SEMINAR ON CHILDHOOD EPILEPSY

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Declaration of Interests

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JHC has acted as an investigator for studies with GW Pharma (Jazz), Zogenix (UCB), Vitaflo, Stoke Therapeutics, Encoded, Ultragenyx and Marinius. She has been a speaker and on advisory boards for GW Pharma (Jazz), Zogenix (UCB), Biocodex, Takeda and Nutricia; all remuneration has been paid to her department. JHCs research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. JHC holds an endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from NIHR, EPSRC, GOSH Charity, ERUK, the Waterloo Foundation and the Great Ormond Street Hospital Biomedical Research Centre.

Search strategy

We searched the Cochrane Library (2018-2024), MEDLINE (2010-2024) and EMBASE (2010 -2024). We used search terms 'epilepsy' and 'childhood', 'antiepileptic drugs', 'epilepsy surgery', 'ketogenic diet'. We largely selected publications in the past 5 years but did not exclude commonly referenced and highly regarded older publications. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. The reference list was modified on the basis of comments from the peer reviewers.

Contributor statement

RM drafted the manuscript with initial literature review; RM and JHC both contributed to edits, reviews, and finalising of the manuscript.

Abstract:
The epilepsies presenting during childhood pose unique challenges. They include the developmental and epileptic encephalopathies, certain distinctive constellations and epilepsies with seizure subtypes such as epileptic spasms, myoclonic-atonic and myoclonic-absences. Self-limiting focal epilepsies are also evident in this period in addition to genetic generalized epilepsy phenotypes. However determining the cause, whether structural, genetic, metabolic, infectious or autoimmune, is becoming increasingly relevant. While history and clinical examination form the fundamental basis of diagnosis, exclusion of epilepsy mimics in childhood can prove challenging requiring specialist input and supportive electrophysiology. With crucial evidence-based medicine emerging on treatment of Infantile Epileptic Spasm Syndrome, Dravet and Lennox Gastaut syndromes focussed on improving outcomes, early identification of surgically remediable epilepsies is crucial as 'time is brain' with regard to neuro-developmental outcomes. Practical questions remain with regard to pathophysiology, impact of aetiology and inter-ictal epileptiform activity on cognition and efficacy of precision medicine based approaches based on recent insights from epilepsy genetics.

1. Introduction

Epilepsy remains the most common chronic neurological disease in children. Epileptic seizures occur the direct result of a primary change in electrophysiological activity of the brain; they are indeed a symptom of many different causes and therefore more accurately should be referred to as the epilepsies. The world-wide prevalence of epilepsy increases with age, with bimodal peaks at 5–9 years (374·8 [280·1–490·0]/100,000 population) and in the elderly > 80 years of age (545·1 [444·2–652·0]/100,000 population).[1,2]The incidence of epilepsy in childhood ranges from 41-187/100,000 with higher incidence reported from low-middle income countries (LMIC), especially in rural areas, at the two extremes of age **(table S1a and b appendix).**[3,4] The epilepsies start in childhood in more than half of cases.

Across all ages, epilepsy is diagnosed if an individual experiences at least two or more unprovoked or reflex seizures more than 24 hours apart.[5] Additionally risk stratification using investigations permits extension of the definition of epilepsy to either diagnosis of an epilepsy syndrome or after the occurrence of one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk that exceeds 60% after 2 unprovoked seizures, occurring over the next decade. While this definition is acceptable

across all ages, challenges are often encountered in children, especially neonates wherein recognition of seizures can be difficult and aetiology is often 'acute symptomatic'. It is also important to consider that febrile seizures, seizures occurring within seven days of a head injury or cerebro-vascular hemorrhage, seizures during the course of an active central nervous system (CNS) infection, and in acute systemic or metabolic disturbances such as hypoglycaemia, hypocalcaemia, hyponatremia and hypoxia are by definition epileptic seizures but are not considered epilepsy.

2. Symptoms and signs with approach to epilepsy classification in childhood:

Clinical evaluation

The initial approach towards a child with suspected epilepsy is to clarify that reported paroxysmal episodes are epileptic seizures rather than non epileptic events, which can prove to be particularly challenging (**See S2 appendix))**. This will prevent inappropriate treatment as well as unnecessary investigations and allay parental anxiety, especially considering the potential life-time implications and stigma attached to the diagnosis.

