving in place the frontal and occipital lobes and their blood supply. This procedure has a much lower risk of the complication of hemosiderosis (in a series of 20 patients none had hemosiderosis[133]) compared with up to 30% of patients undergoing anatomical hemispherectomy,[134] although it should be stressed that some series of patients undergoing anatomical hemispherectomy also report no cases of haemosiderosis.[135] The disadvantage of the functional hemispherectomy is that the potentially epileptogenic insula is left in situ, although the seizure freedom

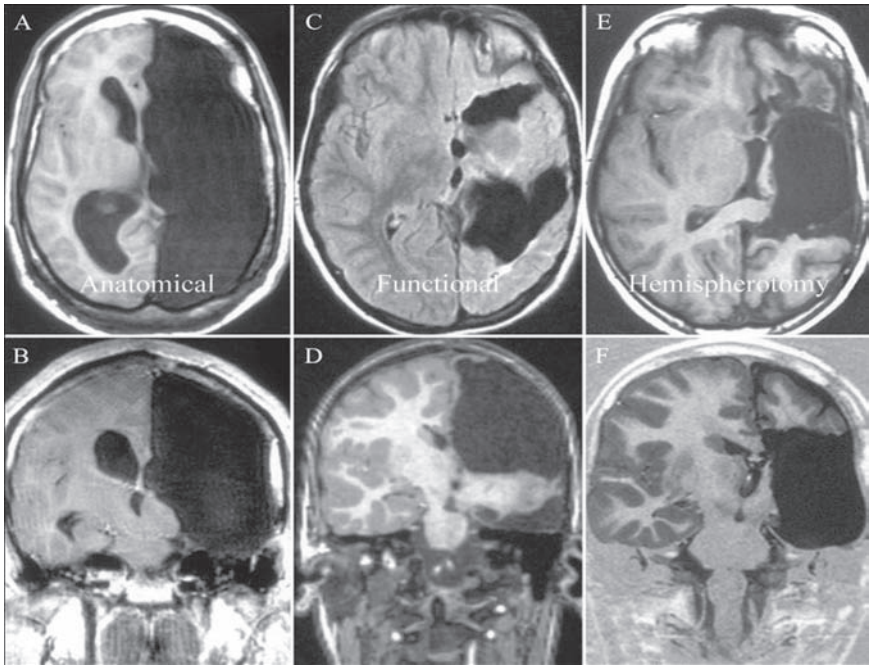

Fig. 9.6 Hemispherectomy. T1-Weighted MRI scans of examples of anatomical (A and B) and functional (C and D) hemispherectomy, and hemispherotomy (E and F)

rates compare favorably with the conventional procedure.[136] Other more restricted procedures include hemicorticectomy (only grey matter is resected) and hemispherotomy (disconnection of the epileptogenic hemisphere from the subcortical centers, thereby reducing brain excision (See Figure 9.6)).

Patients with the diffuse hemispheric disorders discussed here often have severe epilepsy with profound developmental and cognitive delay and hemiplegia. In childhood this is the patient group with potentially the most to gain from successful epilepsy surgery, as this can provide dramatic benefits not only in terms of seizure control but particularly cognitive development, and further work needs to be done to enable us to make an appropriate judgement on the timing of surgery.

Evaluating the Outcome of Resective Epilepsy Surgery in Patients with ID

The immediate aim of resective epilepsy surgery is to reduce, and hopefully stop, seizures. However, there are many other additional factors that are vitally important in assessing the overall outcome in terms of quality of life. The ultimate aim has to be to improve quality of life, which is not achieved if the patient has fewer seizures

but an adverse cognitive or psychiatric outcome. Even seizure freedom does not necessarily improve quality of life, and many such patients may continue to lead a "disabled" life with no discernable functional benefit.[34, 137]

An essential part of the presurgical evaluation is to assess the patient's and/or caregiver's expectations of surgery, and careful counseling at this point may ensure that these are not unrealistically high. This is particularly relevant in patients with ID in whom even the most favorable seizure outcome may not lead to as much of an improvement in functioning as caregivers may hope for or expect. However, the possibility of a reduction of seizure frequency and severity and a reduction in the drug burden are valid reasons to consider epilepsy surgery in this patient group, which may have particularly severe and frequent seizures, and so be in a particularly high-risk group for seizure-related injury and death (SUDEP).

