Approach to refractory childhood seizures

Up to 40% of children with epilepsy will not achieve seizure freedom with antiepileptic drugs. Refractory epilepsy has devastating consequences, both for the child and their carers. Early recognition of those with refractory epilepsy, in order to minimize these consequences, has proven difficult. Currently, most patients with refractory epilepsy wait many years before being referred for evaluation at a specialist center. The clinicians taking care of children with epilepsy must have a clear approach to both the diagnosis and appropriate pathways for investigation of patients with refractory seizures. We present a structured approach to both the diagnosis and evaluation of refractory seizures; we review the current therapeutic options available to treat those suffering from refractory seizures and explore potential therapeutic options for the future.

KEYWORDS: children, deep-brain stimulation, diet, epilepsy, refractory, surgery, vagal-nerve stimulation

Epilepsy, defined as recurrent unprovoked seizures, occurs in 1–2% of the pediatric population [1,2]. The peak incidence of childhood epilepsy occurs in the first year of life, which coincides with a critical time in neuronal development [1,2,3].

Up to 40% of children with epilepsy will not achieve seizure freedom with antiepileptic drugs (AEDs) [4–7]. Early diagnosis of refractory seizures is vital, as is recognition of the next appropriate therapeutic step for the patient.

Refractory epilepsy has devastating consequences. It impacts upon every aspect of the child’s development, including their academic performance and social development [8,9]. It affects those involved in caring for the child, with many carers experiencing comorbid complications, commonly depression [9,10]. Siblings often experience a negative impact [10] and, within the classroom, many teachers fail to recognize the impact of seizures on education [11–15]. Uncontrolled seizures can result in a decline in school performance, even when they are brief and involve subtle symptoms [8,15].

Patients with refractory seizures are exposed to multiple AEDs, often many drugs in combination, which has a significant negative impact on cognition [8,10,15]. Early recognition of those with refractory epilepsy, to minimize these consequences, has proven difficult [4,16–19].

Currently, most patients with refractory epilepsy wait many years before being referred for evaluation at a specialist center. Recently, the International League Against Epilepsy presented a definition of refractory seizures that one hopes will provide clarity and improve timeliness of these referrals. It requires the clinician who is taking care of the child with epilepsy to have a clear approach to both the diagnosis and appropriate pathways for investigation of patients suffering from refractory seizures.

In order to develop a successful approach to refractory seizures, we must first answer two questions for each patient. Does this patient have epilepsy, and is it refractory?

Re-evaluating the diagnosis of epilepsy

The diagnosis of epilepsy is often difficult [20]. It has been estimated that 20–30% of patients referred for management of refractory seizures do not have epilepsy [21,22]. Many paroxysmal events may be mistaken for seizures, such as syncope, tics or migraine [23].

Studies of patients investigated for possible diagnosis of epilepsy demonstrated that between 10 and 40% of those investigated had non-epileptic seizures [24–26]. In one study, over a third of the children who had a diagnosis of intractable seizures and were referred to a specialist center for management, were subsequently diagnosed with non-epileptic events [27]; many were on multiple AEDs. Psychogenic nonepileptic seizures (PNES) are events that clinically resemble epileptic seizures, without electrographic evidence of seizure on an EEG. The events are psychological in nature and often thought of as a conversion disorder. The incidence of PNES is highest in
people aged 15–24 years, with a strong female preponderance described [28]. Nonepileptic seizures are more common in patients with epilepsy; therefore, clinicians caring for children with epilepsy that is difficult to treat, must pay heed to a change in seizure semiology or particular features suggestive of nonepileptic events. Correct diagnosis and appropriate treatment of PNES will avoid inappropriate exposure to AEDs and their potential side effects, and may avoid escalation of underlying psychological issues.

A careful history of the events and triggers may lead a clinician to suspect them to be nonepileptic in nature, but the conclusive test involves video EEG monitoring to capture one or two typical events on both EEG and video. Previous authors have suggested guidelines for clinicians for detecting features suspicious for PNES [29]. A recent presentation at the American Academy of Neurology Meeting presented a simple scoring system that can aid clinicians in identifying those who may witness clinical events that are suspicious for nonepileptic seizures [30]. Their scoring system for a witnessed event included eight clinical features to assist in recognizing a likely nonepileptic event: waxing and waning symptoms, eye closure, side-to-side head movements, duration longer than 3 min, pelvic thrusting, crying, out-of-phase limb movements and patients carrying an age-inappropriate soft toy. Commonly encountered clinical features suggestive of either PNES or epileptic seizures are reviewed in Box 1.

