JICNA® | Journal of the International Child Neurology Association
A peer reviewed open access e-journal in Child Neurology

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REVIEW ARTICLE

Rational Approach to Children with Drug-Resistant Epilepsy

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https://doi.org/10.17724/jicna.2021.191

Received: April 8, 2020
Accepted: June 24, 2021

Abstract

Epilepsy is one of the most common neurological disorders to affect children and has its highest incidence in infancy. Approximately one quarter of children have seizures which are drug resistant and place the child at increased risk of cognitive delays, as well as attention, behaviour and psychiatric disorders, injury, sudden unexpected death, and poor quality of life. This article presents a rational approach to the investigation and management of children with drug-resistant epilepsy.

Keywords: Drug resistant epilepsy; epilepsy surgery; ketogenic diet

Introduction

Epilepsy is one of the most common neurological disorders seen in children with an estimated incidence of approximately 44 per 100,000 per year [1, 2]. Drug-resistance – which is defined as a failure of adequate trialing of two tolerated, appropriately dosed and chosen antiseizure medications (either in mono- or combination therapy) to achieve sustained seizure remission [3] – is not uncommon, and effects approximately 20-25% of all children [4, 5]. In addition to ongoing seizures, those with drug-resistant epilepsy are at greater risk for intellectual disability and learning problems, attention and behavioural problems, and emotional difficulties such as anxiety and depression, injury and sudden unexpected death in epilepsy, and poor quality of life.

Predictors of drug resistance have been evaluated in several studies [4, 5]. Factors that have been quite consistent include certain syndromes (developmental and epileptic encephalopathies, and lesional focal epilepsy), high initial seizure frequency, neonatal seizures, onset prior to or greater than age 12 years, associated intellectual disability or abnormal neurologic examination, abnormal neuroimaging, and failure to respond to the first antiseizure medication [5]. Additionally, the presence of febrile seizures, status epilepticus, and discharges or focal slowing on EEG have been reported by some, but not most studies, to correlate highly with drug-resistance [4, 5].

Although some cases with drug resistance may present after many years, most cases present in the first two to three years after onset of epilepsy [4, 5].

Given the significant impact on multiple aspects of well-being, it is essential to have a framework to assess children presenting with drug-resistant epilepsy.

Q1. Does the patient truly have epilepsy?

One of the most common reasons for failure to respond to antiseizure medications is that the diagnosis of epilepsy is incorrect. There are multiple paroxysmal events which occur in children and adolescents which may be mistaken for epilepsy. These are listed in Table 1. Several studies have found that approximately 15% of events captured in a paediatric epilepsy monitoring unit are not epileptic [6, 7]. Before age six, psychogenic nonepileptic events are rare, and most nonepileptic conditions are other physiologic disorders. In adolescence, psychogenic nonepileptic events are conversely the most common etiology for nonepileptic events.

Psychogenic nonepileptic seizures have been reported to have two main semiologies in children [6]. The first are typically prolonged periods of unresponsiveness without motor phenomena and the second are motor phenomena with bizarre irregular jerking and thrashing. Importantly however, frontal lobe seizures may also present with bizarre motor phenomena and must be distinguished from psychogenic nonepileptic events. Other characteristic features of psychogenic nonepileptic spells include prolonged duration (often longer than 15 minutes), no incontinence or tongue-biting, an often-minimal postictal phase, events that are frequent and medically intractable from onset, events that occur in situations such as school, events that are elicited by specific triggers, and an underlying psychiatric diagnosis or personality disorder.

It can be very helpful to have the family take a video of the child or adolescent's event using a cell phone, to be reviewed by the physician. If resources permit, recording of the video EEG during the spell of interest will be helpful to distinguish seizures from nonepileptic events.

Table 1. Common Seizure Mimics in Children.