There is not an established health-related quality of life measure that reliably assesses the impact that epilepsy surgery has on the quality of life of an individual with ID or their family. To measure this is complex and requires the evaluation of multiple domains and so requires the use of a variety of instruments of quality of life.

Conclusion

The traditionally held view that patients with ID will not be candidates for consideration of epilepsy surgery has been challenged in recent years. No longer are palliative procedures such as corpus callosotomy the only surgical options in such cases, and prospects of seizure freedom are realistic for many with ID. It would seem that a subgroup of patients with focal epilepsy and ID can be identified and treated successfully without drastic cognitive consequences. However, resective epilepsy surgery in the ID population remains a significant challenge. The identification of suitable candidates may be difficult, and the evaluation procedure may require special considerations and adaptations for those with ID. Newer techniques such as higher-resolution MRI have aided us in identifying potentially resectable epileptogenic foci, and in the future advances in technologies such as fMRI, SISCOM, and MEG may help further to localize foci more accurately and noninvasively, which would carry benefits for all patients with refractory focal epilepsy, including those with ID.

References

1. Huttenlocher PR, Hapke RJ. (1990) A follow-up study of intractable seizures in childhood. Ann Neurol 28:699–705.
2. Nashef L, Fish DR, Allen P et al. (1995) Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral centre. J Neurol Neurosurg Psychiatr 58: 462–4.
3. Falconer MA.(1973) Reversibility by temporal lobe resection of the behavioural abnormalities of temporal-lobe epilepsy. N Engl J Med 289: 451–5.

4. Rasmussen T. (1975) Surgical treatment of patients with complex partial seizures. Adv Neurol 11:415–49.
5. Engel J, Jr. Surgery for seizures. (1996) N Engl J Med 334:647–52.
6. Chelune GJ, Naugle RI, Hermann BP, et al. (1998) Does presurgical IQ predict seizure outcome after temporal lobectomy? Evidence from the Bozeman epilepsy consortium. Epilepsia 39:314–8.
7. Gleissner U, Johanson K, Helmstaedter C, et al. (1999) Surgical outcome in a group of low-IQ patients with focal epilepsy. Epilepsia. 40: 553–9.
8. Gleissner U, Clusmann H, Sassen R, et al. (2006) Postsurgical outcome in pediatric patients with epilepsy: A comparison of patients with intellectual disabilities, subaverage intelligence, and average-range intelligence. Epilepsia. 47: 406–14.
9. Bjornaes H, Stabell KE, Heminghyt E, et al. (2004) Resective surgery for intractable focal epilepsy in patients with low IQ: Predictors for seizure control and outcome with respect to seizures and neuropsychological and psychosocial functioning. Epilepsia. 45: 131–9.
10. Indaco A, Carrieri PB, Nappi C, et al. (1992) Interictal depression in epilepsy. Epilepsy Res 12: 45–50.
11. Bladin PF. (1992) Psychosocial difficulties and outcome after temporal lobectomy. Epilepsia 33: 898–907.
12. Barraclough B. (1981) Suicide and epilepsy. In: Reynolds EH, Trimble MR (eds.). Epilepsy and psychiatry. Edinburgh: Churchill Livingstone, 72–6.
13. Fenwick P. (1991) Long-term psychiatric outcome after epilepsy surgery. In: Luders HO (ed.). Epilepsy surgery. New York: Raven Press, 647–52.
14. Savard G, Andermann F, Olivier A, et al. (1991) Postictal psychosis after partial complex seizures: A multiple case study. Epilepsia 32: 225–31.
15. Reutens Dc, Savard G, Andermann F, et al. (1997) Results of surgical treatment in temporal lobe epilepsy with chronic psychosis. Brain 120: 1929–36.
16. Inoue Y, Mihara T. (2001) Psychiatric disorders before and after surgery for epilepsy. Epilepsia 42(Suppl 6): 13–18.
17. Koch-Stoecker S. (2001) Psychiatric outcome. In: Luders HO, Comair YG (eds.). Epilepsy surgery. Philadelphia: Lippincott Williams & Wilkins, 837–44.
18. Mace CJ, Trimble MR. (1991) Psychosis following temporal lobe surgery: A report of six cases. J Neurol Neurosurg Psychiatr 54: 639–44.
19. Trimble MR. (1992) Behaviour changes following temporal lobectomy, with special reference to psychosis. J Neurol Neurosurg Psychiatr 55: 89–91.
20. Bruton CJ. (1988) The neuropathology of temporal lobe epilepsy (Maudsley Monographs 31). Oxford: Oxford University Press.
21. Dreifuss FE. (1987) Goals of surgery for epilepsy. In: Engel J Jr (ed.). Surgical treatment of the epilepsies. New York: Raven Press, 31–49.
22. Wilson SJ, Saling MM, Kincade P, et al. (1998) Patient expectations of temporal lobe surgery. Epilepsia 39: 167–74.
23. Wheelock I, Peterson C, Buchtel HA. (1998) Presurgery expectations, postsurgery satisfaction, and psychosocial adjustment after epilepsy surgery. Epilepsia 639: 487–94.
24. Baker GA. (2001) Psychological and neuropsychological assessment before and after surgery for epilepsy: Implications for the management of learning-disabled people. Epilepsia 42(Suppl. 1): 41–3.
25. Baxendale S, Thompson P, Duncan J, et al. (2003) Is it time to replace the Wada test? Neurology 60: 354–5.
26. Taylor DC, Falconer MA, Bruton CI, et al. (1971) Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatr 34: 369–87.
27. Sisodiya SM. (2000) Surgery for malformations of cortical development causing epilepsy. Brain 123: 1075–91.
28. Bast T, Ramantani G, Seitz A, et al. (2006) Focal cortical dysplasia: Prevalence, clinical presentation and epilepsy in children and adults. Acta Neurol Scand 113: 72–81.
29. Chung CK, Lee SK, Kim KJ. (2005) Surgical outcome of epilepsy caused by cortical dysplasia. Epilepsia 46(Suppl 1): 25–9.