### Establishing those with refractory seizures at an early stage

Refractory epilepsy was recently defined by the International League Against Epilepsy as failure to achieve sustained remission following a trial of two or three appropriate drugs [31]. This is similar to the definition used by many clinicians prior to this, defining refractory seizures as failure of two or more AEDs and the occurrence of one or more seizures per month over 18 months [19]. The new definition, from the International League Against Epilepsy, specifies selection of the appropriate AED as part of the definition. It does not allude to seizure frequency as part of the definition, acknowledging the fact that infrequent seizures can have a significant impact on lifestyle, wellbeing and independence.

Key to accurate and early detection of refractory seizures is determination of patients most at risk. Several factors have been investigated as predictors of development of intractability (Box 2). Failure of response to the first AED accurately predicts those who will develop intractable seizures [32,33]. Certain epilepsy syndromes are associated with a higher risk of medical intractability in children, for example West syndrome and Landau–Kleffner syndrome [34–37].

A retrospective study, examining 10 years of patients at a Canadian center, concluded that multiple seizure types (hazard ratio of 6.5), mental retardation at onset of seizures (hazard ratio of 7.2) and seizure recurrence in the first 6–12 months of treatment were predictive of intractability [38]. Similar risk factors have been reported by others [39].

The age of onset of seizures is not as clearly predictive. An initial study by one group concluded that seizure onset in the first year of life was the predominant predictor of the development of intractability; their subsequent analysis of the patients, according to their syndromic diagnosis, did not support this finding [4]. Other authors have also concluded that seizure onset in the first year of life is not clearly associated with the development of intractability [37].

The predictive features in Box 2 are apparent within the first few months of the patient’s epilepsy in many instances. Once two appropriate AEDs have been trialed in adequate doses and are unsuccessful in controlling seizures, the chance of a third agent being successful and providing seizure freedom is less than 5–10% [18,33,37,40,41]. Diagnosis or suspicion of intractability, which leads to referral to a tertiary center for specialist assessment for the consideration of surgical or other interventions is delayed by many years in most. Of the patients referred for epilepsy surgery in the USA, the average duration of their seizures prior to referral was 18 years, with a range from 2–58 years [42].

Ongoing medical therapy exposes the patient to increased risk of adverse drug responses and side effects, and prolonged medical therapy with AEDs can lead to development of tolerances, which may explain the loss of drug efficacy of most AEDs with prolonged use [43,44]. Undue prolongation of medical therapy, despite poor seizure control, is not justified in the face of viable surgical options to treat these children [45].

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**Box 1. Clinical features of events suspicious for psychogenic nonepileptic seizures versus epileptic seizures.**

- Psychogenic nonepileptic seizure:
  - Tongue-tip bite, longer then 3 min, eyes closed, side-to-side head movement, gradual onset, fluctuating and no injury
- Epileptic seizure:
  - Severe tongue bite/mouth injury, eyes open, automatisms, injury and incontinence
It is probably an oversimplification to assign patients to being either refractory or not, given the heterogeneous nature of those patients with epilepsy. Several studies of the natural history of epilepsy have found that patients with epilepsy may fit into each of these categories at different periods in time. This finding is particularly true when one considers seizures in children. A study carried out in Finland followed 144 children presenting with seizures from diagnosis for an average of 37 years [46]. Only 16% of the patients were immediately seizure free and remained so, uninterrupted by relapse, and only 19% were treatment resistant throughout, without ever experiencing a remission. The remaining patients had some periods of seizures and some periods of remission.

**Evaluating children with refractory seizures**

- **Presurgical evaluation**

All patients with refractory seizures should be referred to a specialist center for further investigation of their seizures and for advice regarding therapy. An approach to their assessment is outlined in Box 3.