Diagnosis of epilepsy on history, or documentation of convulsive or non-convulsive seizures is based on rigorous observation, description of stereotyped, brief, repetitive events of sudden onset and offset with pre- and post-ictal symptoms, usually unprovoked. Clinical examination is paramount to document not only neurological deficits but also dysmorphology, associated malformations, developmental and psychomotor issues and evidence of neuro-cutaneous syndromes. When eye-witnesses report that an activity can reliably be stopped or modified by intervention, non-epileptic events need to be considered. Post-ictal manifestations such as drowsiness, confusion, aphasia or amnesia are also more consistently reported after epileptic seizures. Events that occur in sleep need to be explored especially if these are brief, stereotyped and recur multiple times with arousals before concluding sleep-related disorders such as parasomnias.

Febrile seizures are the second most common type of seizures in the paediatric population, with maximum prevalence during infancy and early childhood. Simple febrile seizures seem to have few consequences, but prolonged complex febrile seizures have been hypothesized to correlate with the development of MRI changes such as hippocampal sclerosis (HS) with consequent temporal lobe epilepsy in later life. This aside, literature reports the likely

presence of pre-existing hippocampal abnormalities in such circumstances.[6,7] Risk factors identified for recurrence in children with febrile seizures include: early age of onset (<12 to <18 months), epilepsy in first-degree relatives, febrile seizures in first-degree relatives and frequent febrile illness. However it is clear that febrile seizures, particularly prolonged febrile seizures may also be the presentation of a genetically determined epilepsy, such as Dravet syndrome or other syndromes within the Genetic Epilepsy with Febrile Seizures plus (GEFS+) spectrum. Seizures related to vaccines (e.g. Pertussis) in a small subset of children have now been shown to have an underlying genetic basis, and the likely presentation of Dravet syndrome.[8,9]

It needs to be emphasized that some behaviours in children can occur as a response to a seizure rather than an ictal manifestation, e.g. crying after experiencing an uncomfortable aura or distressing seizure. A caveat in especially neonates, infants, non-verbal children with autism or even children who are verbal with underlying intellectual impairment is they cannot express themselves or clearly describe their symptoms. Smart-phone and video camera recordings have emerged as a valuable tool for parents to document episodic paroxysms.. Lastly when in doubt, referral for further opinion and possible diagnostic video-EEG confirmation can help.

Seizure classification is the fundamental first step in the evaluation of a child presenting with paroxysmal events suggestive of epileptic seizures. The seizures may be classified as focal, generalised or unknown-onset, based on clinical description in accordance with the current International league Against Epilepsy (ILAE) framework with a separate schema for neonatal seizures also proposed[10,11]

Questions unique and challenging in CWE which form the fundamental basis for classification are as shown in **Box A:**

Box A

a) Are events suggestive of epileptic seizures Whatis the level of certainty that the paroxysmal events are provoked or unprovoked seizures or seizure mimics?
b) If yes, what types of seizure
c) Do the seizure types and EEG enable a diagnosis of an epilepsy syndrome?
d) Is this a self-limiting syndrome with a good long-term prognosis (may have short term implications on cognitive performance of the child) or does it run the risk of recurrence with impact on the child's development and other activities?
e) Is this a syndrome which runs the risk of drug-resistance or has a potential for accruing disabilities and needs detailed investigation, aggressive management and application of targeted therapeutic approaches?
f) Can a cause be found?
g) What are the co-morbidities that are associated with or linked etiologically to the child's epilepsy including motor disorder, cognitive disability as well as mortality risk.

An EEG (electroencephalogram) should be undertaken in all children where there is a suspicion of epilepsy; where clinical events are thought, on the basis of description, to be epileptic in origin. A recent meta-analysis showed that an adult with interictal epileptiform discharges (IED) on routine EEG after a first unprovoked seizure has a post test 77% probability of having a second seizure, whilst a child has a lower probability of 66%.[12] . IEDs while rare in normal individuals can be noted in 1.9–3.5% of children who have no prior history of seizures and are cognitively normal without any focal deficits (15% may go on to develop epilepsy).[13] The EEG is used to support the diagnosis of epilepsy, help to classify whether a focal or generalized epilepsy syndrome exists and in certain specific epilepsy syndromes, the morphology assists in defining that syndrome, e.g., SeLECTs, childhood absence epilepsy, Infantile Epileptic Spasms Syndrome and LGS, epilepsy with spike wave activation in sleep. Technical standards, with at least 30-45 min of EEG record to adequate capture of sleep wake cycle in children along with activation procedures, are essential.[14] If a wake EEG recording is normal, in the light of a high suspicion of epilepsy, a sleep recording should be ascertained. This may increase the yield of abnormality from 50 to 85%.[15]