30. Hamiwka L, Jayakar P, Resnick T, et al. (2005) Surgery for epilepsy due to cortical malformations: Ten-year follow-up. Epilepsia. 46: 556–60.
31. Siegel AM, Cascino GD, Meyer FB, et al. (2006) Surgical outcome and predictive factors in adult patients with intractable epilepsy and focal cortical dysplasia. Acta Neurol Scand 113:65–71.
32. Fauser S, Schulze-Bonhage A, Honegger J, et al. (2004) Focal cortical dysplasias: Surgical outcome in 67 patients in relation to histological subtypes and dual pathology. Brain 127: 2406–18.
33. Hader WJ, MacKay M, Otsubo H, et al. (2004) Cortical dysplastic lesions in children with intractable epilepsy: Role of complete resection. J Neurosurg (Pediatrics 2). 100: 110–7.
34. Srikijvilaikul T, Najm IM, Hovinga CA, et al. (2003) Seizure outcome after temporal lobectomy in temporal lobe cortical dysplasia. Epilepsia 44: 1420–4.
36. Hudgins RJ, Flamini JR, Palasis S, et al. (2005) Surgical treatment of epilepsy in children caused by focal cortical dysplasia. Pediatr Neurosurg 41: 70–6.
37. Cohen-Gadol AA, Ozduman K, Bronen RA, et al. (2004) Long-term outcome after epilepsy surgery for focal cortical dysplasia. J Neurosurg 101: 55–65.
38. Chassoux F, Devaux B, Landre E, et al. (2000) Stereoelectroencephalography in focal cortical dysplasia: A 3D approach to delineating the dysplastic cortex. Brain 123: 1733–51.
39. Tassi L, Colombo N, Garbelli R, et al. (2002) R. Focal cortical dysplasia: Neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 125: 1719–32.
40. Kral T, Clusmann H, Blumcke I, et al. (2003) Outcome of epilepsy surgery in focal cortical dysplasia. J Neurol Neurosurg Psychiatr 74: 183–8.
41. McIntosh AM, Kalnins RM, Mitchell LA, et al. (2004) Temporal lobectomy: Long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain 127: 2018–30.
42. Sisodiya SM. (2004) Surgery for focal cortical dysplasia. Brain 127: 2383–4.
43. Hirabayashi S, Binnie CD, Janota I, et al. (1993) Surgical treatment of epilepsy due to cortical dysplasia: Clinical and EEG findings. J Neurol Neurosurg Psychiatr 56: 765–70.
44. Palmini A, Najm I, Avanzini G. (2004) Terminology and classification of the cortical dysplasias. Neurology 62(Suppl 3): S2–8.
45. Li LM, Dubeau F, Andermann F, et al. (1997) Periventricular nodular hetrotopia and intractable temporal lobe epilepsy: Poor outcome after temporal lobe resection. Ann Neurol 41: 662–8.
46. Takahashi A, Hong S-C, Seo DW, et al. (2005) Frequent association of cortical dysplasia in dysembryoplastic neuroepithelial tumor treated by epilepsy surgery. Surg Neurol 64: 419–27.
47. Salanova V, Markand O, Worth R. (2004) Temporal lobe epilepsy: Analysis of patients with dual pathology. Acta Neurol Scand 109: 126–31.
48. Li LM, Cendes F, Andermann F, et al. (1999) Surgical outcome in patients with epilepsy and dual pathology. Brain 122:799–805.
49. Bautista JF, Foldvary-Schaefer N, Bingaman WE, et al. (2003) Focal cortical dysplasia and intractable epilepsy in adults: Clinical, EEG, imaging and surgical features. Epilepsy Res 55: 131–6.
50. Kuzniecky RI, Barkovich AJ. (2001) Malformations of cortical development and epilepsy. Brain Dev 23: 2–11.
51. Gupta A, Raja S, Kotagal P, et al. (2004) Ictal SPECT in children with partial epilepsy due to focal cortical dysplasia. Pediatr Neurol l31: 89–95.
52. Van Paesschen W. (2004) Ictal SPECT. Epilepsia 45(Suppl 4): 35–40.
53. O'Brien TJ, So EL, Mullan BP, et al. (1998) Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. Neurology. 50: 445–54.
54. O'Brien TJ, So EL, Cascino GD, et al. (2004) Subtraction SPECT co-registered with MRI in focal malformations of cortical development: Localization of the epileptic zone in epilepsy surgery candidates. Epilepsia 45: 367–76.
55. Barkovich AJ, Normand D. (1988) MR imaging of schizencephaly. Am J Radiol 150: 1391–6.

