Chapter

Emerging Trends in the Management of Cryptogenic Epilepsy

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Abstract

Cryptogenic epilepsy, accounting for ~40% of adult-onset epilepsies and a lesser proportion in paediatrics, is defined as epilepsy of presumed symptomatic nature in which the cause has not been identified. It has a higher prevalence of refractory seizures when compared to those with idiopathic epilepsy (40 vs. 26%). These patients are usually treated with multiple anti-epileptic drugs, yet the total number of which used is inversely proportional to their efficacy. Moreover, these children may have significantly worse behavioural problems and can result in substantial cognitive impairments when older. Luckily, the number of cryptogenic epilepsy cases is diminishing due to better diagnostic abilities in recent years. We aim to divide this chapter into three parts. First, we hope to discuss our working algorithm and explain the use and advantages of different imaging modalities including high-field 3-Tesla MRI with morphological analysis for accurate localisation of the epileptogenic foci. We shall then elaborate the concept of the epileptogenic circuit and explore the selection criteria for more invasive approaches, such as depth electrodes and SEEG. Last but not the least, we aim to discuss the surgical treatments, including VNS and DBS, and their outcomes in these patients.

Keywords: cryptogenic epilepsy, MRI-negative epilepsy, invasive monitoring, SEEG, MEG, TMS, FUS

1. Introduction

Cryptogenic epilepsies account for ~ 40% of adult-onset epilepsies and a lesser proportion in the paediatric age group. The majority of the cause is not identified, but it has a higher prevalence of refractory seizures and a worse surgical outcome. This group of patients also present with diagnostic difficulties as there are no abnormalities found in the magnetic resonance imaging (MRI) of these patients most of the time. Yet, the seizure frequency cannot be reduced by medications, and the prolonged use of anticonvulsants also poses detrimental long-term neuro-cognitive effects, particularly in children.

The pre-surgical evaluation is a crucial step in the identification of possible epileptogenic foci in these patients. An exhaustive list of investigations, for example

3T MRI, positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetoencephalography (MEG) and even invasive electrode monitoring, may be indicated for suitable candidates. The pros and cons of each of these investigations may vary, but they may provide the essential clues for the underlying disease region. Treatment methods may vary widely due to the concordance of the results, laterality of the language area and the resectability of these lesions. Despite surgical advances, genetics in epilepsies may also shed light on the treatment of idiopathic epilepsies in the future.

2. Cryptogenic epilepsy

2.1 Definition and causes

The aetiological causes of epilepsy are typically classified by the seizure type or syndrome. However, aetiology is also an important and major determining factor in the treatment, prognosis and clinical course of the disease. In the recent report by the International League Against Epilepsy (ILAE), the aetiology can be divided into three main categories, namely genetic, structural/metabolic and unknown causes. Shorvon et al. [1] have further divided them into four distinct categories:

1. Idiopathic epilepsy

2. Symptomatic epilepsy

3. Provoked epilepsy

4. Cryptogenic epilepsy

Cryptogenic epilepsy is defined as epilepsy of presumed symptomatic nature in which the cause has not been identified. The key difference between idiopathic and cryptogenic epilepsy is that idiopathic epilepsy is an inherited type with predominantly genetic or presumed genetic origin.

2.2 Epidemiology

It is difficult to tell the exact number of cryptogenic epilepsies due to problems with assigning causation in usual practice. For example, the distinction between idiopathic and cryptogenic epilepsies is often blurred and can be arbitrary, and the cause can be multifactorial in some patients. However, cryptogenic epilepsy is still one of the most common causes in adult-onset cases, accounting for approximately 40% of the total cases [1]. In another population-based study done in the 80s in the US, the annual age-adjusted incidence per 100,000 population was 17.2 for cryptogenic epilepsies [2].

2.3 Prognosis

In general, most epilepsy cases can be treated with anti-epileptic drugs. The remission rates are as high as 80, and 50% of patients are able to continue a life without

seizures after treatment discontinuation [3, 4]. However, cryptogenic epilepsies tend to have uncertain or poor prognosis in which seizures tend to recur despite exhaustive treatments. The risk of relapse in 2 years for idiopathic/cryptogenic seizure with an abnormal electroencephalogram (EEG) is 48% [5, 6].

These patients are often on multiple anti-epileptic drugs (AEDs) for a long period of time. The adverse effects of individual AEDs vary from fatigue, dizziness, mental slowness and skin reactions to haematological disturbances. Some patients may develop intolerability to AEDs and have to discontinue treatment early, yet the majority of patients will continue to be exposed to the AEDs for the rest of their lives. The prolonged use of AEDs may result in neurological symptoms of ataxia, dysarthria, tremors and deranged liver function [7]. Irritability and hostility are often seen with levetiracetam [8]. In the paediatric population, behavioural side effects combined with mental slowness may significantly affect the child's attention and schooling performance in the long run. Moreover, growth may also be stunted as suggested by some authors who found low serum calcium levels in children taking long-term valproic acid [9]. Hence, surgical treatment methods can be an alternative in the patients with refractive epilepsies for seizure control and to reduce the exposure to AEDs in the future.

3. Pre-surgical investigation

3.1 Clinical characteristic

To start the journey of pre-surgical workup for consideration of possible epilepsy surgery for drug-resistant epilepsy (DRE), a detailed interview with patient, patient's family and careers who can provide detailed witness history and past background is mandatory. A constructive interview includes a detailed description of patient's types of semiology during seizure attacks, recapitulation of all relevant past history, possible risk factors or aetiological factors. All possible epilepsy surgery cases are advised to be evaluated by a multi-disciplinary team conference according to the neuro-imaging, electrophysiological, neuropsychological and psychiatric findings based on the concept of 'six cortical zones' (**Figure 1**) [10]. This concept is based on the findings of all the pre-surgical evaluation tools and postulates the different zoning around the lesion identified. The goal of epilepsy surgery is to have maximal resection of epileptogenic zone but to have no or minimal surgical disruption of the surrounding eloquent cortex that may lead to permanent postoperative neurological deficit.