After exclusion of epilepsy mimics, and a diagnosis of epileptic seizures, the clinician needs to go through the steps outlined in **Figure 1,** through detailed history and examination as to arrive at the classification of epilepsy. This fundamentally is based on description of the

seizure subtype, epilepsy subtype, the age-dependent electro-clinical syndrome **(Figure 2)**, cause **(Table 1)** and associated comorbidities. To understand any classification approach with regard to unique aspects in CWE, certain definitions are relevant:

Electroclinical syndrome-
This is defined as a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, infectious or unknown) The diagnosis of a syndrome in an individual with epilepsy frequently carries prognostic and treatment implications. Syndromes often have age-dependent presentations and a range of specific comorbidities.[16] Specifically, childhood onset epilepsy syndromes are classified presently under self-limited focal epilepsies (SeLFEs), genetic generalized epilepsies (GGE) and developmental-epileptic encephalopathies (DEE).[17]

SeLFEs: These account for 25% of paediatric epilepsies which are presumed to have a genetic basis, have an age-dependent onset and are usually pharmacoresponsive with remission by adolescence. Cognitive and neurological deficits are not noted except in children with atypical evolutions. These include self-limited familial and non familial neonatal infantile convulsions, self-limited epilepsy with autonomic seizures (SeLEAS), self-limited epilepsy with centrotemporal spikes (SeLECTS), childhood occipital visual epilepsy (COVE), photosensitive occipital lobe epilepsy (POLE).

GGE: These include conditions characterized by seizure types such as absences, eyelid myoclonia or myoclonic absences with spontaneous or activated generalized interictal epileptiform discharges on EEG. They have a genetic etiology with complex or polygenic inheritance. A positive family history of epilepsy is often noted. Cognition, neurological examination and response to ASM are variable

Epileptic encephalopathy (EE): the epileptic activity itself leads to psychomotor and behavioural impairments above and beyond what might be expected from the underlying pathology alone. This is a concept that may be seen with an epilepsy diagnosis at any age.

Developmental and epileptic encephalopathy (DEE)- an enduring condition wherein either there is a combination of developmental impairment or regression as a consequence of the

aetiology, independent of the epilepsy, as well as an epileptic encephalopathy.[18-21] These impairments can potentially worsen over time. Often it may not be possible to disentangle whether the epileptic or developmental component is more important in contributing to an indivdiual's neurobehavioural impairment.

A detailed account of each epilepsy syndrome is beyond the scope of this review; onset of the syndromes may be characterised by a specific age spectrum; key syndromes and age of onset are highlighted in figure 2. Criteria for diagnosis for each syndrome, with review of names were finalised by the International league Against Epilepsy in a series of papers according to age category in 2022.[17, 22-25]

3. Causes of childhood onset epilepsy

Increasingly the aetiology to the epilepsies has become important, giving us an insight into the true underlying mechanisms and possible alternative treatments where individuals are resistant to standard therapies. At the turn of this century the cause of many epilepsies, especially the DEE was unknown. Advances in neuroimaging and genomics however have led to an aetiological answer (**Table 1**), in early onset DEEs being achieved in 60-70%.[26]

Insert Table 1 here

A structural basis deserves consideration by the clinician as many cases of early-life seizures are associated with external insults, such as hypoxic ischaemic encephalopathy (HIE), or trauma. These often commence as 'acute symptomatic' seizures and raise the susceptibility of the immature brain towards establishment of epileptogenic foci.

Similarly, malformations of cortical development (MCD) e.g. focal cortical dysplasias (FCD), cortical tubers of tuberous sclerosis (TSC) or hemimegalencephaly can be associated with epilepsy[27] (**Figure 3**). In such situations, the pathophysiological basis of these malformations are often genetic, either germline or somatic,.[28-30] Animal models have significantly contributed to our understanding of epileptogenesis, eg. gene knock-out mice models in TSC have reproduced early ontogenic aspects of electroencephalographic (EEG) abnormalities, focal seizures, and an increased propensity for spasms as in humans.[31]