	Typical age	Description
Movement Disorders		
Jitteriness	Neonates, infants	Tremor-like movements in one or more limbs which attenuate or stop when the infant is wrapped or the affected limb is gently flexed.
Hyperekplexia	All ages	Abnormal excessive startle. In infants, can present with abnormal stiffness and apnoea due to a loud noise or unexpected tactile stimulus.
Shuddering attacks	Infants and preschoolers	Shiver-like movement typically lasting seconds only, which can be triggered by certain activities.
Benign paroxysmal tonic upgaze	Infancy	Sustained upward eye gaze with intact awareness.
Tics	Children and adults	Brief, frequent movements such as head-shaking or shoulder-shrugging, or brief repetitive noises such as throat-clearing or sniffing.
Stereotypies	Children	Repetitive movements such as body-rocking, head-banging or finger movements which can be interrupted.
Alternating hemiplegia	Infants and children	Recurrent attacks of weakness that affect one or the other side of the body, which can last minutes to more than half an hour.
Sleep Disorders		
Benign neonatal sleep myoclonus	Neonates	Brief tremor-like movements of one or more limbs, only in sleep, that stop when the baby wakes up.
Sleep-related rhythmic movement disorders	Young children	Repetitive body-rocking or head-banging that typically occur as the child is falling asleep.
Hypnic jerks	Any age	Sudden twitches during sleep which may wake the person.
Parasomnias	Children	Behaviours such as talking, walking or agitation that usually arise from deep sleep, often in the first third of the night, lasting several minutes. The child may appear agitated or frightened, but has no recall of the event.
Narcolepsy-cataplexy	Children and adults	Excessive daytime sleepiness, cataplexy, hallucinations when waking or on falling asleep, sleep paralysis.

Continues on next page.

Table 1. Common Seizure Mimics in Children (continued).

Migraine equivalents		
Benign paroxysmal torticollis	Infants and toddlers	Forced turning of the head to one side with retained awareness, lasting minutes to hours. Infants may appear distressed and can vomit during the event.
Benign paroxysmal vertigo	Young children	Child appears off balance, ataxic and often clutches onto an adult. Nystagmus can be seen. Typical duration is minutes.
Cyclical vomiting	Children	Episodic recurrent vomiting which may last hours to days, separated by periods where the child is well.
Psychological disorders		
Daydreaming	Children	Blank staring, typically during times when the child is tired or bored. Child is immediately responsive to tactile stimulation.
Tantrums/rage attacks	Children/teens	Rage episodes with screaming, swearing or aggression, often with directed violence, typically lasting minutes up to an hour.
Panic attacks	Any age	Brief episodes of sudden apprehension, feeling of impending doom, and sensation of breathlessness, choking, palpitations or chest pain, lasting minutes. May be situational.
Non-epileptic behavioural spells (psychogenic nonepileptic seizures)	Older children, teens, adults	Episodic bizarre irregular jerking or prolonged periods of unresponsiveness, unassociated with EEG change.
Other		
Tetralogy of Fallot spells	Infants and toddlers	Cyanosis often after crying, feeding or agitation. Toddlers will often squat during these events.
Breath-holding spells	Infants and preschoolers	Provoked by pain or fright. The child usually cries, then holds their breath at end expiration with cyanosis or pallor. Tonic stiffening of the body may be seen, followed by irregular myoclonic jerks.
Sandifer syndrome	Infants and young children	Arching of back and tilting of head to one side, often with stiffening of the limbs and crying. Most commonly seen in children with neurological disability and associated with gastro-oesophageal reflux.
Vasovagal syncope	All ages	Pallor, blurring of vision, ringing in the ears, dizziness leading to loss of tone. Often triggered by prolonged standing, pain, dehydration.
Long QT or cardiac syncope	All ages	Lightheadedness, dizziness, palpitations, often triggered by fright, exercise, surprise or submersion in water.

Q2. If this is epilepsy, is the seizure type, epilepsy type and epilepsy syndrome correctly diagnosed?