Temporal lobe epilepsy (TLE) is the most frequent syndrome in DRE. It accounts for ~40% of all patients with partial seizures and 15–20% of all types of epilepsy. Hippocampal sclerosis accounts for 60–70% of all TLE cases, while other structural aetiologies, including focal cortical dysplasia, tumours, vascular lesions, trauma, etc., happen in 10–15%. Remaining 15–20% patients are classified as Cryptogenic TLE. A study from Korea tries to elucidate the clinical phenotypes related to the prognosis. Good drug response group showed clinical characteristic including older age of onset, less initial precipitating events including febrile seizures, central nervous system infection, head trauma, less aura and automatism, less generalization of seizure and less EEG abnormality [11]. Such correlation of older age of onset of seizure with better seizure control prognosis was observed also in Italy group [12].

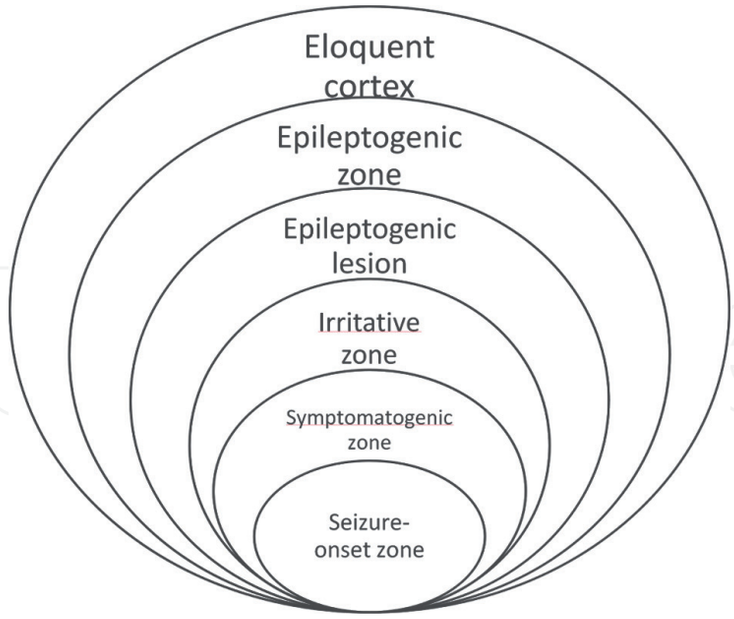

Figure 1.
Six cortical zones.

3.2 Neuro-imaging

About 20–40% of adult DRE patients can be classified as MRI negative or non-lesional or cryptogenic epilepsy. While no single investigation modality can provide optimal localization of epileptogenic foci in all cases, the use of multimodal imaging with a combined analysis of the findings of MRI, interictal PET and ictal SPECT can maximize the detection of the culprit [13, 14].

MRI scan of the brain constitutes the foundation of the imaging modalities. The recommended MRI epilepsy protocol in our hospital, the Queen Elizabeth Hospital, includes the following:

1. Volume acquisition T1W sequence acquired in oblique coronal orientation, orthogonal to long axis of hippocampus, covers whole brain in 0.9–1 mm partition

2. Oblique coronal T2WTSE and T2W FLAIR sequences orientated perpendicular to long axis of hippocampus, 2–3 mm slice thickness

3. Axial T2W or T2W FLAIR sequence of 3 mm slice thickness of whole brain

3T MRI system has better signal-to-noise ratio, spatial and tissue contrast resolution than 1.5T system and, therefore, it should be the gold standard of choice of MRI system for the epilepsy cases, together with Diffuse Tensor Imaging (DTI) and functional MRI functions [15]. The previous so-called 'cryptogenic epilepsy' cases by 1.5T MRI system turned out to be lesional cases after being rescanned by 3T MRI system with multichannel phased-array coils (**Figure 2**). Some centres are now using a 7T MRI system to confirm the suspicion in 3T MRI and locate any subtle lesions [16–18]. Apart from the increased signal-to-noise ratio, post-processing of MRI images by the application of voxel-based morphometric analysis

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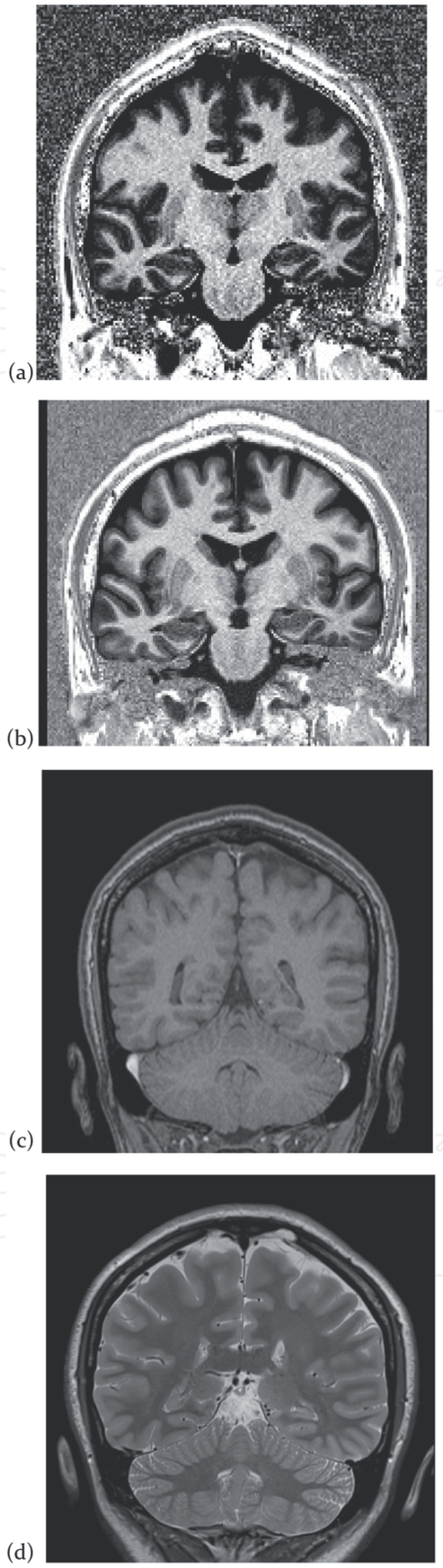


Figure 2.
A patient was regarded to be non-lesional epilepsy initially in 1.5T MRI (a); found to have cortical dysplasia in left temporal stem in 3T MRI (b); another epilepsy patient had very subtle lesion in right subependymal region in 1.5T MRI (c); and confirmed to be subependymal heterotropia by 3T MRI (d).

using morphometric analysis program (MAP) is another emerging direction to detect those subtle epileptogenic foci [13, 19, 20]. Wang et al. reviewed the use in 78 patients. About 56% had positive MAP, and complete surgical resection of MAP-positive regions was positively associated with good seizure outcomes. MAP-positive group rates were observed in 45% of TLE patients and 63% of extra-TLE patients [21].