Over the past decade, monogenic causes have been established in complex epilepsies including the DEEs, with many novel genes emerging but with considerable genotype and phenotype heterogeneity.[32-37] A pragmatic genetic classification of epilepsies of childhood is adapted and detailed in **Table 2**.[30, 38-40] The proof of pathogenicity of a genetic variant/mutation is heavily weighted towards in-vitro functional modelling of receptor or ion-channel dysfunction which is key towards proving functionality of the derived protein (eg. gain vs loss of function) and its impact on the cascade of molecular, cellular and neuronal network alterations that lead to chronic epilepsy.[26] Genetic heterogeneity is apparent in many childhood onset syndromes .eg.epilepsy with myoclonic atonic seizures seen in early childhood may be consequent to *SCN2A, CHD2* or *SLC2A1* gene variants. The function of the gene, whether loss or gain of function variants may also be important, when considering response to some medications. Loss of function *SCN1A* variants are the most common cause of Dravet syndrome, but can cause a wide spectrum of epilepsy syndromes including milder phenotypes such as genetic epilepsy with febrile seizure plus syndromes (GEFS+).[41,42] In such circumstances sodium channel blocking antiseizure medications should consequently be avoided eg carbamazepine. A gain of function *SCN1A* variant has been associated with a severe neonatal onset phenotype. Many factors contribute to this phenotypic pleiotropy such as type (missense versus truncating mutation) and timing (germ-line mutation in parental gametes or somatic mutation in post-zygote cell development/maturation) of mutations during development; timing and location of physiological gene expression; epigenetic factors; and modifier genes.[43-45]

While genetic causes are exhaustive as enumerated in **Table 2**, *de-novo* mutations in the affected individual are most commonly reported because familial variants without phenotypic expression in family members are usually considered non pathogenic. This is now refuted with understanding of germ-line (parental) mosaicism wherein phenotypic expression may not be homogeneous across generations, yet it impacts recurrence risk in offspring.[46,47] Based on work focussed on DEE using cell-specific expression of genes and animal models, there is evidence that dysfunction in specific cell types, brain regions and molecular networks leads to epileptogenesis.[26,38] Furthermore it has been shown in certain monogenic epilepsies that the timing of expression of genes often predicts the temporal evolution of epilepsy. This is especially with regard to ion-channel (*SCN1A, SCN2A, KCNQ2*) and receptor pathway (*GRIN2A*) genetic variants which typically present at around the age at which the

physiological expression is necessary for normal neuronal development.[45,48,49] Downstream effects of genetic mutations in the severe epilepsies also contribute to cognitive impairment, and are unlikely to be impacted favourably by timely initiation of conventional antiepileptic drug therapies.[21,38]

Knowledge of genetic factors underlying childhood onset epilepsy is likely to exponentially rise in the coming years, as whole genome sequencing (WGS) and multiple epilepsy-specific gene panels are applied to many DEE's and identification of disease causative mutations becomes validated on bio-informatic platforms as well as in-vitro functional assays.[46] Given the many neurobiological consequences, despite the considerable advances in gene discovery and gene function, our understanding of the mechanisms in childhood epileptogenesis is still gaining momentum. This has the potential to identify biomarkers for stratifying patients at risk of developing epilepsy or for monitoring disease progression in addition to facilitating the introduction of novel targeted therapy which act on signalling pathways and consequences of the putative process.

Cerebral head trauma, infections and tumours may occur at any age and may lead to the development of epilepsy. Infections of the CNS in children are major risk factors for epilepsy. The reported risk of epilepsy in population-based cohorts with sequel of infections from HIC countries varies between 6.8-8.3 %, but is much higher in LMIC.[50] Apart from the direct effects from the infection with subsequent localized and systemic inflammation and oedema, residual scarring or gliosis is often the cause of these epilepsies.

Auto-antibody mediated immune encephalitis has emerged as a major cause of late childhood and adolescent epilepsy in the past decade with seropositive, as well as seronegative diffuse encephalopathies appearing to respond to immunosuppressive therapies. Rasmussen's syndrome, an acquired progressive encephalitis of one hemisphere has long been thought to be autoimmune in aetiology, with immune therapy slowing the disease process, but no specific antibody has been isolated, and surgery is likely to be the only cure to seizures. A distinctive acute syndrome is febrile-infection related epilepsy syndrome (FIRES) which is a cause of new-onset refractory status epilepticus (NORSE), more often seen in school-age children that requires a prior febrile infection starting between 2 weeks and 24 hours prior to onset of SE, with or without fever at onset of SE.[51-53] The mechanism is believed to be

consequent to a stormy 'sterile' inflammation of the CNS with refractory epilepsy as a long term sequel, with the diagnosis made after firm exclusion of infectious encephalitis.[54]

Insert table 2 here

4. Management of seizures in CWE

4a Acute management of prolonged seizures

Timely intervention is key to stopping seizures in the convulsing child. The initial step would be securing the airway and positioning the child to prevent injury and aspiration. Pre-hospital care and first line ASM, for which parent education is the key, would be with benzodiazepines administered via rectal (diazepam), or buccal, sub-lingual, nasal and even intra-muscular route (midazolam, lorazepam) where parenteral access has not yet been achieved.[55–57] Usual advice would be for this to be administered if a convulsive seizure reaches 5 minutes. Second line agents include parenteral phenytoin, fosphenytoin, levetiracetam, sodium valproate, lacosamide and phenobarbitone (an option in many LMIC; https://www.who.int/mental_health/mhgap/en/).

