EPILEPSY

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Seizures are amongst the most common of neurological disorders in the pediatric age range. The incidence of new-onset epilepsy in children is approximately 40 per 100,000 per year [1, 2](Camfield, Wirrell). Of these, approximately 20-30% will be medically intractable [3].

Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and can result from diverse etiologies. The Classification Commission of the International League Against Epilepsy (ILAE) has recently proposed a "roadmap" to develop a classification system and the framework for this model is shown in Figure 1 [4]. This framework allows for diagnosis at multiple levels, depending on which resources and information are available. It also allows physicians to take advantage of the remarkable diagnostic advances that have occurred in genetics, neuroimaging and neuroimmunology.

Level 1 – Confirmation of epilepsy and seizure type(s)
The first level requires the clinician to determine that the paroxysmal events are seizures and identify the specific seizure type(s). The ILAE has proposed an operational definition of seizure types which is available for download on their website (http://www.ilae.org/Visitors/Centre/documents/ClassificationSeizureILAE-2016.pdf)

Level 2 – Epilepsy type
At the second level, epilepsy type is established. Although many epilepsies can be divided into "focal" versus "generalized", not all can be dichotomized into these two groups. In some children, epilepsy can be both focal and generalized (i.e. Dravet syndrome, Lennox-Gastaut syndrome, CSWS), and in others, it is unknown if the epilepsy is generalized or focal (i.e. spasms, which can result from both diffuse as well as focal brain abnormalities).

Level 3 – Epilepsy syndrome
At level three, one determines whether there is an epilepsy syndrome present or not. Epilepsy syndromes can be defined in approximately one third of children with epilepsy, are often age-related and are comprised of distinctive clinical (seizure types, development, etc) and EEG patterns. They may have associated imaging, etiological, prognostic and treatment implications. Epilepsydiagnosis.org (an educational ILAE website) provides a concise overview of distinctive features seen with specific epilepsy syndromes.

Level 4 – Epilepsy Etiology
At the fourth level, epilepsy is classified based on its definitive etiology. Using such a classification system for children with epilepsy assists in selecting appropriate diagnostic investigations and identifying specific etiologies, which allow for individualized selection of the most effective therapy for each patient.

a. Genetic
Genetic etiologies can be divided into two main groups – those in which there is a known, causative genetic mutation, and those in which the actual gene is not known, but there is strong evidence based on family and twin studies for genetic inheritance, such as is the case for the genetic generalized epilepsies such as childhood absence, juvenile absence or juvenile myoclonic epilepsy.

In early life epilepsies, genetic testing, particularly broad sequencing methods such as epilepsy panels or whole exome sequencing, have high diagnostic yields, and should be incorporated as part of the initial evaluation in all patients, not only those with severe presentations and poor outcomes. In a large cohort of children presenting to multiple sites in the US with newly-diagnosed epilepsy, pathogenic variants were found in nearly 40% of cases. Yields were 16.2% for chromosomal microarrays, 28.8% for epilepsy gene panels, 35.3% for whole exome sequencing, 60% for mitochondrial panels and 29.8% for other tests (Berg et al, in press). Determining a specific genetic cause provides a definitive answer to the family, avoiding the expense and risk of further diagnostic studies, allows for genetic counselling of family members, and importantly may provide key information on precision treatment of the epilepsy. Increasing numbers of genes are being recognized that are associated with clear therapeutic implications for management (Table 1). For example, in Dravet syndrome, which is associated

with an SCN1A mutation, sodium channel agents should be avoided as they exacerbate seizure. Conversely, stiripentol, when used in combination with clobazam and valproate, significantly reduces both seizure frequency and severity in the majority of patients.

b. Structural

Structural etiologies are common causes of epilepsy in children, accounting for approximately 28% of all epilepsies beginning prior to 18 years of age, and one half of cases presenting before 12 months of age (Wirrell 2011). Structural etiologies can be further divided into congenital versus acquired causes. Malformations of cortical development are one of the most common etiologies for focal epilepsy in early life, and have a high association with medical intractability. If focal, such patients may be excellent candidates for resective surgery. Guidelines for imaging infants and children with new onset epilepsy have been published [5]. In children under the age of 2 years, immature myelination may limit the detection of cortical dysplasia, and thus additional sagittal, axial and coronal T1 images are recommended. Furthermore, if MRI imaging done prior to 2 years of age is normal, and seizures persist, MRI should be repeated after age 24-30 months, when more mature myelination will allow detection of cortical dysplasia.