The classification of epilepsy begins with identifying which specific types of seizures a patient has, and utilising that information, deciding if their epilepsy is generalised, focal, both generalised and focal, or unknown [8]. Approximately one quarter to one third of children with epilepsy can be further classified as having a specific electro-clinical syndrome [2]. Choice of antiseizure medication is very much influenced by epilepsy type and syndrome. In some cases, specific antiseizure medications can worsen epilepsy and result in 'pseudoresistance'. The class of medications that is most likely to result in worsening seizures is the sodium channel agents which include oxcarbazepine, carbamazepine, eslicarbazepine and phenytoin [9, 10, 11, 12, 13]. These agents commonly exacerbate generalised epilepsies with absence, myoclonic and atonic seizures. They can also worsen progressive myoclonic epilepsies, electrical status epilepticus in sleep, and Dravet syndrome [13]. Tiagabine and vigabatrin can also exacerbate juvenile myoclonic epilepsy and absence seizures [13, 14]. Lamotrigine is contraindicated in young children with Dravet syndrome as it exacerbates this condition [15]. There are also reports of high-dose benzodiazepines exacerbating tonic seizures [13].

If a patient is confirmed to have epilepsy, yet their seizures are drug-resistant, one should exclude inappropriate medication which may exacerbate seizures as a cause of 'pseudo resistance'.

Q3. Is there a specific etiology-focused treatment?

a. If there is an underlying structural etiology, is the child a surgical candidate?

   Structural etiologies are amongst the most common causes of drug-resistant epilepsy in children [16, 17, 18, 19]. Common structural etiologies include focal cortical dysplasia, mesial temporal sclerosis, low-grade tumours, vascular abnormalities, and focal encephalomalacia or scarring [19]. Many of these children have an early onset of epilepsy which is drug-resistant [20]. It is important to recognise that some of these children may be candidates for surgical resection, as frequent and ongoing seizures early in life may have a significant negative impact on development and learning. Indeed, surgery is the only curative treatment for structural lesions.
   Children with focal structural lesions are generally considered good surgical candidates if they have (1) a single, well-defined epileptogenic zone, and (2) no involvement of eloquent cortex within that zone that would result in postoperative deficits. A single semiology at onset and a single focal lesion on imaging – concordant with the EEG – would suggest a high likelihood of a well-defined epileptogenic zone, although not all children have clear imaging abnormalities. Furthermore, some children who have multifocal or even co-existing generalised interictal EEG discharges have only a single ictal onset [21, 22, 23]. Multifocal interictal discharges should therefore not necessarily exclude a child from surgical candidacy.
   In young children with severe epilepsy due to a focal or hemispheric lesion, with a poor prognosis for seizure control long term, one must balance the risk of ongoing seizures (mortality, morbidity and the impact on cognition) with the risk of deficit caused by surgery [24, 25, 26]. Examples where deficit-incurring surgery is often performed would include children with drug-resistant epilepsy due to Sturge-Weber syndrome, Rasmussen encephalitis, or severe focal epilepsy in a young child, leading to a developmental and epileptic encephalopathy. In general, in such challenging cases, earlier surgery is associated with greater recovery if a deficit will be incurred, given greater brain plasticity (Figure 1A and B). In such cases, epilepsy surgery represents the only hope for a true 'cure' and may prevent further cognitive regression and ameliorate other comorbidities [24].

b. Is there an underlying metabolic cause with a specific targeted therapy?

