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Surgery for Intractable Non-lesional Partial Epilepsy

Epilepsy surgery is a well recognised, time-honoured treatment modality for medically intractable partial epilepsy. It is generally recommended if two to three first-line antiepileptic drugs (AEDs) have failed to control seizures and the patient's epilepsy syndrome fulfils the criteria of "surgically remediable epilepsy syndromes (SRES)": SRES indicates an epilepsy syndrome for which (i) the natural history is relatively well known to be medically refractory or even progressive, (ii) presurgical evaluation can be accomplished largely non-invasively, and (iii) surgery offers an excellent chance that disabling seizures will be completely eliminated. Applicable syndromes include mesial temporal lobe epilepsy (MTLE), partial epilepsy with focal lesions, and hemispheric epilepsy in infants and children. The place of resective surgery in the management pathways of other types of epilepsy syndrome is still controversial, and may be considered only after the failure of exhaustive trials of AED therapy.

Resective surgery aims to completely resect or disconnect the "epileptogenic zone (EZ)" without precipitating any new neurological deficits. The EZ is a hypothetical zone defined as the brain area essential and sufficient for the generation of seizures, which can be confirmed only after surgery.¹

Identification and localisation of the EZ is the essential element of presurgical evaluation consisting of a set of different investigative procedures identifying various related zones: symptomatic zone, functional deficit zone, irritative zone, ictal onset zone, epileptogenic lesion, and eloquent cortex. Correct identification and logical correlation of these related zones is essential for the successful localisation of the EZ (Figure 1).

Recently, there has been a growing interest in surgery for partial epilepsy having no demonstrable structural abnormalities on MRI, "non-lesional partial epilepsy (NLPE)". This interest was precipitated by increasing proportions of patients suffering from refractory NLPE in epilepsy clinics, widely available intracranial EEG investigations, and advances in diagnostic technologies spanning from EEG telemetry to high-quality functional neuroimaging studies. Previously, Scott et al.² reported that the chance of successful resective surgery was unlikely in patients with NLPE, however, recent outcome studies for surgery of NLPE have been more encouraging, suggesting that it may provide a good chance of seizure control.^{3,4} McGonigal et al.⁵ reported that the surgical outcome in patients undergoing stereo-EEG investigations was not different between epilepsies with and without MRI lesions.

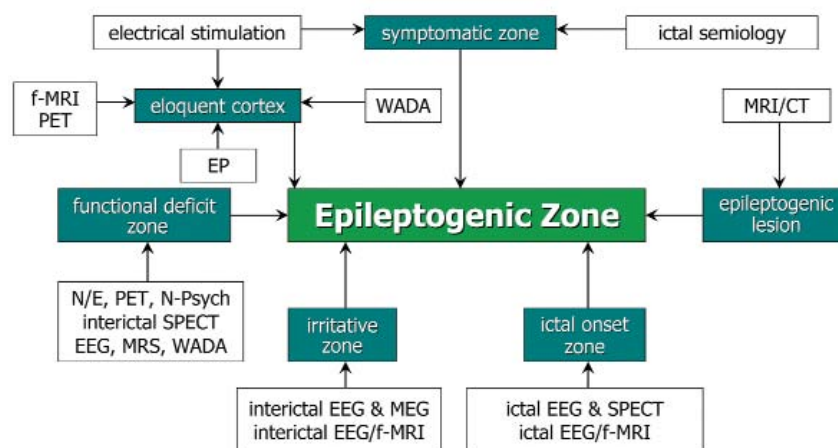


Figure 1: General concept of presurgical evaluation.

f-MRI, functional magnetic resonance imaging; WADA, intracarotid sodium amytal test (Wada test); EP, evoked potential; N/E, neurological examination; N-Psych, neuropsychological tests; MEG, magnetoencephalography; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Surgical outcome in non-lesional partial epilepsy

The clinical experience of surgery for NLPE before the beginning of this century was generally unfavourable with the seizure free rate (SFR) ranging from 20% to 50%,^{6,7} which was much poorer than that for lesional epilepsy surgery (55-70%). SFR of non-lesional temporal lobe epilepsy (TLE) was higher than that of extra-TLE: 31-50% vs. 20-29%, respectively. On the other hand, the surgical outcome of NLPE in recent series shows SFR between 36% to 65% (Table 1). There was a trend for SFR being higher in TLE than extra-TLE: 31-70% vs. 17-57% respectively, however, this was not a consistent feature among centres.^{8,9} We found the same trend towards improvement in the surgical outcome of NLPE in our own case series: SFR was only 17% in 18 patients who were operated on in the 1990's,¹⁰ compared to 57% in 14 patients who were operated on after 2005 (unpublished data). Therefore, we are convinced that the surgical outcome of NLPE has greatly improved over the past decade. Although explanations for the outcome improvement are not readily available yet, we speculate that:

- more cautious patient selection for invasive EEG investigations;
- more extensive and comprehensive brain coverage by invasive EEG;
- the advent of high resolution functional neuroimaging studies;
- application of improved analytical methods for data processing⁷
- greater clinical experience with epilepsy surgery in general.