A comprehensive history must be obtained; a detailed drug history is important for identifying if appropriate AEDs were received, and adequate doses and therapeutic drug levels were obtained. Physical examination may lead to further investigations, such as the detection of neuro-cutaneous stigmata, suggesting tuberous sclerosis, or the presence of subtle asymmetry in power or fine motor skills, indicating a possible laterality of seizures causing functional deficits.

Further investigation of etiology is often patient specific, but will generally include baseline blood and urine analysis for inborn errors of metabolism, karyotype analysis, fragile-X and cerebrospinal fluid (CSF) analysis. A child presenting with treatment-resistant atypical absence seizures and a history of early morning seizure clustering may have glucose transporter 1 deficiency syndrome and a low ratio of CSF to serum glucose. Many advocate that CSF analysis should be performed in all children with refractory seizures to rule out this condition, which has a favorable response to treatment with the ketogenic diet [47,48]. A recent review of the clinical and genetic spectrum of glucose transporter 1 deficiency highlights the importance of lumbar-puncture testing, as it can dramatically reduce diagnostic delay and allow an early start of the ketogenic diet [49].

Video EEG monitoring forms the cornerstone of any assessment for refractory seizures [50]. Admission to an in-patient epilepsy monitoring unit offers many advantages. Tapering of AEDs, often required to ensure seizures are obtained during the stay, can be safely undertaken in the hospital setting with close nursing care and access to emergency treatment. Video EEG allows lateralization and localization of the epileptogenic zone. Seizure semiology from video recording can allow classification of the patient’s seizure type and may guide therapy. At times, subtle, brief or nocturnal seizures are identified that were not previously recognized. Prolonged recording of the interictal activity during wakefulness and sleep is obtained. It offers an objective way of assessing response when new treatments are introduced.

Newer methods of EEG analysis, such as dipole analysis and EEG source imaging, exist. These provide us with additional ability to localize the epileptogenic zone, particularly in patients with extratemporal-lobe epilepsy, who can be a very difficult group to undertake surgery in, owing to the epileptogenic zone being located near to the eloquent motor, sensory and language regions of the brain [51,52].

Analysis of video EEG categorizes the patient with refractory seizures as having focal or generalized onset of seizures [53]. For the patient with generalized onset epilepsy, the options for further therapy decision may be considered once appropriate imaging and video EEG monitoring has been performed. They may be a candidate for further medication trial (with low chance of success), vagal-nerve stimulation (VNS) or

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**Box 2. Predictors of development of refractory seizures.**

- **Patient factors:**
  - Intellectual or developmental delay at presentation
  - Structural malformation evident on imaging
  - Seizure onset under 1 year of age
- **Epilepsy factors:**
  - Epileptic syndrome associated with intractability, multiple seizure types, status epilepticus and failure to respond to first antiepileptic drug
the ketogenic diet. For children with intractable seizures that cause drop attacks, a corpus callosotomy may be considered as a palliative surgery procedure. These patients often have many seizure types and the drop attacks can occur multiple times per day, leading to repeated injury necessitating a protective helmet be worn. Significant improvement of quality of life can be obtained with callosotomy; although seizure freedom is rare.

If the analysis of video EEG monitoring shows a focal/lateralized onset of seizure activity, workup for potentially curative epilepsy surgery is appropriate. This is best performed in a specialist center with appropriate expertise to perform and analyze the detailed imaging sequences required. Neuroimaging provides detailed structural analysis to identify discrete lesions or regions of potential cortical malformation that may represent epileptogenic zones. It can also be used to provide details of eloquent regions of the brain involved in motor, sensory, language and memory function. It provides us with a noninvasive technique to assess the relationship between these eloquent regions and the epileptogenic zone. MRI is better for the detection of subtle structural abnormalities than CT. MRI with a specified epilepsy protocol is the imaging study of choice and is the mandatory primary imaging modality according to the International League Against Epilepsy guidelines [54].

Newer 3-Tesla magnetic resonance machines have finer imaging resolution to identify subtle focal abnormalities in epilepsy patients. MRI techniques, such as diffusion tensor imaging, allow detailed views of white-matter tracts and detection of subtle abnormalities in white matter [55]. The absence of a lesion or structural abnormality on imaging does not preclude surgery. Other tests, such as scalp, and invasive EEG monitoring and magnetoencephalography (MEG), can be utilized to provide adequate localization information for resective surgery.