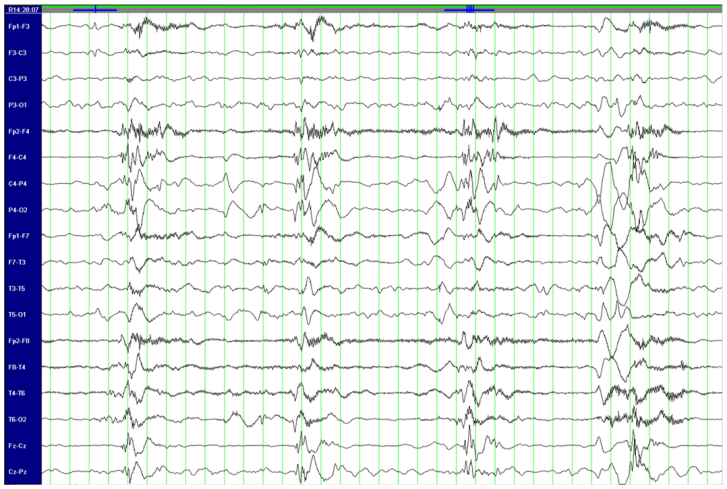
   Overall, metabolic etiologies are relatively rare causes of epilepsy in children. Many of these entities can also be detected on current epilepsy gene panels (i.e., SLC2A1 pathogenic variants associated with glucose transporter deficiency, CLN2 pathogenic variants associated with late infantile neuronal ceroid lipofuscinosis, and POLG1 pathogenic variants associated with Alper-Huttenlocher syndrome). Metabolic disorders more commonly present early in life with developmental stagnation followed by regression, or with acute metabolic crisis, often associated with intercurrent infection, surgery or fasting. Timely diagnosis and, where possible, initiation of targeted therapy is critical to prevent further developmental regression [27]. Important treatable metabolic causes, along with the typical clinical presentation and recommended therapy are listed in Table 2.

c. Is there an underlying genetic cause with a highly effective antiseizure medication?

   Over the last two decades, there has been a rapid expansion in our understanding of the genetic contributions to epilepsy as well as our ability to identify specific pathogenic variants. There are presently relatively few targeted genetic treatments for specific pathogenic variants causing rare epilepsies, but over the next decade, this is likely to grow considerably.
   Many of the underlying developmental and epileptic encephalopathies which present early in life are the result of a single gene mutation [28, 29]. Some of these mutations may also lead to structural brain changes [30, 31]. Thus, an epilepsy gene panel or whole exome-sequencing should be strongly considered in any early onset, drug-resistant epilepsy, where no clear etiology has been found.
   Even though we presently lack precision genetic therapies for many of the pathogenic variants, understanding the underlying genetic etiology can be enormously helpful

Figure 1. A two-month-old child presented with focal spasms and focal seizures affecting his left arm and leg. His EEG showed right hemispheric periodic sharp wave activity (20 microvolt/mm) (Figure 1(a)). His MRI showed a markedly dysplastic right hemisphere, consistent with right hemimegalencephaly (Figure 2(b)). He was treated with vigabatrin and achieved seizure control until eight months of age, when he relapsed with very frequent focal seizures with left-sided clonic activity. Seizures were resistant to two further antiseizure medications, and he began to show regression of developmental skills. He underwent a functional right hemispherotomy at 12 months of age, and became seizure-free. He showed marked improvement in development. At five years of age, he has borderline intellectual disability, a stable left hemiparesis but is off antiseizure medication.

(a)



(b)

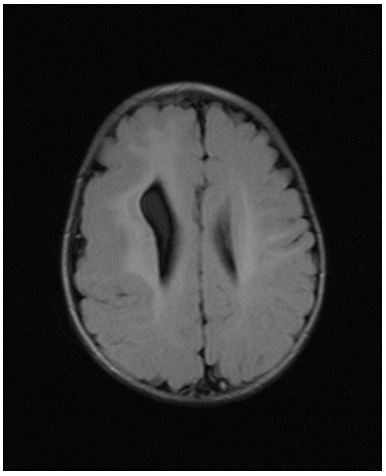


Table 2. Examples of Treatable Metabolic Conditions Associated with Epilepsy in Children.