FDG-PET (fluorodeoxyglucose positron emission tomography) scan is routinely used in pre-surgical evaluation. It is particularly helpful in cryptogenic TLE cases, as many of them displayed unilateral temporal hypometabolism in PET imagings. The predictive value of good surgical outcome is regarded up to 80%. In a retrospective review of 60 cases in China with unilateral TLE, one-third of all patients were cryptogenic groups with positive PET findings. There was no significant difference between surgical outcomes of lesion group and non-lesion group (Engel class I 68.3 and 68.4%, respectively) [22]. Similar study was carried out by LoPinto-Khoury et al. with 46 PET-positive cryptogenic TLE cases and 147 mesial temporal sclerosis cases. Engel class I rate did not differ significantly between two groups in two and five years (76% in 2 years and 75% in 5 years vs. 71% in 2 years and 78% in 5 years, respectively) [23]. Newer viewing platforms for PET scan including statistical parameter mapping (SPM) and three-dimensional stereotactic surface projection (3D-SSP) were employed to improve the sensitivities to detect epileptic foci in cryptogenic cases up to 60–70% [24].

With technological advancements, MRI scan images can be coregistered with FDG PET scan images and the MRI/PET scan. This further helps clinician to identify the subtle lesions in those previously believed cryptogenic epilepsy cases [25]. Toth et al. in Hungry had a prospective study of MRI/PET scan on 30 non-lesional and 30 lesional cases with discordant pre-surgical results. They concluded that the results of MRI/PET scan significantly altered the original plans in 19 of 60 cases [26]. In Hong Kong, this technology has been introduced since 2017 and we have more epilepsy patients that showed promising results in pre-surgical workup (**Figure 3**).

Ictal single photon emission computed tomography (SPECT) is used to provide information about regional cerebral perfusion, alteration of which is regarded to be hyper-activity and may be suggestive to be epileptogenic focus. Among those common substances used for ictal SPECT, 99mTc-bicisate (99mTc-ECD) had shorter injection latencies and a higher number of accurate ictal injections compared with 99mTc-hexamethyl propylene amine oxime (99mTc-HMPAO). It can correctly localize the epileptogenic focus in up to 97% of cases with known unilateral TLE and up to 90% in known or suspected extratemporal lobe epilepsy. For its application in cryptogenic epilepsy cases in order to improve the detection of epileptogenic foci, Yassin et al. proposed some innovative methods including subtraction ictal SPECT coregistered to MRI (SISCOM), statistical ictal SPECT coregistered to MRI (STATISCOM) and PET interictal subtracted ictal SPECT coregistered with MRI (PISCOM) [27].

Magnetoencephalography (MEG) helps to localize the epileptogenic zone and delineate the relationship between the suspected abnormality and the relevant regions in the brain. The placement of invasive electrodes can be guided by the MEG findings. A MEG-guided review of MRI may reveal subtle abnormalities and permit a precise surgical excision of the irritative zone. MEG is also indicated in patients with multiple intracerebral lesions, such as multiple cavernomas, in whom a sole epileptogenic lesion may be identified for lesionectomy [28]. In cryptogenic epilepsy

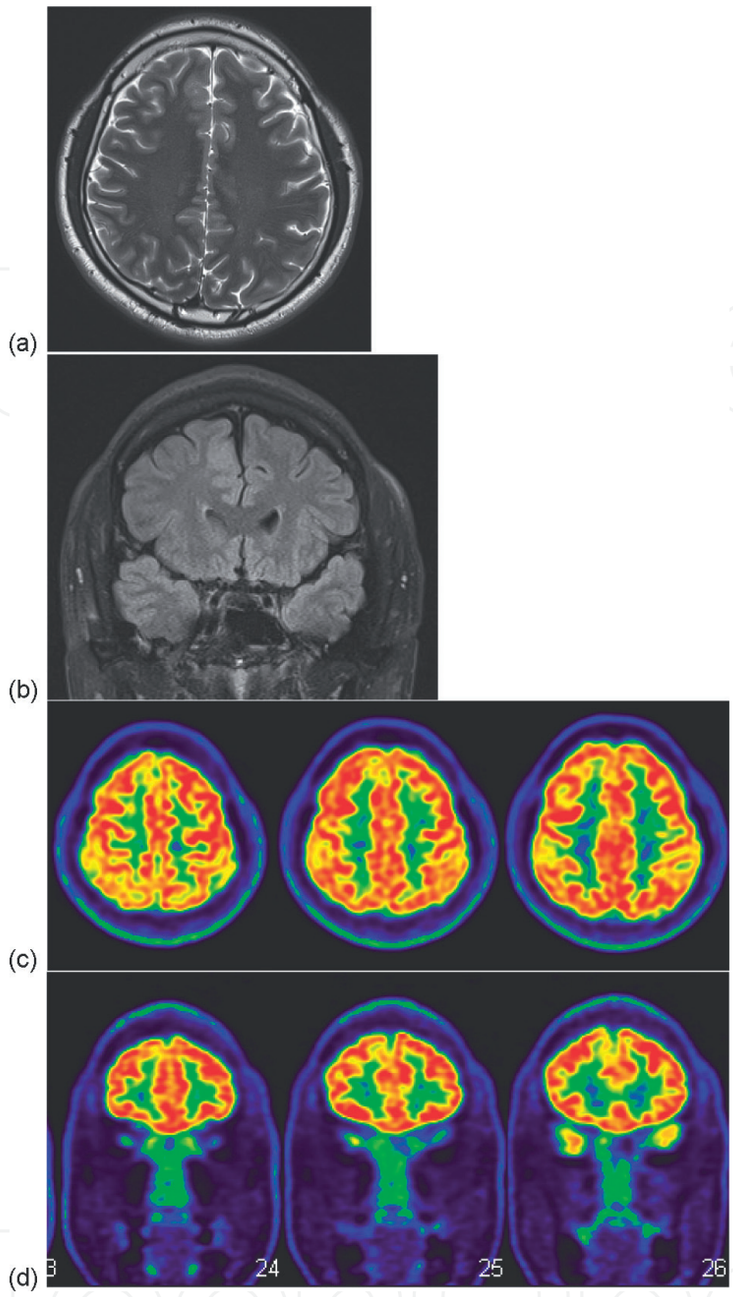


Figure 3.
A patient with frontal lobe epilepsy had negative 3T MRI finding (a) and (b); and subsequently, MRI/PET scan showed hypometabolism over left mesial frontal region (c) and (d).

cases, electric and magnetic source imaging (ESI/MSI) facilitate the prognostic assessment [29, 30].