56. Leblanc R, Tampieri D, Robitaille Y, et al. (1991) Surgical treatment of intractable epilepsy associated with schizencephaly. Neurosurgery 29: 421–9.
57. Landy HJ, Ramsey RE, Ajmoine-Marsan C, et al. (1992) Temporal lobectomy for seizures associated with unilateral schizencephaly. Surg Neurol 37: 477–81.
58. Silbergeld DL, Miller JW. (1994) Resective surgery for medically intractable epilepsy associated with schizencephaly. J Neurosurg 80: 820–5.
59. Jansky J, Ebner A, Kruse B, et al. (2003) Functional organization of the brain with malformations of cortical development. Ann Neurol 53: 759–67.
60. Cascino GD, Buchhalter JR, Sirven JI, et al. (2004) Peri-ictal SPECT and surgical treatment for intractable epilepsy related to schizencephaly. Neurology 63: 2426–8.
61. Cross JH, Jayakar P, Nordli D, et al. (2006) Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the subcommission for pediatric epilepsy surgery. Epilepsia 47: 952–9.
62. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, et al. (1988) Dysembryoplastic neuroepithelial tumor: A surgically curable tumor of young patients with intractable partial seizures: A report of thirty-nine cases. Neurosurgery 23: 545–56.
63. Daumas-Duport C, Varlet P, Bacha S, et al. (1999) Dysembryoplastic neuroepithelial tumors: non-specific histological forms: Study of 40 cases. J Neurooncol 41: 267–80.
64. Daumas-Duport C. (1993) Dysembryoplastic neuroepithelial tumors. Brain Pathol. 3: 283–95.
65. Honovar M, Janota I, Poekey CE. (1999) Histological heterogeneity of dysembryoplastic neuroepithelial tumor: Identification and differential diagnosis in a series of 74 cases. Histopathology 34: 342–56.
66. Lee DY, Chung CK, Hwang YS, et al. (2000) Dysembryoplastic neuroepithelial tumor: Radiological findings (including PET, SPECT, and MRS) and surgical strategy. J Neurooncol 47: 167–74.
67. Raymond AA, Halpin SFS, Alsanjari N, et al. (1994) Dysembryoplastic neuroepithelial tumor: Features in 16 patients. Brain 117: 461–75.
68. Raymond AA, Fish DR, Sisodiya SM, et al. (1995) Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumor and dysgenesis of the archicortex in epilepsy: Clinical, EEG, and neuroimaging features in 100 adult patients. Brain 118: 629–60.
69. Nolan MA, Sakuta R, Chuang N, et al (2004) Dysembryoplastic neuroepithelial tumors in childhood: Long-term outcome and prognostic features. Neurology 62: 2270–6.
70. Sandberg DI, Ragheb J, Dunoyer C, et al. (2005) Surgical outcomes and seizure control rates after resection of dysembryoplastic neuroepithelial tumors. Neurosurg Focus 18: E5.
71. Chan CH, Bittar RG, Davis GA, et al. (2006) Long-term seizure outcome following surgery for dysembryoplastic neuroepithelial tumor. J Neurosurg 104: 62–9.
72. Kameyana S, Fukuda M, Tomikawa M, et al. (2001) Surgical strategy and outcomes for epileptic patients with focal cortical dysplasia or dysembryoplastic neuroepithelial tumor. Epilepsia 42(Suppl 6): 37–41.
73. Sakuta R, Otsubo H, Nolan MA, et al. (2005) Recurrent intractable seizures in children with cortical dysplasia adjacent to dysembryoplastic neuroepithelial tumor. J Child Neurol 20: 377–84.
74. Valenti MP, Froelich S, Armspach JP, et al. (2002) Contribution of SISCOM imaging in the pre-surgical evaluation of temporal lobe epilepsy related to dysembryoplastic neuroepithelial tumors. Epilepsia 43: 270–6.
75. Degen R, Ebner A, Lahl R, et al. (2002) Various findings in surgically treated epilepsy patients with dysembryoplastic neuroepithelial tumors in comparison with those of patients with other low-grade brain tumors and other neuronal migration disorders. Epilepsia. 43: 1379–84.
76. Aronica E, Leenstra S, van Veelen CW, et al. (2001) Glioneuronal tumors and medically intractable epilepsy: A clinical study with long-term follow up of seizure outcome after surgery. Epilepsy Res 43:179–91.