While a discussion on management of convulsive and non-convulsive status epilepticus (SE) is beyond the scope of this review, pre-hospital management is often the key to reduce morbidity and mortality secondary to SE in established epilepsy.[58] The current definition of convulsive SE focuses on time windows[59] - "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures." In the case of convulsive (tonic–clonic) SE, both time points (t_1 at 5 min and t_2 at 30 min) are based on information gained from animal experiments and clinical research. Similarly for focal motor/non-motor SE with impaired awareness, t_1 is 10min and t_2> 60min. For absence SE which usually does not lead to irreversible neuronal injury t_1 may be 10-15minutes. With regard to GTCS earlier initiation of treatment results in shorter total seizure duration. In established epilepsy GTCS and focal seizures are expected to abate within 2-3 minutes; convulsive seizures or repetitive seizures without recovery of consciousness between episodes lasting more than 5 min require emergency management.[60] Criteria for non-convulsive SE (NCSE) is crucially EEG-based.[61]

Certain genetic syndromes such as ring 20 chromosome epilepsy**,** Angelman and Rett syndromes may be prone to prolonged spells of NCSE or myoclonic SE which may not be life-threatening although atypical absence SE in LGS can lead to obtundation. NCSE can also be precipitated due to the wrong choice of medications as seen in absence SE in JAE following introduction of narrow spectrum ASM such as oxcarbazepine or phenytoin.

4b Long term pharmacological management of CWE (Table 4)

First line management of CWE is antiseizure medication (ASM), designed to prevent seizures regardless of cause. With a wide array of ASM (>25) to choose from, pragmatic issues in choice of ASM exist (other than the epilepsy subtype and electro-clinical syndrome **Table 3**). These include a) pharmacokinetic (dose loading and titration), pharmacodynamic effects (mechanism of action) and interactions with other ASM when used as duo- or polytherapy or with other medicines administered for associated comorbidities; b) adverse events with monotherapy or combination including allergy and idiosyncratic reactions; c) effects on body metabolism and bone metabolism in the growing child; d) impact of ASM in the presence of associated comorbidity including pre-existing psychopathology such as autism, ADHD or intellectual disability and systemic illness such as hepatic, renal, haematological or oncological issues; e) compliance issues during administration, drug-resistance and paradoxical aggravation of certain seizure types with specific ASM.

Evidence concerning the efficacy and safety profile of older ASM is robust through studies and clinical observations gathered over many years. The effectiveness of newer ASM (2nd and 3rd generation) in terms of efficacy has only been reported in placebo controlled studies and often, off-label use in the children is based on evidence of efficacy in children >12 yrs age. Overall, newer ASM seem to have better tolerability with lower adverse effect profile.[62] However, safety information is based on short follow-up periods and on randomized controlled studies assessed on the basis of efficacy with only data recently emerging on long-term safety.[63] The considerably higher costs of newer ASM should also be taken into account in the prescription process. The nature of side effects, pharmacokinetic profile, interactions and pharmacodynamics of individual ASM are beyond the scope of this review and detailed in literature[64]

Insert table 3 here

5. Alternatives when standard ASMs fail

Certain factors intrinsic to the epilepsy syndrome predict refractoriness. Drug resistant epilepsy (DRE) is defined as failure of 2 tolerated, appropriately chosen, and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (all types of seizures) for 12 months, or 3 times the inter-seizure interval before treatment was initiated.[73] The pooled-estimate of incidence of DRE in children <17 yrs in a recent meta-analysis is 15% as compared to 34% in adults with a combined estimation of 24% and no significant change in the figures if one narrows to newly-diagnosed epilepsy.[75] The pooled prevalence estimate of DRE is around 30%.[76] Certain epilepsy syndromes of childhood, especially the DEE have an inherent propensity for drug resistance. An underlying cause may provide an alternative way forward with treatment eg sodium channel blockers in gain of function sodium channel variants (**See Table S3 Appendix)**.