3.3 Invasive intracranial electroencephalogram (EEG) studies

In general, the indications to consider invasive EEG monitoring are as the followings:

1. To define precisely the epileptogenic zone when non-invasive data are not concordant

2. To conclude the divergence of non-invasive data in different regions

3. To map eloquent cortical and subcortical function for respective surgery planning

4. To further validate the epileptogenic zone or provide information on prognostic value

5. To perform therapeutic treatment for active regions using thermocoagulation

Traditional invasive EEG modalities include subdural electrodes, intracerebral depth electrodes, epidural peg electrodes and foramen ovale electrodes. A comprehensive review on risks and benefits of using subdural and depth electrodes showed that the related complications include epidural or subdural haemorrhage, intracerebral haemorrhage or contusion, meningitis, oedema around the electrode, cerebral oedema, increased intracranial pressure, etc. The overall complication rate ranges from 0.4 to 6.6%.

Stereo-electroencephalography (SEEG) is gaining popularity to enable precise recordings from deep cortical areas in bilateral and multiple lobes without subjecting the patients to have bilateral large craniotomies. The key and most important concept in considering SEEG is to test individualised *anatomo-electro-clinical hypothesis*. Based on clinical history, semiology, preoperative imaging and vEEG data, the findings of SEEG help the clinicians to understand the spatial and temporal dynamics of seizures, that is where it starts, when and when it spreads. Study from the Italian group showed that SEEG is a useful and relatively safe tool to localize the epileptogenic zone with procedure-related morbidity of 5.6%. Other centres incorporate the neuro-robotic system in performing SEEG and showed comparable results. In general, SEEG had equivalent efficiency in determination of epileptogenic zone with lower operative morbidities and complications including CSF leak, intracranial haemorrhage and better tolerance to patients [31–34] (**Figure 4**). The application of SEEG in paediatric epilepsy patients was evaluated by Kim et al. Half of cryptogenic paediatric patients achieved postoperative seizure freedom [35].

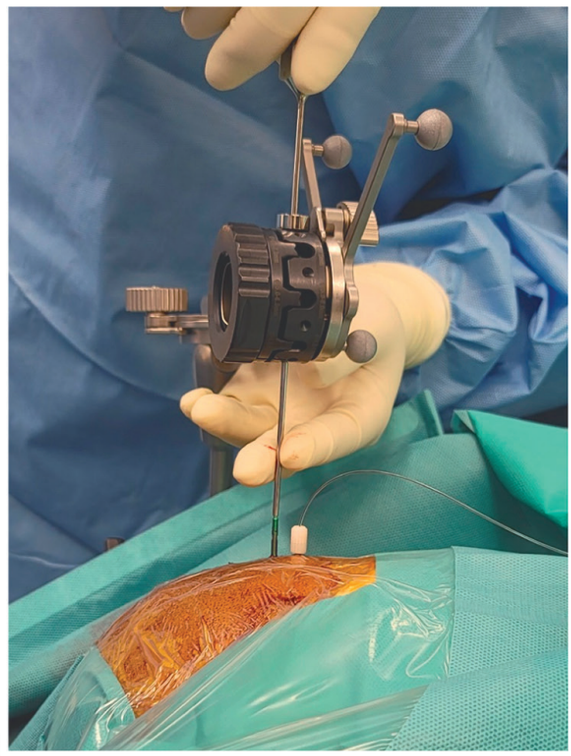
Resective surgery in cryptogenic epilepsy cases usually can achieve Engel Class I seizure control in 30–60%. Invasive monitoring in terms of subdural grid, strip, depth electrodes and more advanced use of SEEG is a tool to attain a more precise localization of seizure. McGrath et al. in Yale have compared the surgical outcome of 48 cryptogenic epilepsy patients. Eleven patients underwent surgery without invasive monitoring, while 37 patients had invasive monitoring before their resective surgery or neuromodulative surgery. More patients with Engel Class I & II or III & IV outcomes underwent invasive monitoring (100 and 83%, respectively) [36].

4. Surgical treatment options

4.1 Multidisciplinary approach

As mentioned in the previous section, about 20–40% of adult DRE patients can be classified as MRI negative, non-lesional or cryptogenic epilepsy. Despite having more

(a)



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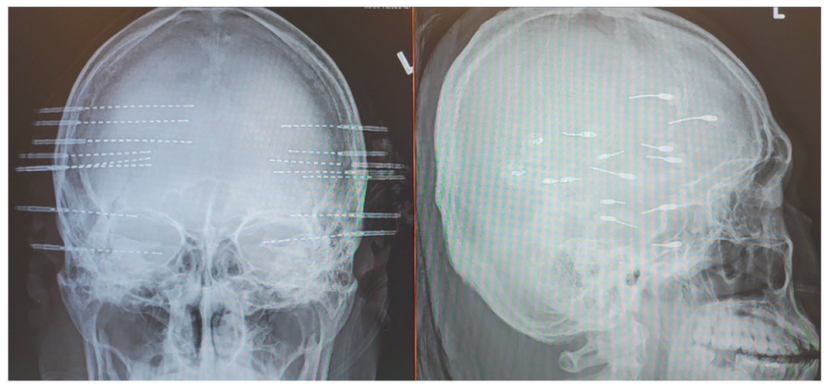

(c)

Figure 4.
Stereo-electroencephalography (SEEG) implantation in a patient with suspected right posterior temporal cryptogenic epilepsy (SEEG implantation) (a); post-implantation skull X-ray (b); and SEEG position coregistration with postulated epileptogenic zone in the neuro-navigation system (c).

advanced diagnostic methods in our armamentarium, the identification of the epileptogenic foci can still be an exercise of chasing the wind and clutching at shadows. The decision on how to treat these cryptogenic cases thus relies on a multidisciplinary approach to ensure the concordance of our findings.