77. Fomekong E, Baylac F, Moret C, et al. (1999) Dysembryoplastic neuroepithelial tumors. Analysis of 16 cases. Neurochirurgie 45: 180–9.
78. Hennessey MJ, Elwes RD, Binnie CD, et al. (2000) Failed surgery for epilepsy. A study of persistence and recurrence of seizures following temporal resection. Brain 123: 2445–66.
79. Kirkpatrick PJ, Honavar M, Janota I, et al. (1993) Control of temporal lobe epilepsy following en bloc resection of low-grade tumors. Neurosurgery 78: 19–25.
80. Prayson RA, Estes ML, Morris HH. (1993) Coexistence of neoplasia and cortical dysplasia in patients presenting with seizures. Epilepsia 34: 609–15.
81. Roach ES, Gomez MR, Northrup H. (1998) Tuberous sclerosis complex consensus conference: Revised clinical diagnostic criteria. J Child Neurol 13: 624–8.
82. Jambaque I, Chiron C, Dumas C, et al. (2000) Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients. Epilepsy Res 38: 151–60.
83. Cusmai R, Chiron C, Curotolo P, et al. (1990) Topographic comparative study of magnetic resonance imaging and electroencephalography in 34 children with tuberous sclerosis. Epilepsia 31: 747–55.
84. Ganji S, Hellman CD. (1985) Tuberous sclerosis: Long-term follow up and longitudinal electroencephalographic study. Clin Electroenceph 16: 219–24.
85. Pampiglione G, Moynahan EJ. (1976) The tuberous sclerosis syndrome: Clinical and EEG studies in 100 children. J Neurol Neurosurg Psychiatr 39: 666–73.
86. Westmoreland BF. (1988) Electroencephalographic experience at the Mayo clinic. In: Gomez HR (ed.). Tuberous sclerosis. New York: Raven Press, 37–49.
87. Jansen FE, Braun KPJ, van Nieuwenhuizen O, et al. (2003) Diffusion-weighted magnetic resonance imaging and identification of the epileptogenic tuber in patients with tuberous sclerosis. Arch Neurol 60: 1580–4.
88. Koh S, Jayakar P, Dunoyer C, et al. (2000) Epilepsy surgery in children with tuberous sclerosis complex: presurgical evaluation and outcome. Epilepsia 41: 1206–13.
89. Koh S, Jayakar P, Resnick TJ, et al. (1999) The localizing value of ictal SPECT in children with tuberous sclerosis and refractory partial epilepsy. Epileptic Disord 1: 41–6.
90. Rintahaka PJ, Chugani HT. (1997) Clinical role of positron emission tomography in children with tuberous sclerosis complex. J Child Neurol 12: 42–52.
91. Szelies B, Herholz K, Heiss WD, et al. (1983) Hypometabolic cortical lesions in tuberous sclerosis with epilepsy: demonstration by positron emission tomography. J Comput Assist Tomog 7: 946–53.
92. Asano E, Chugani DC, Chugani HT. (2003) Positron emission tomography. In: Curatolo P (ed.). Tuberous sclerosis complex: From basic science to clinical phenotypes. Cambridge: Cambridge University Press, 124–35.
93. Chugani DC, Chugani HT, Musik O, et al. (1998) Imaging epileptogenic tubers in children with tuberous sclerosis complex using α[^{11}C]-methyl-L-tryptophan positron emission tomography. Ann Neurol 44: 858–66.
94. Juhasz C, Chugani DC, Musik O, et al. (2003) Alpha-methyl-L-tryptophan PET detects epileptogenic cortex in children with intractable epilepsy. Neurology 60:960–8.
95. Chandra PS, Salamon N, Huang J, et al. (2006) FDG-PET/ MRI coregistration and diffusion-tensor imaging distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex: A preliminary report. Epilepsia 47: 1543–9.
96. Kamimura T, Tohyama J, Oishi M, et al. (2006) Magnetoencephalography in patients with tuberous sclerosis and localization-related epilepsy. Epilepsia 47: 991–7.
97. Jansen FE, Huiskamp G, van Huffelen AC, et al. (2006) Identification of the epileptogenic tuber in patients with tuberous sclerosis: A comparison of high-resolution EEG and MEG. Epilepsia 47: 108–14.
98. Romanelli P, Verdecchia M, Rodas R, et al. (2004) Epilepsy surgery for tuberous sclerosis. Pediatr Neurol 31: 239–47.
99. Bebin EM, Kelly PJ, Gomez MR. (1993) Surgical treatment for epilepsy in cerebral tuberous sclerosis. Epilepsia 34: 651–7.