Magnetoencephalography is an increasingly available neuroimaging technique, which is useful in evaluating intracranial neural activity and functional mapping. It is a technique that maps interictal magnetic dipole sources onto MRI to produce magnetic source imaging. A recent review of MEG outlined its role in epilepsy surgery, both in localizing the epileptogenic zone and in functional mapping of the eloquent cortex [56]. MEG is also useful in those with persistent seizures following resective surgery. In these patients, it has been suggested that MEG is superior to scalp EEG, because the magnetic field is not distorted by the skull defects and CSF collections, which can lead to false localization on scalp EEG [57].

Functional imaging with ictal SPECT and PET scans are established techniques in epilepsy localization. The imaging reflects the seizure-related changes of cerebral perfusion, glucose metabolism and neuro-receptor status. These techniques are increasingly available in many centers and can be especially useful where there is no MRI-detected lesion. Further detailed discussion is beyond the scope of this review; an up-to-date publication on the topic is recommended [58].

Functional assessment with lateralization of language and assessment of memory function is imperative. Neuropsychological assessment is performed for each patient. The Wada test has routinely been used to assess and lateralize language and memory before epilepsy surgery [59]. This study requires an intra-carotid injection of amobarbital sodium. Blood oxygen level-dependent functional MRI provides a noninvasive method of assessing language lateralization and memory. Many studies have demonstrated that functional MRI is a suitable noninvasive replacement for Wada testing of language lateralization [60,61]. A recent study has demonstrated functional MRI can also be used instead of Wada to predict postoperative memory changes in temporal-lobe epilepsy surgery patients [62].

Once the investigations are complete, a multidisciplinary group in a specialist epilepsy surgery center should review the data. From this review of the data, a number of possible recommendations can arise. First, the patient is not a suitable candidate for surgery and options of VNS, ketogenic diet or continued medical therapy are discussed, and a specific plan is tailored for each patient. Second, the patient may be a surgical candidate but further details are required regarding the localization of the epileptogenic zone and of its relationship to the eloquent cortex. In these cases, invasive EEG monitoring is recommended with subdural EEG electrode placement. Information obtained from invasive monitoring is used to guide specific resections. Third, the patient is a candidate for resective surgery of a structurally abnormal region, which is remote from the eloquent cortex. This resection may also include a cluster as defined by MEG. Finally, the surgery may be considered as a palliative procedure rather than a potentially curative one. As discussed previously, corpus callosotomy may be performed for drop attacks or multiple sub-pial transections may be performed when resective surgery is not possible, owing to the location of the epileptogenic zone in
relation to the eloquent cortex. Any recommendation is discussed in detail with the patient and their family with appropriate discussion of risks and benefits, and a consensus decision is reached.

For those patients in whom surgical resection is possible, they have the best chance of obtaining seizure freedom. For those patients who are not candidates for potentially curative surgery, the decision regarding the appropriate next step can be difficult. Deciding on an AED versus considering a trial of ketogenic diet or implantation of a VNS device must be tailored for each patient. Seizure freedom is difficult to obtain in this group, but significant improvements in seizure frequency and seizure duration and overall quality of life can be obtained.

**When epilepsy surgery is not an option**

- **Pharmacotherapy**
  The last decade has seen a significant increase in the number of AEDs available for the treatment of epilepsy [63]. These newer agents are associated with fewer side effects; however, they have not shown an improved efficacy.

  Despite the low chance of a third AED being successful if two have failed, many more AEDs are often trialed in patients where no other options are deemed appropriate or when they have been trialed and been without success. Any previous medication or combination of medications that had some success are often trialed. The pediatric neurologist caring for these children is always seeking novel medications that may show promise.