In the usual practice, multidisciplinary epilepsy conferences are held regularly between neurosurgeons, neurologists, epileptologists, neuroradiologists and neuropsychologists to incorporate the different test results and opinions formulated for each case. Neuropsychologists are of particular importance in the evaluation of the baseline cognitive ability, lateralization of seizure focus and academic or occupational accommodations. This allows for a more tailored and holistic focus to assist the patient to return to work and normal life. However, some potential confounding factors may affect the test performance and its interpretation. For instance, patients on long-term AEDs may already have some cognitive side effects irrespective of the seizure semiology. Tasks that require memory may also be hindered, thus affecting the interpretation of laterality. Nevertheless, these results may be further dissected and correlated with the presenting symptoms in the conference meetings for the final decision management. We shall focus on the surgical approach in MRI-negative epilepsy patients in this chapter.

4.2 Resective surgery

Temporal lobe epilepsy (TLE) remains the most common cause of focal seizures in adults. Up to 30% of TLE cases can be non-lesional in MRI and requires complex pre-surgical workup. The surgical outcomes for non-lesional TLE patients are typically worse than lesional TLEs, with a pooled proportion of seizure-free patients 51 vs. 75% [37], and only 41–81% were documented to have Engel class 1 outcome at 1 year [38]. In TLE patients with concordant findings of the epileptogenic focus, anterior temporal lobectomy and selective amygdalohippocampectomy are indicated. Because these patients have no obvious lesion found in the temporal lobe and no hippocampal sclerosis, a formal neuropsychological evaluation, functional MRI +/- WADA test, is strongly encouraged to determine the language laterality and memory status prior to surgery. Invasive EEG monitoring can be an advantageous investigation, especially with dominant-side TLE patients, as the hippocampus may be spared if the invasive electrodes showed no activity during the ictus period.

Extra-temporal non-lesional epilepsy is even more difficult to visualize and resect completely. The outcomes of extratemporal non-lesional surgery are fair, with only 42% being seizure free at 2 years after surgery [39, 40]. Frontal lobes are the most common location for extra-temporal epilepsies; however, resection has a limited role in this group as it is not easy to identify the epileptogenic zone. Firstly, the interictal spikes may spread rapidly, making it difficult to even lateralize the lesion. Secondly, automatic clinical features may be due to a spread from other locations rather than a frank frontal seizure, as epileptogenic zones can be widespread. Lastly, the seizure focus may overlap with eloquent areas, such as the Broca's area and motor strip regions, which may limit the extent of resection. parieto-occipital lesions only account for ~ 1% of resections in some series.

In these cases, awake surgery may be indicated to help preserve function and excise the epileptogenic foci as much as possible. The use of intraoperative electrocorticography (ECOG) is another useful adjunct to ensure that the epileptogenic focus is completely resected (**Figures 5** and **6**). The region of abnormal

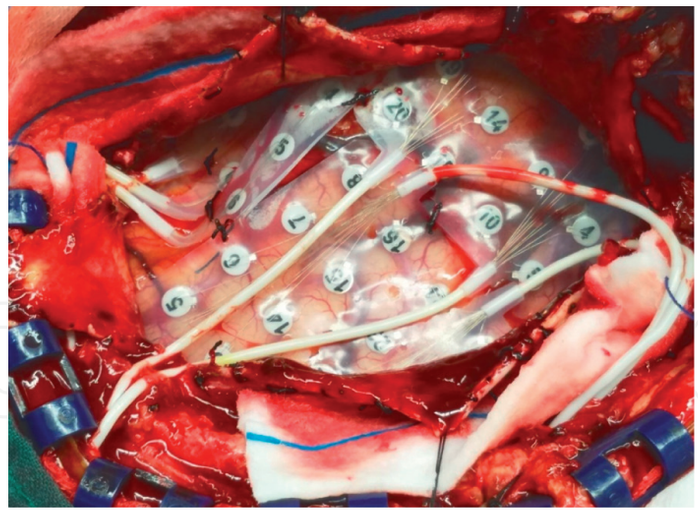

Figure 5.
Intraoperative photo of subdural grids used as electrocorticography. The epileptogenic foci were found to be in the area labelled '14, 15'.

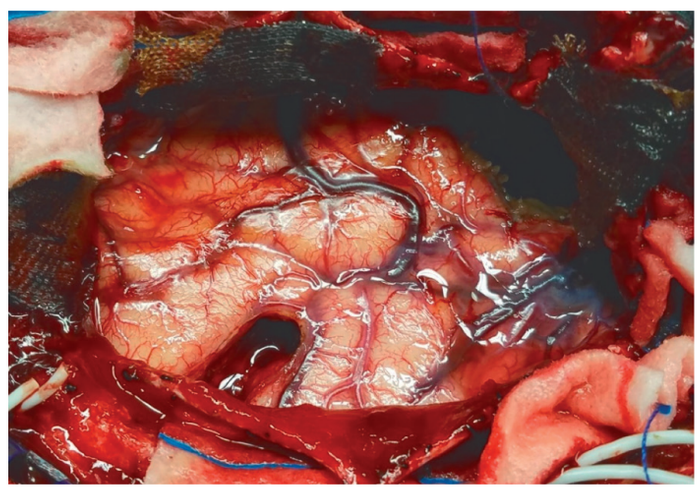

Figure 6.
Epileptogenic foci resected according to the labelled number '14, 15' on the grid with cavity seen.

electrical activity can be narrowed down using the labelled numbers prior to the procedure during the invasive monitoring period. The surgeon can then limit the zone of resection so as to avoid unnecessary neurological deficits, especially in lesions close to eloquent areas. Additionally, the ECOG enables the monitoring of inter-ictal spikes during the procedure, which is usually reduced after resection of the ictal zone.

Interestingly, the histopathological results were not entirely 'normal' in these patients. Focal cortical dysplasia (FCD) is the most commonly found pathology in MRI-negative epilepsy surgeries, with other aetiologies including gliosis, hippocampal neuronal loss or no pathology identified. In patients with non-concordant findings, resection is not recommended.