A) Ketogenic diet therapies (KDT)

Ketogenic diet therapies, high fat low carbohydrate therapies aimed to generate ketones, is an alternative treatment in children after who have failed ASMs. They have been shown to be of particular benefit in disorders such as GLUT-1 deficiency disorder, where ketones provide an alternative fuel source,[77] or epilepsy with myoclonic-atonic seizures. There are four possible KDT options (Long Chain fat (Classical), Medium Chain Triglyceride, Modified Ketogenic Diet and Low Glycaemic Index treatments) and the choice is largely individualized to that of the family, culture and the child's likely adherence. Dedicated KDT teams to ensure appropriate treatment and monitoring for side effects are essential. Apart from seizure control, beneficial reduction in ASM doses may also be achieved. Although response rates as adjunctive therapy in DRE (often estimated as proportion of CWE with 50% seizure reduction as in most DEE trials) are around 30-40%,[78] up to 80% seizure-free responders may not experience seizure relapse even after discontinuation of KD.

B) Epilepsy surgery

Surgical management is now standard of care, mandating careful selection of candidates.[79] Although drug resistance has previously been considered a pre-requisite, it is clear that with the possibility of cure, and a wean of medication, carefully selected candidates with structural lesions in non eloquent areas may be suitable for earlier surgery. An RCT demonstrated

seizure freedom in >75% of children operated (temporal, extra-temporal, hemispherotomy, hypothalamic hamartoma resection/disconnection) along with significant behavioural and quality of life gains at 12m in comparison to children who underwent continued medical treatment.[79] Surgical series on children with a wide variety of substrates have demonstrated high seizure freedom rates in temporal lobectomies (80.6%, 63.9% off ASM), posterior cortex surgery (60% seizure free; 30% off ASM), frontal lobe surgeries (63% seizure free, 37% off ASM) and hemispherotomy (75% seizure free, 44% off ASM).[80-82] Pre-operative cognitive performance and seizure freedom has been found to determine higher full-time employment rates among adults who underwent epilepsy surgery during childhood or adolescence.[83] Cognitive improvements are seen in the longer term highly associated with seizure freedom and weaning from ASM.[84,85] Cognitive deterioration is unlikely and data consequently suggests that children should be referred early for evaluation.[86,87]

In surgically remediable syndromes the pre-surgical investigative battery is aimed at determining the minimum amount of brain tissue that needs to be resected or disconnected in order to maximise the potential of seizure freedom (**Figure S1 Appendix)**.[88] Clinical evaluation, short term and long-term video EEG, MRI, neuropsychological evaluation are cost-effective and essential components of pre-surgical evaluation; there may however be limitations in LMIC with regard to availability of investigative modalities as well as in the number of trained neurologists or epileptologists.[89-91] The International League Against Epilepsy Task Force for Paediatric Epilepsy Surgery has recently outlined criteria for level 1 and level 2 centres for assessment and treatment of children, based on complexity and personnel/technology required.[92]

Palliative options for reduction in the seizure burden in children who are not candidates for resective/disconnective surgery include, corpus callosotomy for atonic drop attacks, vagus nerve stimulator implant for inoperable focal/multifocal epilepsy/ DEE, anterior thalamic deep brain stimulation, and responsive neurostimulation (RNS) for regional neocortical epilepsy.[93,94]

6. Outcomes in CWE

Worldwide, short and long term outcomes in CWE are determined by the nature of the epilepsy syndrome especially with respect to aetiology, comorbidities and treatment gap. The

latter issue is at the cornerstone in many LMIC which have several pertinent challenges, some of which may be inherent to local health care systems (cost of treatment, limited availability of ASM disparity of resources between public and private health care, limited number of neurologists and epilepsy specialists, constraints on accessibility to augmentative diagnostic modalities including MRI and EEG) or to patients and their community (cultural beliefs, social stigma, alternative and traditional treatments, negative attitudes towards treatment, residence in rural areas and travel for comprehensive epilepsy care centres concentrated in urban areas). [95] Early referral to complex epilepsy services is highly recommended if epilepsy is drug-resistant, a child is under 2 years, if there are unacceptable side effects of medicines, there is a unilateral structural lesion, psychological and or psychiatric comorbidity or if there is diagnostic uncertainty.

A) To stop or not to stop ASM in children?

With the definition of sustained seizure freedom provided earlier, at some point ASM withdrawal may be considered in children with sustained seizure freedom. While the decision is fairly straightforward in self-limited epilepsies, pertinent issues exist in other syndromes.. Recent data from the Finnish cohort suggest that among patients with remission on or off ASM, the ability to predict lower relapse rate increased markedly from 2 to 5 years of remission, and further from 5 to 10 years. [96] Recurrence risk is thus lowest if 5 years of terminal remission and subsequent ASM freedom is attained. Clinical variables which can be useful predictors ASM withdrawal outcome are listed in **Box B**.