  One example of refractory and catastrophic epilepsy of childhood is Lennox–Gastaut syndrome. Considered by many as an epileptic encephalopathy, this is a symptomatic generalized epilepsy syndrome. Children present with multiple seizure types and nonconvulsive status epilepticus is common. They have significant cognitive impairment with moderate-to-severe intellectual disability and behavioral disorders, such as autism, are common. Lennox–Gastaut syndrome is difficult to treat [64]. Many of these children are exposed to polypharmacy in an attempt to treat seizures. Some novel AEDs are emerging for this condition. One such AED is rufinamide, which was approved by the US FDA for the treatment of Lennox–Gastaut syndrome in children over 4 years of age, in January 2009. It is structurally different from other AEDs. Its exact mechanism of action is unknown, but it has been reported to act on sodium channels and prolong their state of inactivation, preventing repetitive firing [65]. Rufinamide has good safety and a low side-effect profile. Its efficacy has been reported in a recent double-blind randomized placebo-controlled study [66]. Glauser et al. reported a 32% reduction in seizure frequency with rufinamide and a low incidence of adverse effects [66]. This novel agent provides hope in the treatment of devastating refractory epilepsy and is suitable for many seizure types, which may lead to broadening of its applications in the future.

- **Vagal-nerve stimulation**
  Vagal-nerve stimulation is a useful treatment in refractory seizures. It utilizes a small implanted device that stimulates the left vagus nerve intermittently with an electrical stimulus. The exact mechanism of its antiseizure action is not known but it has been demonstrated to affect blood flow to different parts of the brain and to affect certain neurotransmitters. The device is generally well tolerated with side effects described as an alteration in quality of voice when the stimulus is being delivered to the vagus nerve, hoarseness, cough, dyspnoea and paraesthesia. Seizure freedom is rarely achieved, but it is associated with improvement in seizure frequency and improved quality of life. The reduction in seizure frequency achieved is similar to that achieved with newer add-on drug therapies for refractory epilepsy [67,68]. The improvement in quality of life is not clearly established. A recent prospective study examined VNS efficacy and reported that almost half of those treated with VNS had a greater than 50% reduction in their seizure frequency [69]. The same group examined the impact of VNS on the quality of life for the patients, and did not detect a significant improvement with VNS after 1 year. The authors acknowledge that their study population represents children with severe intractable epilepsy, which may not be representative of the entire population treated with VNS. Furthermore, they suggest the lack of statistically significant improvement in 1 year may represent a cessation in further deterioration in quality of life, and warrants longer follow-up. Anecdotally, it is our observation that a significant majority of parents report an observed improvement in the level of alertness and responsiveness when their child has a VNS placed, independent of an objective reduction in seizure frequency.

- **Ketogenic diets**
  The ketogenic diet, modified Atkins diet and low-glycemic-index diet provide us with an additional therapeutic option for children with intractable seizures. Most clinical data exist for the traditional or classic ketogenic diet. The more
modern adaptations, such as the modified Atkins diet, demonstrates a greater than 50% reduction in seizure burden in 40–50% of patients after 3–6 months [70–75]. Compared with VNS, the ketogenic diet appears to work faster, typically within 2–4 weeks [76]. Its benefits extend beyond seizure control, with improvements in development and behavior reported [77]. The effect of the ketogenic diet can be long lasting, with many patients experiencing sustained benefit, even after returning to a normal diet [78,79]. The International Ketogenic Diet Study Group have recently produced a consensus paper that sets forth clear recommendations for those administering the diet [80].

Outcome of refractory seizures

Sudden unexplained death in pediatric patients with epilepsy is rare [81,82]. However, risk of sudden unexpected death in epilepsy is of particular concern in those with ongoing refractory seizures.

Outcome data for patients with refractory seizures are most impressive for those who undergo resective surgery. Excellent short-term outcomes are published, with the best outcomes reported for temporal-lobe resections [83,84]. One large study shows 65% of patients to be seizure free following temporal-lobe resection performed for focal epilepsy of the temporal lobe. Evidence from extratemporal surgery is weaker. Long-term outcome following surgery was recently reported in patients followed for a mean or median of at least 5 years after their resective surgery [85]. Similar to short-term studies, the outcome for temporal-lobe surgery remains good, with 66% of patients becoming seizure free. For extratemporal groups, seizure freedom is sustained in 46% with occipital and parietal resections, and 27% with frontal resections. The same group reported improved psychosocial outcomes with epilepsy surgery, including employment, education, driving status, satisfaction and quality of life [86]. Long-term outcome in patients with focal epilepsy, who were investigated for possible epilepsy surgery and deemed not to be suitable candidates, are also reported [87]. Following their surgical assessment, 21% of patients were seizure free for at least 4 years. Quality of life assessments demonstrate that quality of life in those still experiencing seizures is poorer than that measured in patients with other chronic conditions, such as diabetes or hypertension [88–90]. In recent years, the outcome figures have improved. A recent publication examined pediatric epilepsy surgery outcomes over a 22 year period – comparing the first 11 years from 1986 to 1997 with the most recent 11 years from 1998 to 2008. They found the most recent period showed more patients to be seizure free up to 5 years postsurgery and there were fewer complications among this group compared with the earlier years [91].