4.3 Neuromodulative surgery

Neuromodulative surgeries in terms of application of implanted devices and electrodes are regarded as palliative treatment for DRE cases that are not indicated for

resective surgeries or disconnection surgeries. Vagus nerve stimulation (VNS) was approved by the U.S. Food and Drug Administration (FDA) in 1995, while the other two treatment modalities, Responsive neurostimulation (RNS) and Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT), had approval granted in 2014 and 2018, respectively [41]. Their mechanism of action and indications can be summarized as the followings (**Table 1**) [42, 43]:

	Mechanism of action	**Indications**
VNS	1. Alteration of noradrenergic projection system from the locus coerulus to connected regions including hippocampus, thalamus, hypothalamus, orbitofrontal cortex and cerebellum 2. Other involved possible circuitries including reticular activating system, central autonomic network and limbic system	1. Patients 4 years of age and older with focal onset seizures 2. Effective in individuals with primary generalized epilepsy
RNS	1. Only closed-loop system for epilepsy treatment 2. Stimulation of cortical neurons induces both immediate and long-term changes in local and distant sites involved in epileptic network	Patients 18 years of age or older with focal onset of seizures with less than two epileptogenic foci
DBS	1. Increased transmission of both excitatory and inhibitory neurotransmitters within basal ganglia-thalamocortical circuitry 2. Inhibition of action potential through sodium channel-mediated depolarization inhibition, direct distal axonal synaptic inhibition, depletion of neurotransmitters at distal terminals and potentiating the above mechanisms *via* direct stimulation	Patients 18 years of age or older with both focal or generalized onset of seizures

Table 1.
Possible mechanism of action and indications of VNS, RNS and DBS.

When we decide which neuromodulative surgical modality is most suitable for our patients, there are a few considering factors including the mechanism of action, device features, tolerability, patient preference and co-morbidities and disease focality. Concerning the long-term 0utcomes, the number of studies showed no major differences in seizure control between different neuromodulative modalities with sustained improvement in quality of life [44–46]. In principle, VNS is effective for generalized-onset seizure. It has a diffuse effect and does not require localization. RNS depends on the localization of seizure-onset zones, which requires the analysis of invasive intracranial EEG recording results. DBS also does not require localization of seizure-onset zone, but seems it is more effective in patients with strong limbic system involvement. Besides, the safety profile of individual devices is another aspect to be considered (**Table 2**) [47–51].

In paediatric epilepsy patient group, VNS is traditionally believed to be the only choice of neuromodulative modalities. There is a recent review paper about the safety and efficacy of DBS in paediatric patients. Forty patients aged from 4 to 18 years old had received DBS treatment with targets including anterior nucleus of thalamus, centromedian nucleus of thalamus, hippocampus, subthalamic nucleus, hypothalamus and mammillothalamic tract. Overall, 12.5% of patients had achieved Engel class I seizure control, and 85% of patients had post-stimulation seizure reduction [52].

Devices	Safety profile
VNS	Possible stimulation-related adverse effects, for example hoarseness, cough and largyneal paresthesia. Worsening of obstructive sleep apnoea
RNS	Procedure-related primary burden. Possible adverse effects, for example haemorrhage, implant site pain or infection, headache and dysesthesia
DBS	Procedure-related primary burden. Possible adverse effects, for example implant site pain, paresthesia or infection, lead mistargeting, stimulating-related depression and memory impairment

Table 2.
Comparison of safety profiles of different neuromodulative surgeries.

In Hong Kong, VNS and DBS were available for our patients with DRE. First VNS was implanted in 1995. Since the government policy in funding subsidization in 2018, more cases were performed and totally, 70 devices were implanted. Half of them were adult patients and half of them were paediatric patients. DBS for refractory epilepsy cases were performed since 2015. Totally, 10 cases were performed by 2 epilepsy centres. In our hospital, Queen Elizabeth Hospital, we had four adult cases performed since 2020. The targets were all ANT *via* trans-ventricular route. There were no major perioperative surgical complications and neurological deficits, and there was no stimulation-related depression noticed. The mean seizure reduction rate >50% was ~60% at 3 months.

As mentioned, VNS, RNS and DBS have different mechanisms of action, preferred indications and their own unique adverse side effects, some centres borrow the concept of pharmacologic treatments with multiple anti-epileptic medications, and they had tried to consider polyneurostimulation in patient that had a suboptimal response to VNS treatment [53]. Mayo Clinic had a review on 131 patients who underwent neuromodulative surgeries from 1998 to 2021. Among those with VNS implanted, active dual stimulation occurred in 3 of 28 patients using RNS and 8 of 8 patients using DBS ($p = 0.006$). Patients who received VNS-DBS achieved a similar previous response to VNS ($p = 0.025$) and were unresponsive to more anti-epileptic drugs ($p = 0.02$). The VNS-RNS side had focal seizures more likely to have better electroclinical localization ($p = 0.005$), and more invasive intracranial EEG monitoring ($p = 0.026$) [54].

5. Emerging trends in cryptogenic epilepsies

5.1 Epilepsy genetics and future development

The modern era of technological advancement has pushed forward the progress of gene therapy. Since the completion of the Human Genome Project, more than 1800 disease genes have been identified. The first epilepsy-associated gene was discovered in 1995 in a family of autosomal dominant nocturnal focal lobe epilepsy (ADNFLE), the gene found was CHRNA4. In the recent decade, about 20 major genes were found to be associated with epilepsy, and they can be classified into different categories of voltage-gated, ligand-gated ion channels, subunits of acetylcholine receptors (CHRNA2, CHRNA4 and CHRNB2), subunits of sodium channels (SCN1a, SCN1B, SCN2A) and subunits of potassium channels (KCNQ2, KCNQ3), GABA (GABRA1, GABRA2).

Genetic disease accounts for approximately 70% of epileptic syndromes [55, 56]. In most circumstances, a syndromal diagnosis can be reached within the first few months

of the disease in the infant onset epilepsies [57]. However, the diagnosis remains cryptogenic in about one-third of these patients despite clinical and EEG characteristics [57, 58]. In the routine clinical setting, testing of the autoantibodies, organic acids and neurotransmitters is used to find underlying autoimmune or metabolic causes for seizures. Genetic testing is the next step of investigation if the blood tests were negative. But the diagnostic yield is merely 10% in infantile epilepsies and 5% in epileptic developmental encephalopathies [56] using conventional methods. These methods may include genomic microarrays to detect DNA copy number variants (CNV), karyotyping for chromosomal abnormalities and single-nucleotide polymorphism (SNP) arrays to reveal regions of homozygosity. The reason for the low diagnostic yield is due to the fact that most epilepsies are actually associated with single-gene mutations instead. Traditional Sanger sequencing has been used by physicians to determine the nucleotide sequence of the exons of different genes; however, only one fragment of DNA can be run at a time. The cost is high when multiple genes are to be examined.