Box B

Favourable predictors of ASM withdrawal:

a) seizure freedom of > 2years
b) response to low dose of one ASM
c) no prior relapse on AED withdrawal, normal neurological examination and EEG, GGE (except as stated below)
d) self-limiting epilepsies of childhood.

Factors associated with relapse after ASM withdrawal:

a) older age at epilepsy onset
b) later age at remission
c) high number of seizures before remission
d) Failed prior attempts at ASM withdrawal/ seizure-free interval before ASM withdrawal
e) remote symptomatic cause-Neonatal seizures, trauma, birth asphyxia or vascular insult
f) syndromes such as JME or myoclonic absence epilepsy; DEE
g) family history of seizures
h) febrile seizures
i) intellectual disability
j) abnormal MRI findings
k) polytherapy
l) epileptiform EEG abnormalities.

B) Epilepsy and cognition- two sides of the same coin?

Baseline cognitive ability has emerged as an important predictor of long-term psychosocial wellbeing. A combination of having epilepsy and poor cognitive skills are more likely to be associated with adverse outcomes in adulthood compared to having poor cognitive development alone.[97] The likelihood of achieving sustained seizure freedom into adulthood is virtually non-existent with profound ID as opposed to children with normal cognition.[97] On the other hand, children with continuing seizures when followed into adulthood exhibited poor performance on measures of language, semantic and visuomotor skills in comparison to normal controls and those with remitted epilepsy.[97] Cognitive problems (prevalent in 42.9% versus 6.6% in the general population) ranging from behavioural and emotional disorders (10.5% including anxiety and depression with ADHD in 12.1%), developmental delay (7.5%), disorders of psychological development (21.3% with autism in 7.8%) to ID (17%) have been documented in a population cohort of CWE.[99] Features of autism have also been shown to be more common in CWE even in the absence of ID.[100] There is no evidence that a few seizures lead to cognitive decline with the debatable exception of DEE wherein the genetic basis or etiology may also have a role and not the nature of epilepsy, intervention or EEG abnormalities alone. In DEE an enduring tendency to have no improvement or to cognitively worsen over time remains a genuine concern despite early control of seizures. SeLECTs is unusual in that possibly one-third of patients have transient mild cognitive, especially learning and behavioral difficulties during the active phase of epilepsy but later have normal adult social outcome.[101]

C) Mortality in CWE

CWE have an increased risk of death in comparison to the general population with one study estimating the standardized mortality rate (SMR) in a longitudinal cohort to be three-fold higher[97] Mortality has been found to be higher with more impaired cognition versus children with normal cognition.[98] It is clear that epilepsy is associated with premature mortality, especially in children and in LMIC, with values of SMR that can approach up to six times higher in poor regions than in HIC.[102] The major proportion of epilepsy-related deaths can be prevented, especially those attributable to falls, drowning, burns, and SE. All CWE require risk assessment focussed on risk of falls and injuries particularly while bathing and showering, nutrition goals, using electrical equipment, managing prolonged or repetitive

seizures, impact of epilepsy in social settings, suitability for independent living to balance rights of the child in relation to the carer and last but not the least risk of sudden unexpected death in epilepsy (SUDEP).

SUDEP is defined as a sudden, unexplained, witnessed or unwitnessed, non-traumatic and non-drowning death in people with epilepsy, with or without evidence for a seizure, and excluding SE, in which post-mortem examination does not reveal a toxicological or anatomic cause for death.[103] Rates of SUDEP in children appears to be similar to adults[104] and yet childhood-onset epilepsy is a risk factor during young adulthood.[105] The risk of SUDEP was estimated at 7% in a 40-year longitudinal study investigating childhood-onset epilepsy.[106] Adult literature suggests that frequent GTCS, nocturnal seizures, poor ASM compliance and frequent changes in ASM are risk factors and limited literature from children suggests that poorly controlled epilepsy and neuro-developmental as well as intellectual comorbidities as in the DEE may be contributory.[107] However a recent registry from patients with an age range of 1-70 years at death, reported that a sizeable minority of SUDEP occurred in patients thought to be treatment responsive or to have self limiting epilepsies indicating that care-giver education is paramount.[108] Certain ion channelopathies have also demonstrated a genetic risk for SUDEP among populations with epilepsy including *SCN1A, SCN2A, SCN5A, SCN8A, KCNQ1, KCNQ2, STXBP1* with many other potential genes also being investigated, particularly because of phenotypic coherence for concurrent cardiac dysrhythmia eg.long QT syndrome.[109,110] While preventive strategies against SUDEP focused on positioning during sleep as well as seizure and apnea detection devices have been advocated without robust evidence, control of epilepsy, particularly GTCS should be advocated. Counselling of families needs to be individualized, with communication on SUDEP risk, the focus needs to be on questions such as risk factors (eg. GTCS, seizures in sleep, ion-channel variants) and prevention (seizure control, ASM compliance).