Disorder	Investigation	Treatment
Pyridoxine, P5P-dependent, seizures	↑ AASA (CSF, serum and urine), ↓ P5P in CSF	Pyridoxine, P5P
GLUT1 transporter deficiency	Low CSF glucose and low CSF/plasma glucose ratio	Ketogenic diet
Creatine deficiency	Urine creatine metabolites, MR spectroscopy	Creatine
Serine deficiency	CSF and serum amino acids	Serine
Biotinidase deficiency	Serum biotinidase	Biotin
Cerebral folate deficiency	CSF methyltetrahydrofolate	Folinic acid
Mitochondrial disorders	Lactate, pyruvate (CSF, serum), muscle biopsy, mitochondrial genetics	cocktail (thiamine, carnitine, Coenzyme Q10, riboflavin). Avoid valproic acid. Consider trial of the ketogenic diet (not in pyruvate carboxylase deficiency)
Late infantile Neuronal Ceroid Lipofuscinosis (CLN2 disease)	Genetic studies, TPP1	Cerliponase alfa

AASA, alpha amino adipic semialdehyde; P5P, Pyridoxal-5-phosphate; TPP1, tripeptidyl peptidase 1.

in choosing an optimal therapy and avoiding medications which could exacerbate seizures. Table 3 provides some examples of common pathogenic variants seen in early onset epilepsy, the clinical phenotypes associated with these, as well as recommended and contraindicated treatments.

Table 3. Common pathogenic variants seen in early onset epilepsy, the clinical phenotypes associated and recommended, and contraindicated treatments.

Gene	Typical age at onset	Clinical phenotype	Optimal therapies	Contra-indicated therapies
SCN1A – severe phenotype	Infancy	Dravet syndrome	Valproic acid, clobazam, topiramate, stiripentol, cannabidiol, fenfluramine, ketogenic diet	Sodium channel agents Lamotrigine
SCN2A	Early infancy	Epilepsy in infancy with migrating focal seizures	High dose phenytoin or other sodium channel agent (in gain of function variants)	
SCN8A	Infancy	Early infantile DEE with severe seizures, intellectual disability and movement disorder	High dose phenytoin or other sodium channel agent (in gain of function variants)	
KCNQ2	Neonates	Self-limited neonatal seizures Less commonly early infantile DEE	Carbamazepine or oxcarbazepine	
KCNT1	Infancy/early childhood Epilepsy in infancy with migrating focal seizures, other	Quinidine		
PRRT2	Infancy	Self-limited infantile seizures	Low dose carbamazepine	
TSC1 or 2	Usually early childhood	Infantile spasms, focal, LGS	Vigabatrin, everolimus, CBD	

Continues on next page.

Table 3. Common pathogenic variants seen in early onset epilepsy, the clinical phenotypes associated and recommended, and contraindicated treatments (continued).

Gene	Typical age at onset	Clinical phenotype	Optimal therapies	Contra-indicated therapies
SLC2A1	Infancy, early childhood	Early onset absence seizures, myoclonic atonic or myoclonic absence seizures, microcephaly, movement disorders	Ketogenic diet	Valproic acid
CLN2	Early childhood	Myoclonic seizures, other focal and generalised seizures, followed by developmental regression and ataxia	Cerliponase alfa	
ALDH7A1	Neonates and early infancy	Early-life drug-resistant DEE, particularly clonic, myoclonic and tonic seizures	Pyridoxine	
PNPO	Neonates and early infancy	Severe, drug-resistant neonatal seizures, early infantile DEE	Pyridoxal-5-phosphate	
POLG1	All ages	Variable but seizures are often focal and involve the occipital regions Elevated transaminases	Mitochondrial cocktail (coenzyme Q10, B vitamins, carnitine, vitamin C, creatine)	Valproic acid
GRIN2A	Childhood	Epilepsy-aphasia spectrum disorders	memantine	

d. Is there an underlying immune etiology which is amenable to immunomodulatory therapy?