Next-generation sequencing (NGS) studies have provided a new light on the diagnosis of epilepsy genetics. There are three forms of NGS testing, epilepsy gene panel, whole exome sequencing (WES) and whole genome sequencing. The epilepsy gene panel can hold over 100–300 genes, which can detect molecular anomalies that could have been missed by traditional Sanger sequencing [59]. Whole exome sequencing (WES) allows simultaneous sequencing of exons of all the coding regions, that is ~1–2% of the whole genome, at a relatively low cost [55, 60], whereas whole genome sequencing (WGS) detects variants on the entire genome for both coding and non-coding regions. The diagnostic yield ranges from 20 to 50% depending on the different genetic panels that are available in the market and the clinical characteristics of patients [56, 61]. The cost of performing these tests was substantial in 2007 [62], but luckily the cost has been brought down to ~USD$1000 as NGS has been increasingly adopted into the routine clinical practice.

As the causes of early onset, infantile epileptic encephalopathies are heterogeneous and are often genetic, and NGS-based tests can be offered as a quicker method if an actionable condition is suspected. For instance, patients with cerebral creatine deficiency syndrome (SLC6AB, GAMT variant) can be treated with creatine replacement and phosphoglycerate dehydrogenase deficiency (PHGDH) with L-serine, or to manage with a ketogenic diet in glycine encephalopathy (GLDC) (**Table 3**). In patients with tuberous sclerosis, clinical trials have shown a reduction in seizures with the use of mTOR inhibitors [59, 65]. More clinical trials may be directed to the mTOR pathway in the future of targeted therapies in these patients. Potassium channel opener, retigabine, is a potential new drug indicated for KCNQ2-associated encephalopathy. This approach of precision medicine can tailor treatment methods for patients' needs and avoid detrimental side effects. Sodium channel blockers such as carbamazepine are the treatment of choice for SCN2A and SCN8A mutations, but they may cause worsening symptoms in Dravet syndrome (SCN1A gene mutation) [63].

Technical difficulties of NGS exist, a large amount of data retrieved need to be handled properly, and the complexity of the results requires a dedicated researcher for interpretation. Epilepsy has a large genetic heterogeneity, and a single epilepsy syndrome may be caused by 1 gene mutation in a family but can be due to many different genetic mutations in another. Moreover, additional studies have found new classes of gene mutations with poor geno-phenotypical relationships. Hence, it can be very challenging to determine the causative role of the detected gene mutation in NGS panels. Epilepsy in infants with migrating focal seizures (EIMFS) is pathologically due to the KCNT1 variant; however, this gene abnormality is also observed in many other epileptic syndromes. More than 20 different genes are also causatively linked to EIMFS in different studies [66, 67].

Gene variant	Target	Related syndromes	Treatment	Contraindications
1. Ion channelopathies and function-based therapies				
SCN1A	Sodium channel	Dravet syndrome, EIMFS, GEFS	N/A	Avoid sodium channel blockers[63] for example carbamazepine, oxcarbazepine, phenytoin
SCN8A	Sodium channel	DEE, familial myoclonic epilepsy, EIMFS	Carbamazepine, Oxcarbazepine, phenytoin	—
KCNQ2	Potassium channel	DEE, BFNE,	Retigabine	—
CACNA1A	Calcium channel	West syndrome, DEE	Ethosuximide, lamotrigine	—
GRIN2B	NMDA receptor	West syndrome, LGS, DEE	Memantine, radiprodil	—
CHRNA4	nAChR	NFLE	Transdermal nicotine	—
2. Metabolic diseases and substitutive therapies				
SLC2A1	Glucose transporter type 1	GLUT1 deficiency	Ketogenic diet	Phenobarbital, valproic acid, benzodiazepine [64]
GAMT	Guanidinoacetate methyltransferase	Cerebral creatine deficiency syndrome 2	Creatine replacement	—
POLG	DNA polymerase gamma	Mitochondrial disease	N/A	Valproic acid
3. Cell-signalling pathways and modification therapies				
NPRL	GATOR1 complex	FFEVF	Rapamycin and derivatives, e.g. everolimus, sirolimus	—
TSC1/2	TSC1/2	Tuberous sclerosis, focal dysplasia		—

BFNE, benign familial neonatal epilepsy; DES, developmental and epileptic encephalopathy; EIMFS, epilepsy in infancy with migrating focal seizures; FEEVF, familial focal epilepsy with variable foci; GEFS, generalized epilepsy with febrile seizures; LGS, Lennox-Gastaut syndrome; NFLE, nocturnal frontal lobe epilepsy; and nAhR, neuronal nicotinic acetylcholine receptors.

Table 3.
Genetic causes of epilepsy syndromes and treatment [56, 58].

Nevertheless, the ability to diagnose patients at an earlier age may prompt the development of specific drug therapies targeted to these mutated proteins in the future. The implications of NGS may also extend to potential therapeutic methods to prevent and avoid epilepsy development, and on-going studies are underway to limit epileptogenesis in tuberous sclerosis and Sturge-Weber syndromes [58, 68]. Other promising directions are towards the understanding of pharmacogenomics, gene therapy, and perhaps combining with artificial intelligence algorithms to predict pharmacoresistant patients [69].