Future perspective

There have been major leaps made in imaging and therapeutic options over the last decade for patients with refractory seizures and the trajectory is set to continue. These can be considered as improvements to help streamline existing therapeutic options and develop novel therapeutic options.

Streamlining current therapeutic options

For those patients being evaluated for potential epilepsy surgery, the advances in imaging modalities mean that the detection of subtle changes in structure that would previously have gone unrecognized are now being detected and widening the potential for surgical intervention for these children. A rapid expansion in the technology available has increased precision in resective surgery. Image fusion allows accurate identification of imaging abnormalities previously assessed by MRI, eloquent cortex identified by functional mapping, MEG spike clusters and diffusion tensor imaging of white tracts. These techniques are constantly being refined. A recent report details a new patient-specific method of surgical navigation and image integration. They describe a minimally invasive frameless stereotactic guidance system that utilizes a patient-specific mouthpiece, which was used in the operating room to allow repetitive noninvasive localization of the patient’s anatomy during imaging integration and during surgery [92].

Our understanding of the mechanism that may underlie the development of pharmacoresistance is improving, and we hope to utilize this for improved AED delivery to the patients brain. It has been suggested that overexpression of multidrug transporters in the blood–brain barrier is responsible for producing pharmacoresistance, by decreasing the AED concentration and, hence, its effectiveness. Therefore, novel methods of administration of AEDs may be successful in bypassing the blood–brain barrier. One such mechanism is intranasal administration of AEDs. There are few studies on this method of drug administration but some recent data have emerged on this topic in the literature, which may show future promise [93].
Novel therapies
For patients whom surgery is not an option or is not successful in treating their seizures, the ketogenic diet and VNS offer real options to improve their seizure control and their quality of life. Newer AEDs, such as rufinamide, offer hope, with similar outcome data reported for many of these agents as with both diet and VNS.

Deep-brain stimulation is another promising modality of treatment for refractory seizures [94,95]. A multicenter, double-blind, randomized trial of deep-brain stimulation in adults with refractory seizures has recently been reported [95]. A total of 110 patients were randomized; half received stimulation and half no stimulation during a 3-month blinded phase; then all received unblinded stimulation. The stimulated group had a 29% greater reduction in seizures versus the control group (p = 0.002). Complex partial and ‘most-severe’ seizures were significantly reduced by stimulation. By 2 years, 54% of patients had a seizure reduction of at least 50% and 14 patients were seizure free for at least 6 months. Complication rates were modest. This study demonstrates the efficacy and safety of this therapy in refractory seizures. Further studies are ongoing in many centers to add clarity regarding which patients are likely to benefit best from this.

Executive summary

**Impact of refractory seizures**
- Up to 40% of those treated with antiepileptic drugs (AEDs) for epilepsy will not achieve sustained seizure freedom.
- Refractory seizures have devastating consequences for the child and their carers.
- Treatment with AEDs exposes the patient to potentially harmful AED side effects/drug toxicity from multiple AEDs.
- It is not reasonable to continue medication trials that have failed when epilepsy surgery is available.
- Epilepsy surgery provides the best chance of seizure freedom in those with refractory seizures.
- Early referral to specialist centers is necessary to maximize outcome and minimize continued exposure to AEDs.

**Diagnosis of epilepsy/refractory epilepsy**
- Of those referred for management of refractory seizures, 20–30% do not have epilepsy.
- Re-evaluation of all patients not responding to AED therapy is vital.
- Psychogenic nonepileptic seizures may be suspected by observing key clinical features but must be confirmed with video EEG monitoring.
- Early identification of those with refractory seizures will maximize outcome – developmental delay at presentation, multiple seizure types and failure to respond to first AED all predict development of refractory seizures.
- The International League Against Epilepsy have defined refractory seizures as failure to achieve remission following trial of two or three appropriate AEDs.