Autoimmune etiologies are increasingly recognised in both children and adults with drug-resistant epilepsy [32, 33, 34, 35]. In children, most antibodies are directed against antigens on the neuronal surface membrane, have a low likelihood of association with tumours, and are generally responsive to immunotherapy [33, 34]. Clinical clues suggesting a possible immune etiology include: a previously healthy child with no history of other factors which could provoke seizures; seizures which are generally severe and drug-resistant from onset, often with status epilepticus; multifocal neurological signs and symptoms which include altered mental status, acquired cognitive dysfunction, associated movement disorders, autonomic dysfunction or sleep disturbances; and a personal or family history of autoimmunity [34]. Laboratory clues to diagnosis include: background slowing, often with multifocal discharges on EEG; inflammatory changes on FLAIR or T2 MRI images, and inflammatory changes in the cerebral spinal fluid with negative cultures; positive oligoclonal bands; and elevated CSF neopterin, although the latter may not be highly sensitive [34]. Autoimmune epilepsy panels in the CSF and blood will often show the causal antibody. In addition to symptomatic management of seizures, immunotherapies should also be started as quickly as possible, as the outcome often depends on prompt recognition and treatment [36]. Indeed, there should be a low threshold to refer children with immune-mediated epilepsy to a specialty centre which offers all modalities of immunotherapy. Initial treatments include IV or high dose oral steroids, intravenous gammaglobulin or plasmapheresis, although the latter is used less frequently in children due to a greater risk of adverse events [33, 37]. In cases where suspicion is high, but the autoimmune epilepsy panel is negative, an immunotherapy trial with steroids or intravenous gammaglobulin could be given, and the patient followed closely to see if clear improvement has occurred [33, 34].

Q4. What if there is no etiology-specific therapy, and seizures are drug-resistant?

Unfortunately, for many children with drug-resistant epilepsy, we are unable to identify a specific etiology with a highly efficacious therapy. In such children, it is important to determine a realistic expectation for seizure control, and to balance that control with antiseizure medication side effects and quality of life. Several studies have shown what clinicians have long recognised, namely that the greater the number of failed antiseizure medications, the lower the likelihood that the next drug will be effective [38, 39, 40].

In children with focal epilepsy, a good outcome with another medication was only achieved in 29% after one antiseizure medication failed to achieve seizure control, and only in 11% after the failure of two antiseizure medications [38]. However, etiology plays a significant role in predicting outcome. In one study of children with focal epilepsy, which excluded those with known self-limited focal epilepsy syndromes and after two antiseizure medications had failed for lack of efficacy, only 7.8% of those with a known structural cause versus 23.5% of those with no known cause responded well to a third medication [39].

As many antiseizure medications have side effects including sedation, exacerbation of behavioural problems, and impact on appetite, amongst others, it is imperative to be weaned off a medication that is not working. If a second drug is added, clinicians should consider whether the patient should be weaned off the first medication. When using medications, one should consider combining them with complementary mechanisms of action, and side effects should always be balanced with seizure control.

The ketogenic diet has been utilised for the last 100 years in the treatment of drug-resistant epilepsy in children [41]. This is a high fat, low-carbohydrate, adequate protein diet that has been historically utilised in younger children. More recently, more 'liberal' forms of the diet, including a modified Atkins diet and the low glycaemic index diet, have been described which are more palatable and thus easier to adhere to [42, 43]. While there is some evidence that the traditional ketogenic diet may be more efficacious in very young children [44], it appears that in older children, adolescents and adults, efficacy of these more liberal forms is similar to the traditional ketogenic diet. A recent international review on the use of the ketogenic diet, including syndromes and etiologies where it has been reported as particularly beneficial, has been published [45, 46]. In any child with drug-resistant epilepsy, in whom two to three antiseizure medications have failed for lack of efficacy, and who is not a candidate for surgical resection or other etiology-specific therapy, a trial of dietary therapy should be considered, if feasible for the patient and family. In some cases, depending on family preference, dietary therapy could be considered even earlier.

Although the goal of resective surgery is typically curative, in some cases this can also be considered on a palliative basis, particularly if there is one focus that contributes to the majority of the seizures, and in cases where intervention is expected to ameliorate the epileptic encephalopathy and improve cognitive outcome [47, 48].

Other palliative surgical options may also markedly improve seizure control, lessen injury risk, and improve quality of life. Corpus callosotomy is an important palliative option for children with drug-resistant drop seizures, including tonic and atonic seizures. Approximately 55% achieve freedom from drop seizures after this procedure [49]. Callosotomy is most considered in children with Lennox-Gastaut syndrome who have significant cognitive disability, and the risk of disconnection complications are rare in this population [50].