100. Avellino AM, Berger MS, Rostomily RC, et al. (1997) Surgical management and seizure outcome in patients with tuberous sclerosis. J Neurosurg 87: 391–6.
101. Baumgartner JE, Wheless JW, Kulkarni S, et al. (1997) On the surgical treatment of refractory epilepsy in tuberous sclerosis complex. Pediatr Neurosurg 27: 311–8.
102. Guerreiro MM, Andermann F, Andermann A, et al. (1998) Surgical treatment of epilepsy in tuberous sclerosis: strategies and results in 18 patients. Neurology 51: 1263–9.
103. Thiele EA, Duffy FH, Poissaint TY. (2001) Intractable epilepsy and TSC: The role of epilepsy surgery in the pediatric population [Abstract]. J Child Neurol 16: 681.
106. Karenfort M, Kruse B, Freitag H, et al. (2002) Epilepsy surgery outcome in children with focal epilepsy due to tuberous sclerosis complex. Neuropediatrics 33: 255–61.
107. Vigliano P, Canavese C, Bobba B, et al. (2002) Transmantle dysplasia in tuberous sclerosis: Clinical features and surgical outcome in four children. J Child Neurol 17: 752–8.
108. Sinclair DB, Aronyk K, Snyder T, et al. (2003) Pediatric temporal lobectomy for epilepsy. Pediatr Neurosurg 38: 195–205.
109. Jarrar RG, Buchhalter JR, Raffel C. (2004) Long term outcome of epilepsy surgery in patients with tuberous sclerosis. Neurology 62: 479–81.
110. Lachhwani DK, Pestana E, Gupta A, et al. (2005) Identification of candidates for epilepsy surgery in patients with tuberous sclerosis. Neurology 64: 1651–4.
111. Weiner HL. (2004) Tuberous sclerosis and multiple tubers: Localizing the epileptogenic zone. Epilepsia 45(Suppl 4): 41–2.
112. Romanelli P, Weiner HL, Najjar S, et al. (2001) Bilateral resective epilepsy surgery in a child with tuberous sclerosis: case report. Neurosurgery 49: 732–5.
113. Quarato PP, Gennero GD, Manfredi M, et al. (2002) Atypical Lennox-Gastaut syndrome successfully treated with removal of a parietal dysembryoplastic tumor. Seizure 11: 325–9.
114. You SJ, Lee JK, Ko TS. (2007) Epilepsy surgery in a patient with Lennox-Gastaut syndrome and cortical dysplasia. Brain Dev 29: 167–70.
115. McKenzie RG. (1938) The present status of a patient who had the right cerebral hemisphere removed. JAMA 111: 168.
116. Krynauw RA. (1950) Infantile hemiplegia treated by removing one cerebral hemisphere. J Neurol Neurosurg Psychiatr 13: 243–67.
117. Rasmussen T. (1983) Hemispherectomy for seizures revisited. Can J Neurol Sci 10: 71–8.
118. Smith SJM, Andermann F, Villemure JG, et al. (1991) Functional hemispherectomy: EEG findings, spiking from isolated brain postoperatively, and prediction of outcome. Neurology 41: 1790–4.
119. Hoffman HJ, Hendrick EB, Dennis M, et al. (1979) Hemispherectomy for Sturge-Weber syndrome. Child Brain. 5: 233–48.
120. Graveline C, Mikulis D, Crawley AP, et al. (1998) Regionalized sensorimotor plasticity after hemispherectomy: fMRI evaluation. Pediatr Neurol 119: 337–42.
121. Graveline C, Hwang PA, Bone G, et al. (1999) Evaluation of gross and fine motor functions in children with hemidecortication: Prediction of outcome and timing of surgery. J Child Surg 14: 304–15.
122. Castroviejo IP, Diaz Gonzalez CD, Munoz-Hiraldo E. (1993) Sturge-Weber syndrome: A study of 40 patients. Pediatr Neurol 9: 283–7.
123. Cross JH. (2005) Neurocutaneous syndromes and epilepsy — issues in diagnosis and management. Epilepsia 46(Suppl 10): 17–23.
124. Hwang PA, Graveline C, Jay V, et al. (2001) The hemispheric epileptic disorders: Indications for hemispherectomy. In: Luders HO, Comair YG (eds.). Epilepsy surgery. Philadelphia: Lippincott Williams & Wilkins, 157–63.
125. Kossoff EH, Vining EPG, Pillas DJ, et al. (2003) Hemispherectomy for intractable unihemispheric epilepsy. Etiology vs outcome. Neurology 61: 887–90.
126. Jonas R, Nguyen S, Hu B, et al. (2004) Cerebral hemispherectomy. Hospital course, seizure, developmental, language, and motor outcome. Neurology 62: 1712–21.
127. Kossoff EH, Buck C, Freeman JM. (2002) Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide. Neurology 59: 1735–8.