Pathology

The pathological features of NLPE are quite variable but generally can be categorised into normal, nonspecific abnormalities (e.g., gliosis, microdysgenesis, etc.), and specific lesions (e.g., focal cortical dysplasia, hippocampal sclerosis, glioma, scars, etc.). The relative frequency of each histological category is variable in different studies but approximately 40% may reveal specific lesions, another 40% may show nonspecific pathologies and the remaining 20% may show normal features (Table 2). The correlation of each pathological category to surgical outcome is also variable to individual studies and inconclusive. In our own case series of 14 patients, focal cortical dysplasia (FCD) type II was associated with seizure-free outcome in 5 of 6 patients, while 3 of 6 patients showing normal or nonspecific abnormalities and neither of 2 patients with FCD type I achieved seizure freedom. In addition, patients with FCD type II were more likely to show focal abnormalities on PET (Figure 2); while other pathologies were more often associated with either normal or widespread abnormalities in PET. We speculate that normal or nonspecific pathology may be associated with the development of widespread epileptogenic networks compared to that of specific lesions, thus rendering the complete resection of EZ more difficult.

Table 1: Surgical outcomes in patients with normal MRI (recent series)

Authors (year) ^{ref.}	F/U (year)	N	Lobar Epilepsy (N)	Engel's classification			
				I	II	III	IV
Siegel et al. (2001) ³	≥ 2	24	TLE (10) Ex-TLE (14)	70% 57%	20% 21%	— —	10% 21%
Blume et al. (2004) ¹¹	≥ 2	70	TLE (43) Ex-TLE (27)	42% 30%	19% 4%	14% 7%	26% 59%
Chapman et al. (2004) ⁸	1-5	24	TLE (13) Ex-TLE (11)	31% 45%	54% 20%	— —	15% 35%
SK Lee et al. (2005) ¹²	≥ 2	89	TLE (31) Ex-TLE (58)	55% 43%	10% 5%	16% 31%	19% 21%
Alarcon et al. (2005) ⁴	≥ 1	19	TLE (13) Ex-TLE (6)	62% 17%	31% 17%	8% 33%	— 33%
RamachandranNair et al. (2007) ¹⁵	1-5	22	combined	36%	4%	32%	28%
McGonigal et al. (2008) ⁵	≥ 1	20	combined	65%	5%	25%	5%
Jayakar et al. (2008) ⁹	≥ 2	101	TLE (47)	47%	15%	17%	21%
			Ex-TLE (54)	41%	15%	17%	28%

ref = references; F/U = follow-up; N = number of patients; TLE = temporal lobe epilepsy; Ex-TLE = extra-temporal lobe epilepsy.

Table 2: Histopathology in surgery of non-lesional partial epilepsies.

Authors (year) ^{ref.}	N	Normal	Gliosis/microdysgenesis	Specific lesion†
Siegel et al. (2001) ³	24	13 (54%)	7 (29%)	4 (17%)
Cukiert et al. (2001) ¹³	10	2 (20%)	4 (40%)	4 (40%)
Chapman et al. (2004) ⁸	24	0	13 (54%)	11 (46%)
Alarcon et al. (2005) ⁴	21	0	7 (33%)	14(66%)
SK Lee et al. (2005) ¹²	80	0	9 (11%)	71 (89%)*
McGonigal et al. (2007) ⁵	23	0	11 (48%)	12 (52%)
Jayakar et al. (2008) ⁹	101	18 (8%)	71 (70%)	13 (13%)

ref = references; N = number of patients.
† includes focal cortical dysplasia, hippocampal sclerosis, dysembryoplastic neuroepithelial tumour, scars, etc. * included patients with microdysgenesis

Predictive factors for surgical outcomes

Despite much effort to find meaningful prognostic factors for surgery of NLPE, no agreed-upon specific markers have been identified yet. However, it should be stressed that the demonstration of focal abnormalities in functional neuroimaging studies, localised interictal epileptiform discharges with or without concordant ictal onset discharges in scalp EEG, and the absence of evidence indicating multifocal epileptogenesis^{11,12} are quite important positive features for undertaking intracranial EEG investigations. Preference for specific intracranial electrodes is dependent on the concepts and experiences of individual centers, but most authors agree on the importance of extensive coverage of suspected brain areas.¹³ The interpretation and clinical significance of various electrophysiological features recorded from the intracranial EEG has also

not been fully assessed. However, low amplitude fast frequency discharges, reproducible and stable ictal onset zones, fast repetitive spike patterns, or ictal onset from the margin of subdural electrodes, have all been reported to have prognostic implications.^{10,14} In addition, many other factors including, for example, MEG dipole clusters, Taylor-type FCD and complete resection of the ictal onset zone, have been claimed to be associated with a favourable outcome.¹⁵ However, it should be stressed that the degree of congruence of results from various independent investigations is of the utmost clinical importance rather than relying solely on any specific features of individual tests.