**Presurgical evaluation**
- All patients with refractory seizures after treatment with two appropriate AEDs should be referred to a specialist epilepsy center for evaluation.
- A comprehensive history, including drug history and physical examination, is performed to guide the investigations.
- Baseline metabolic evaluation of blood and urine, karyotype analysis and fragile X should be considered.
- Analysis of cerebrospinal fluid is recommended for all patients with refractory seizures.
- Prolonged video EEG monitoring and appropriate magnetic resonance brain imaging with specific epilepsy protocol sequences should be performed for all.
- Magnetoencephalography allows further localization of focal epilepsy.
- Multidisciplinary input is required to interpret the results and tailor a patient-specific plan.
- Invasive monitoring with subdual electrodes allows precise localization of the epileptogenic zone and identification of eloquent cortical regions and their relation to each other.
- Timely evaluation and action is important.

**When epilepsy surgery is not an option**
- Most therapies are aimed at minimizing the impact of seizures by reducing seizure frequency and severity and improving quality of life.
- Novel AEDs have been demonstrated to have success in some particular instances, and may be considered.
- The ketogenic diet and modern forms, such as the modified Atkins diet, offer a seizures reduction of greater than 50% in almost half of patients with some achieving seizure freedom.
- Vagal-nerve stimulation has similar seizure reduction rates as ketogenic diet, although seizure freedom is rare and it can be slow in its effects.

**Future perspective**
- Better understanding of the mechanism of development of drug intractability may allow us to develop drugs and drug delivery systems that can bypass these obstacles.
- There has been a significant increase in the number of AEDs available and in development for the treatment of epilepsy.
- Deep-brain stimulation is a promising modality of treatment for refractory seizures, with good early data published on outcomes.
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S Benbadis serves as a consultant and a speaker for Cybernetics, GSK, Lundbeck, Pfizer, Sleepmed, UCB pharma and XLTEK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- Interesting population study looking at the incidence of epilepsy.


- Highlights the fact that there are still many gaps to bridge in the classroom with regard to epilepsy.


- Prospective study of over 600 children diagnosed with epilepsy, followed for a median of 4.8 years to identify predictive factors for the development of intractability.


- Provides clarity on terminology and much more.


- Overlooked 100 patients for an average of 37 years after diagnosis of epilepsy in childhood.


- Followed over 100 patients for an average of 37 years after diagnosis of epilepsy in childhood.


- Challenges us to constantly reconsider our definition of intractability and when it can occur.


- Important review of school attendance and performance for children with epilepsy.


- Challenges us to constantly reconsider our definition of intractability and when it can occur.

11 Bishop M, Beag EM: Teacher’s knowledge about epilepsy and attitudes toward students with epilepsy: results of a national survey. Epilepsy Behav. 8, 397–405 (2006).

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- Educational review of nonepileptic events in children.


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**Approach to refractory childhood seizures**

- **Good review of childhood epilepsy syndromes.**

- **Good educational review of infantile epilepsies.**

- **Interesting paper reporting both genetic and clinical data from over 50 patients.**

- **Interesting new finding of functional MRI.**

- **A good review of current antiepileptic drugs available.**

- **A good review for up to date information on magnetoencephalography.**

- **Epilepsy surgery, delays and referral patterns – are all your epilepsy patients controlled?**

- **Good resource for up to date information on magnetoencephalography.**

- **The Vagus Nerve Stimulation Study Group: A randomised control trial of vagus nerve stimulation for treatment of medically refractory seizures.**

- **A review comparing these two modalities used for surgical evaluation of epilepsy patients.**

- **Determination of language dominance using functional MRI: a comparison with the Wada test.**

- **Interesting new finding of functional MRI superiority to the Wada test in the area of memory.**

- **Good review of current antiepileptic drugs available.**

- **Determinants of outcome.**

- **Good resource for up to date information on magnetoencephalography.**

- **The Vagus Nerve Stimulation Study Group: A randomised control trial of vagus nerve stimulation for treatment of medically refractory seizures.**
Interesting review on the topic of alternative methods of medication administration.


More recent study of outcome figures for epilepsy surgery, with comparison to older figures.


Interesting paper on this topic of alternative methods of medication administration.


Informative review of deep-brain stimulation.