128. Gonzalez-Martinez JA, Gupta A, Kotagal P, et al. (2005) Hemispherectomy for catastrophic epilepsy in infants. Epilepsia 46:1518–25.
129. Cook SW, Nguyen ST, Hu BS, et al. (2004) Cerebral hemispherectomy in pediatric patients with epilepsy: Comparison of three techniques by pathological substrate in 115 patients. J Neurosurg (Pediatrics 2) 100: 125–41.
130. Devlin AM, Cross JH, Harkness W, et al. (2003) Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain 126: 556–66.
131. Arzimanoglou AA, Andermann F, Aicardi J, et al. (2000) Sturge-Weber syndrome. Indications and results of surgery in 20 patients. Neurology 55: 1472–9.
132. Van Empelen R, Jennekens-Schinkel A, Buskens E, et al. (2004) Functional consequences of hemispherectomy. Brain 127: 2071–9.
133. Tinuper P, Andermann F, Villemure J-G, et al. (1988) Functional hemispherectomy for treatment of epilepsy associated with hemiplegia: Rationale, indications, results, and comparison with callosotomy. Ann Neurol 24: 27–34.
134. Delalande O, Fohlen M, Jalin C, et al. (2001) From hemispherectomy to hemispherotomy. In: Luders HO, Comair YG (eds.) Epilepsy surgery. Philadelphia: Lippincott Williams & Wilkins, 741–6.
135. O'Brien DF, Basu S, Williams DH, et al. (2006) Anatomical hemispherectomy for intractable seizures: Excellent seizure control, low morbidity and no superficial cerebral haemosiderosis. Child Nerv Syst 22: 489–98.
136. Villemure J-G. (2001) Functional hemispherectomy: Evolution of technique and results in 65 cases. In: Luders HO, Comair YG (eds.). Epilepsy surgery. Philadelphia: Lippincott Williams & Wilkins, 733–9.
137. Taylor DC, Neville BGR, Cross JH. (1997) New measure of outcome needed for the surgical treatment of epilepsy. Epilepsia 38: 625–30.