Conclusion

In conclusion, we have seen rapidly improving surgical outcomes for intractable NLPE over the past decade. Explanations for this observation

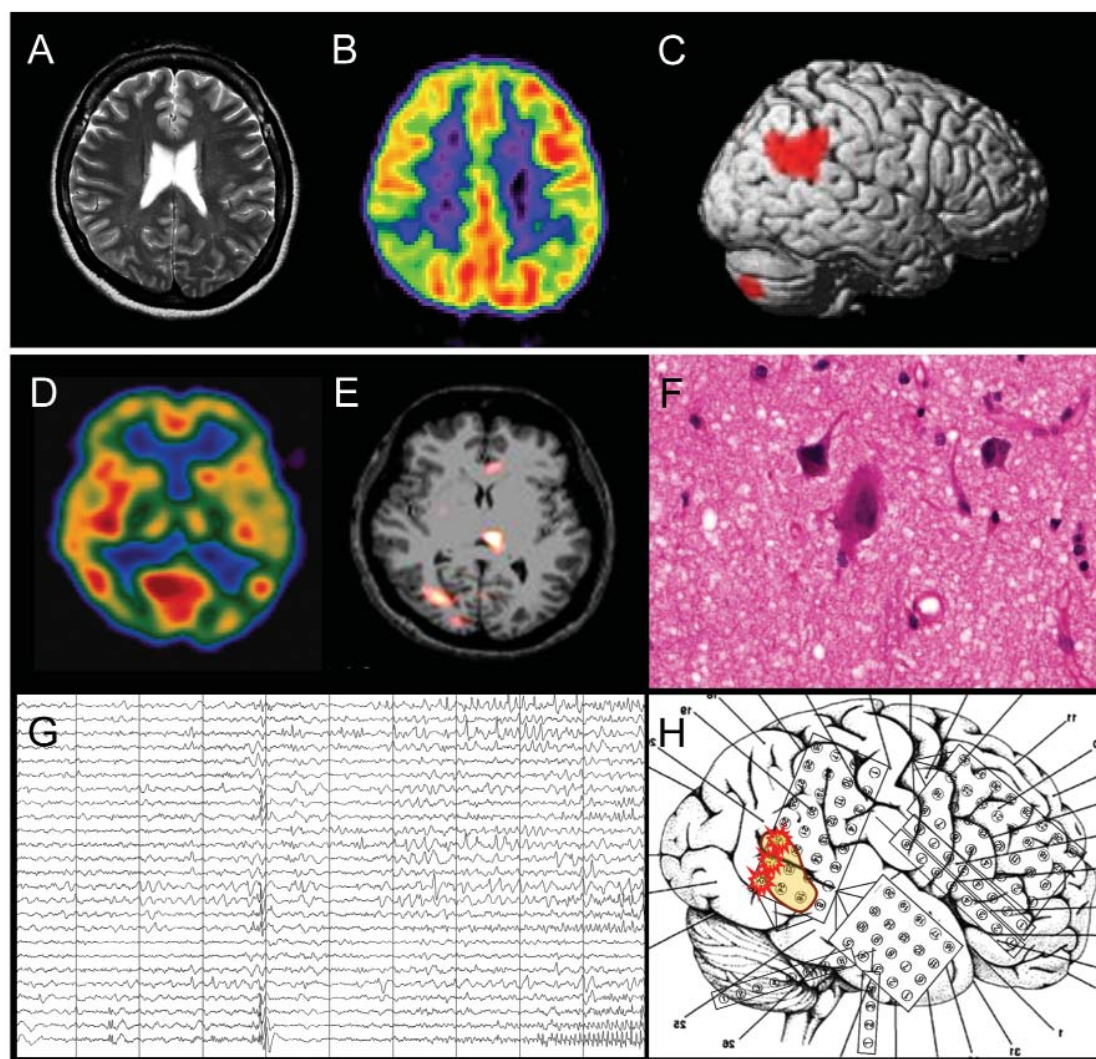


Figure 2: A 38-year-old right-handed woman who underwent resective surgery for chronic intractable complex partial seizures and secondarily generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality (A). Decreased metabolism in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased blood flow. Pathology of the specimen shows a dysmorphic neuron, consistent with FCD type-IIa (F). Focal rhythmic fast ictal discharges were initiated in the right parietal subdural grid (G; H, red), and then spread to the adjacent electrodes (H, orange).

are not readily available, but, it is likely that a more cautious selection of patients based on the assessment of phase-I investigation (correlation of scalp EEG, clinical and functional neuroimaging studies) as well as a more extensive and comprehensive coverage of the brain by intracranial electrodes might be responsible for this. It is also likely that NLPE consists of heterogeneous epilepsy syndromes related to different

types of pathology. From a limited clinical experience, we speculate that the presence of a specific lesion is associated with a higher chance of detecting focal abnormalities in functional neuroimaging studies and a limited epileptic network amenable to focal resection. In contrast, normal or nonspecific abnormalities are often associated with normal or widespread abnormalities in functional neuroimaging stud-

ies and more widely distributed epileptogenic networks, requiring more extensive coverage of the brain by intracranial electrodes as well as a more extensive resection to achieve a better surgical outcome. Recent experiences of surgery for NLPE suggest that undertaking an invasive presurgical evaluation in carefully selected patients is worthwhile and gives a reasonable chance of surgical success. ♦

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