Medically intractable epilepsy, particularly in very young children may have a devastating impact on development [6]. In cases where seizures remain refractory, and the child's development is regressing, or not progressing, early surgical evaluation should be considered, if the child is a candidate for resective surgery, as the longer the duration of untreated seizures, the poorer the developmental outcome [7].

c. Metabolic

Metabolic etiologies are relatively rare causes of epilepsy. In many cases, such disorders do not have an effective therapy, and neurological decline is progressive. However, there are a number of disorders which have specific, curative therapies, and if recognized in a timely manner, such interventions can prevent progressive neurological decline and lead to seizure cessation (Table 2). Some of these disorders will also be identified on epilepsy gene panel studies.

d. Immune

Immune etiologies of epilepsy in children are rare, but important to recognize. This etiology should be considered in children presenting acutely or subacutely with seizures that are typically pharmacoresistant from onset, with a progressive course. In addition to seizures, other multifocal neurological symptoms/signs such as altered mental status/acquired cognitive dysfunction, autonomic dysfunction, sleep disturbances and/or movement disorders are often present. Investigations may show slowing of the EEG background, FLAIR or T2 signal changes on MRI and inflammatory CSF findings with negative cultures. If suspected, antibody testing on serum and CSF is suggested. Cases are typically refractory to antiepileptic drugs, but responsive to immunomodulatory therapy. Prognosis is most favorable if such therapy is initiated early in the course [8].

e. Infectious

Central nervous system infection may result in both acute symptomatic seizures as well as epilepsy. Examples of infectious etiologies include HIV, neurocysticercosis, malaria and tuberculosis.

f. Unknown

This term replaces the previous term of "cryptogenic" and simply denotes that the etiology is not known. This term is used for all types of epilepsy with unknown cause, regardless of the child's development.

Associated Co-morbidities

Seizures are just one symptom of epilepsy. Many children and teens have other co-morbidities including ADHD, behavior disorders, mood disorders including anxiety and depression, sleep disorders, intellectual disability, learning disorders and autism [9]. These associated co-morbidities may be problematic even in cases where seizures are well-controlled, and can have even greater impact on quality of life than the seizures. Such co-morbidities must also be screened for and treated to maximize long-term psychosocial outcome. Medications such as stimulants and SSRIs are safe to use in children and teens with epilepsy.