5.2 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is FDA approved for depression, migraines and obsessive-compulsive disorder (OCD). TMS is one of several newer treatments that can potentially offer epilepsy patients a tool for investigating the brain excitability, and a safe and non-invasive alternative to open traditional surgery. It allows probing the cortical excitability and analysing the excitatory and inhibitory brain mechanisms. TMS also had been used for the preoperative localization of the epileptogenic zone and mapping of eloquent area. Treatment for refractory epilepsy was another potential application [70]. Santiago-Rodriguez et al. in Mexico had conducted an open-label study for twelve epilepsy patients. Repetitive TMS (rTMS) was employed with 900 pulses, intensity of 120% motor resting threshold and 0.5 Hz frequency. Reduction of seizure frequency during the intervention period and follow-up period at 8 weeks were noticed but the differences were not statistically significant ($p = 0.19$) [71]. Application of low-frequency rTMS at 0.9 Hz with resting motor threshold stimulus intensity of 90% as treatment protocol was conducted also in Japan group, and they showed the frequency of all seizure types, complex partial seizures (CPSs) and simple partial seizures were reduced by 19.1, 35.9, and 7.4%. A trend of improvement, though not statistically significant, was demonstrated [72]. Lefaucheur et al. proposed guidelines established by a group of European experts on the therapeutic use of rTMS in other neurological disorders. In his paper, one sham-controlled low-frequency rTMS trial was quoted with seven patients with focal neocortical DRE received three treatment sessions with the following treatment plan: 10 sessions delivered by means of a figure-of-8-coil, a round coil, or a sham coil at 0.5 Hz and 90% of RMT over the cortical focus (1500 pulses/session). No difference in mean seizure rate was detected with one patient who had seizure rebound [73].

The other side of the coin in the use of TMS as potential treatment of refractory epilepsy is that there is a risk of TMS-triggered seizure attack. George and Belmaker mentioned patients with focal or generalized encephalopathy, severe head trauma, non-treated epilepsy, family history of epilepsy in first-degree relatives, heavy alcohol use, severe cardiac disease, increased intracranial pressure, medications that lower seizure threshold, etc., will have a relatively higher risk to have such seizure attack [74]. The general risk of seizures with TMS was ~0.08/1000.

Boston group done a review of over 70 articles related to the use of TMS-EMG and TMS-EEG in elucidating the mechanisms of action of anti-epileptic drugs (AEDs) and discovering potential new AEDs, and the use of rTMS in the treatment of seizures. For diagnostic potential, TMS-derived biomarkers can facilitate the measurement of AED target engagement and the study of pharmacokinetic and pharmacodynamic behaviours in order to predict the efficacy of different AED usage in epilepsy patients. For therapeutic potential, there is a trend to have favourable results [75]. Tsuboyama in the same group had another study to investigate the TMS-EMG metrics (**Table 4**) [76]. These findings imply that TMS may have a potential role in the optimization of AED regimens for epilepsy patients. Similar findings were reported by Bauer et al. also [77].

5.3 Focused USG

Neuromodulative surgeries in terms of DBS, VNS and RNS as treatment of refractory epilepsy cases were well established. Focused ultrasound (FUS) is considered as a non-invasive new armamentarium that can ablate the epileptogenic focus and modulate neuronal circuits or activities. The transducer in FUS is designed to transmit the acoustic energy only and directly to the chosen target according to the

TMS-EMG parameter	Purposed mechanism
Resting motor threshold (rMT)	Cortical motor neuron voltage-gated sodium channel-mediated membrane excitability
Cortical silent period (CSP)	$GABA_B$-mediated and $GABA_A$-mediated motor cortex inhibition
Short-interval intracortical inhibition (SICI)	$GABA_A$-mediated regional cortical inhibition
Intracortical facilitation (ICF)	Glutamate (NMDA and AMAPA receptor types)-mediated excitation
Long-interval intracortical inhibition (LICI)	$GABA_B$-mediated inhibition and (likely) $GABA_A$-mediated network inhibition

Table 4.
Transcranial magnetic stimulation-electromyography (TMS-EMG) metrics.

preoperative planning. Different intensity serves in different mechanisms of treatment. High-intensity FUS (~1000 W/cm^2) execute the thermoablation effect, while low-intensity mode (~3 W/cm^2) showed neuromodulatory effects and suppressive effects on the frequency of epileptic signal bursts. The proposed mechanism of action of low-intensity FUS included the following [78]:

1. Cavitation or eruption of ultrasound-induced gas bubbles causes changes in neural membrane

2. Increase of conductance of potassium channel in membrane and results in reduced resting action potential and increased firing

3. Excitation in mechanosensitive membrane induced by radiation force

Taipei Veterans General Hospital epilepsy surgery team employed a neuronavigation-guided low-intensity FUS system (ceiling spatial-peak temporal-average intensity level = 2.8 W/cm^3, duty cycle = 30%, modulating duration = 10 min) to deliver to the seizure onset zone localized by stereo-electroencephalography (SEEG) in six patients. A decrease in seizure frequency was observed in two patients within 3 days recording with significant changes in spectral power of SEEG at the targeted electrodes [79].

Regarding the safety in application of low-intensity FUS in the treatment of epilepsy, early in 2008, Tyler et al. have investigations with *ex vivo* preparations in mouse. They showed that repeated stimulation of hippocampus slices did not result in significant changes to cytoarchitecture or integrity and integrity of the blood-brain barrier was not disturbed [80]. Zou et al. in China also showed no significant brain tissue damage after low-intensity FUS application to acute epileptic Monkeys [81]. Concerning the application to human cases, Monteith et al. had tested the feasibility of using FUS for temporal lobe epilepsy by using cadaveric skulls [82]. Abe et al. in Japan reported the first case of transcranial magnetic resonance-guided FUS (MRgFUS) for mesial temporal lobe epilepsy [83]. Further study in UCLA group on eight temporal lobe epilepsy patients before and after treatment with FUS using intensities up to 5760 mW/cm showed that there was no detectable damage to the tissue in the histological analysis of the resected specimens, and the neuropsychological testing results showed no significant changes after the treatment [84].

Though there are promising results in treatment of refractory epilepsy, FUS is considered to have some limitations. One of them is the limitation of treatment target size. FUS cannot completely ablate an epileptogenic lesion larger than 1 cm^3 as convergence of ultrasound waves is required. Another challenge is the gantry of ultrasound waves with reference to the location of a target in skull base region. It may be difficult to achieve a high enough treatment efficiency to cause thermal ablation in mesial temporal structure including the hippocampus and amygdala for those mesial temporal lobe epilepsy cases [85].

6. Conclusions

Cryptogenic epilepsy remains a challenging entity and difficult disease to treat. The advanced imaging technologies and invasive monitoring methods help to localize the epileptogenic focus more accurately. Innovative methods of treatment may be an alternative method of treatment particularly in those lesions with high surgical risks.

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Conflict of interest

The authors declare no conflict of interest.

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