Neurostimulation techniques should also be considered in this population. Vagus nerve stimulation is the most used form in children, and results in responder rates of between 40 and 66% [51]. Newer stimulator devices allow for autostimulation with detected heart rate changes at seizure onset, adjustment of settings for specific times in the day, and ability to programme the units remotely. Complications of vagus nerve stimulation are

rare but may include bradycardia, infection and bleeding, injury to the vagus nerve with hoarseness, dyspnoea and dysphagia, throat pain and obstructive sleep apnoea.

Other types of brain stimulation have been used predominantly in adults but have also been performed in a limited number of children, although randomised paediatric trials have not been performed. Additionally, availability of these devices is limited in many regions.

The RNS device (Responsive Neurostimulation) can be considered in individuals with no more than two discrete epileptogenic foci. This technique involves placing leads in up to two seizure onset zones. The device monitors brain signals, providing closed-loop stimulation in response to detection of electrocorticographic seizure activity. There is very limited data on efficacy in children; in adults, however, responder rates (patients with a greater than 50% reduction in seizures) were 64.6% in mesial temporal lobe epilepsy and 55% in neocortical epilepsy [52]. Seizure freedom for three, six and 12 months was 45%, 29% and 15% for mesial temporal lobe epilepsy, and 37%, 26% and 14% for neocortical epilepsy [52].

Deep brain stimulation is a therapeutic option that delivers electrical stimulation, most commonly into the thalamic nuclei, to modulate cortical excitability in people with drug-resistant epilepsy who are not good candidates for focal resection. A large trial in adults, the SANTE (Stimulation of Anterior Nucleus of the Thalamus for Epilepsy) trial documented efficacy in adults with responder rates of 43% and 68% at one and five years [53]. However, there are limited reports of this technique in children [54]. The anterior nucleus of the thalamus is the typical target for frontotemporal epilepsy, whereas the centromedian nucleus has been targeted more for generalised epilepsy. Further controlled studies of this technology in children, especially in those with generalised epilepsies are needed.

Conclusion

While many children with epilepsy will achieve seizure control with medication, drug-resistance is problematic for up to one quarter of cases. In addition to ongoing seizures, children with drug-resistant epilepsy are at higher risk of cognitive, behavioural and psychiatric comorbidities, injury, sudden unexpected death in epilepsy and poor quality of life.

A structured approach is needed for those affected. Firstly, the diagnosis of epilepsy should be confirmed, and epilepsy mimics excluded. Secondly, the epilepsy type and seizure syndrome (if present) should be established, and medications reviewed to exclude 'pseudoresistance'. Thirdly, careful evaluation of the underlying etiology should be undertaken, to determine if there is a 'best' treatment, such as possible surgical resection for a single epileptogenic focus. Ideally, all children and adolescents with ongoing seizures despite trialing two or more antiseizure medications, and infants with frequent seizures which are potentially impacting their development – even prior to established drug resistance – should be referred promptly to specialised epilepsy centres, which have greater access to resources and expertise for specialised testing and support of children with intractable epilepsy, and their families. However, specialised epilepsy centres may not be available in resource-limited regions of the world.

In cases where no specific etiology-based treatment is available, realistic and appropriate goals for seizure control should balance the risk of seizures, treatment side effects and quality of life. Excessive polypharmacy should be avoided, and non-medication options such as palliative surgery, neurostimulation and dietary options should be considered. Comprehensive care should also focus on non-seizure symptoms of epilepsy, including cognitive, behavioural and psychiatric comorbidities to improve the well-being and quality of life of children impacted by drug-resistant epilepsy, and their families.

Competing interests

None.

Cite this article as:
Wirrell, E. C. (2021). Rational Approach to Children with Drug-Resistant Epilepsy . Journal of the International Child Neurology Association, 21(1). https://doi.org/10.17724/jicna.2021.191

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