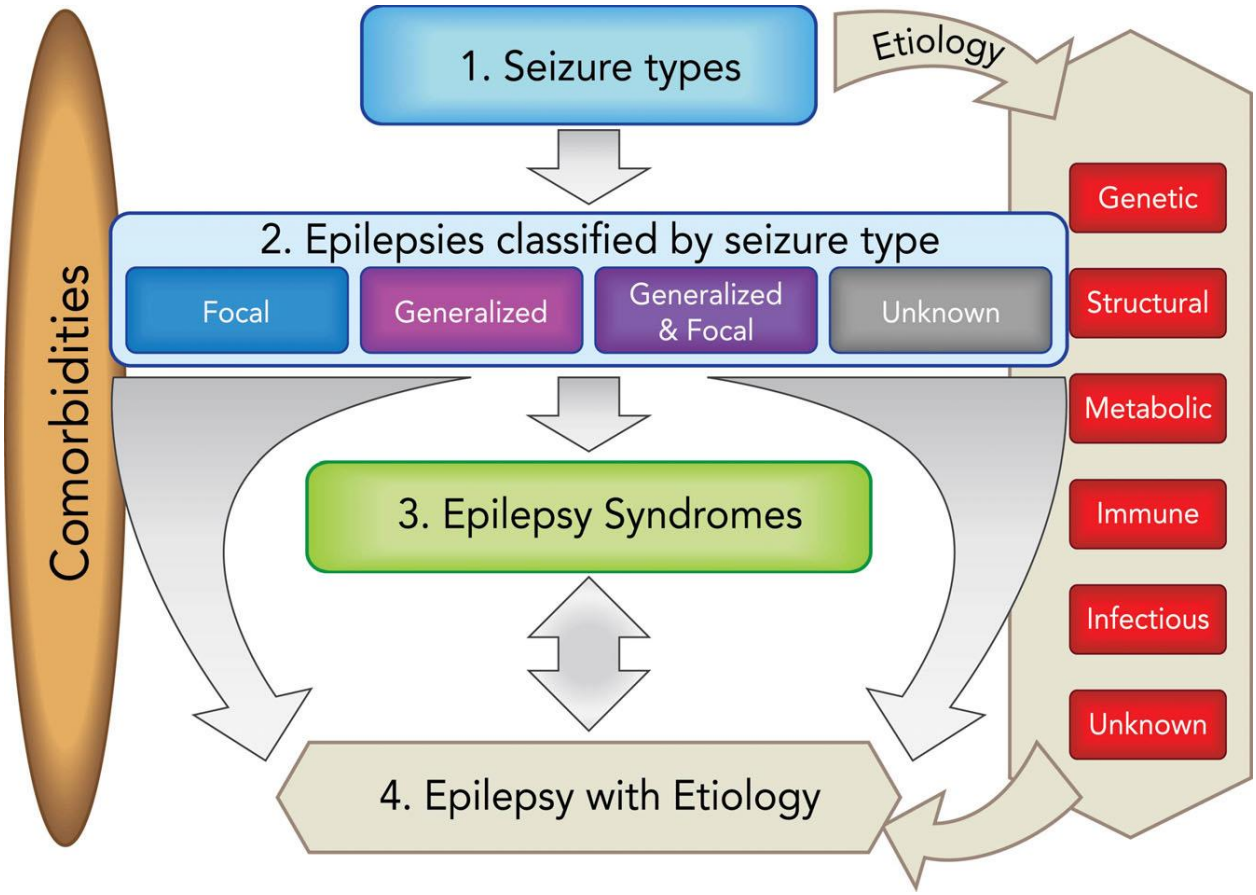

Figure 1: Framework for Epilepsy Classification (from Scheffer et al. 2016)

Gene	Age at onset	Phenotype	Optimal Therapy	Contra-indicated
SCN1A – severe phenotype[10]	<12 mos	Dravet syndrome	VPA, CLB, TPM, STP, ?fenfluramine	Sodium channel agents
SCN2A[11, 12]	Early infancy	EIMFS, movement disorder	High dose phenytoin	
SCN8A[13]	Infancy	Multiple sz types (spasms, focal, generalized), ID. movement disorder	High dose phenytoin	
KCNQ2[14]	Neonates	BFNS	Low dose CBZ or OXC	
KCNT1[15]	Infancy/early childhood	EIMFS, other	Quinidine	

Table 1: Specific genetic etiologies with treatment implications

Disorder	Investigation	Treatment
Pyridoxine, P5P dependent, folinic acid responsive szs	↑ AASA (CSF, serum and urine), ↓ P5P in CSF	Pyridoxine, P5P, Folinic acid
Creatine deficiency	Cr metabolites urine, MRS	Creatine
Serine deficiency	CSF and serum aa	Serine
Biotinidase deficiency	Serum biotinidase	Biotin
Glucose transporter deficiency	CSF/serum glu, CSF lactate	Ketogenic diet
Cerebral folate deficiency	CSF MTHF	Folinic acid
Mitochondrial disorders	Lactate, pyruvate (CSF, serum), muscle bx, mt genetics	Mt cocktail (thiamine, carnitine, CoQ10, riboflavin) Avoid VPA Trial of KD
Nonketotic hyperglycinemia	CSF/plasma glycine	Benzoate, dextromethorphan, avoid VPA

Table 2: Specific Metabolic Disorders with Treatment Implications

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