D) Transitioning of care

Transition from paediatric into adult care can be challenging especially with regard to DRE and DEE, since educational and rehabilitative provisions are of particular concern. [111]At a time of transition there should be a re-evaluation of the epilepsy. Key issues to be addressed are shown in **Box C**. Specialist “transition clinics” or “teenager

clinics" may be useful to ease this transitional process depending on the health care support system of the region.

Box C:

1) Confirmation/revaluation of electroclinical syndrome and etiology; revisit the diagnosis.
2) ASM treatment revaluation: rational therapy for electroclinical syndrome and etiology; ASM withdrawal following sustained seizure freedom.
3) Adolescent girls and young women of child-bearing age: hormonal side effects of therapy (e.g. polycystic ovarian syndrome), weight gain, cosmetic issues, fertility, contraception.
4) Malformation risk posed by older ASM
5) Bone health due to long term exposure to enzyme-inducing ASM
6) Stigma pertaining to further education, employment and travel with its psychosocial implications.
7) Carer burden in children with co-existent intellectual disability, autism, neurological disabilities
8) Concerns on ASM compliance and behavioural side effects given expectations of patients towards functional independence from carers and personal outlook
9) Substance abuse and risk of breakthrough seizures
10) Safety concerns on driving and observance of legal policies
11) Status of social care, psychiatry support systems and the provision of community or residential care- particularly challenging in LMIC.

7. Outstanding research questions

There remain many outstanding questions to address within the field of childhood epilepsy. We are a lot further forward with understanding cause, but are only at the start of the journey with regard to optimising treatments.

The genetic basis of the many poorly defined epilepsy syndromes still remains unclear but may be unmasked by techniques such as deeper sequencing and whole genome sequencing. The importance of epigenetic and other regulatory components of the genome, including microRNAs also remains to be unravelled although clinical utility is still not apparent. It is possible that mechanisms of epigenetic regulation such as methylation profile of genes should also be investigated and will probably contribute to understanding of phenotypic heterogeneity. The ultimate aim would be to translate this process of identification and understanding of functionality of genetic variants to develop a reproducible and robust model of the network dysfunction that leads to epilepsy in an individual patient[53]. It is recognised however that an impact on outcomes in DEEs require treatment beyond that of the seizures.

The recognition of monogenic epilepsies has led to a greater understanding of pathways involved in underlying brain dysfunction in these conditions, and the possibility of alternative therapies, even repurposing of medication[129]. The best example of this has been the utilisation of mTOR inhibitors in Tuberous Sclerosis Complex. Although demonstrated to reduce tumour growth, they have also been demonstrated to reduce seizures[130]. Whether there is also a disease modifying effect over and above reduction of seizures is as yet to be determined. However in other disorders, targeted treatments have been put forward to likely have more success than standard ASMs eg ketogenic diet in GLUT1 DEE,. Novel trial design will need to be considered for appropriate evaluation of further repurposed therapies to cater for the rarity of these disorders. However genetic therapies have also been proposed in monogenic epilepsies, reaching the clinical arena evaluating tolerability and safety eg Anti Sense Oligonucleotide therapy in *SCN1A* Dravet syndrome.[131] Although further evaluation is required, it is recognised that because of the wider brain dysfunction and early onset in complex epilepsies of childhood such as the DEE, early therapy is likely to be required, although how early is unclear. How overall outcomes may be best monitored and determined also requires further work.

The exact relationship between epilepsy, epileptiform activity and cognitive outcome remains under debate. Specifically spikes and seizures may be relatively independent manifestations of epileptogenic tissue or the inter-ictal activity may be a reflection of ongoing subtle seizures based on understanding of network dynamics. This uncertainty is further kindled by invasive-electrode-monitoring based demonstrations of high frequency oscillations as robust biomarkers of epileptogenesis along with the understanding that the epileptogenic zone in focal epilepsy may extend well beyond a lesion evident on imaging.[132] As a consequence cognitive sequelae may be reflective of the network dysfunction that emanates from the central ‘node’ of the network which corresponds to the pathology. This is compounded by surgical outcome data wherein resection of the hypothetical epileptogenic zone does not always guarantee seizure freedom. All functional tests are additionally susceptible to false localization or over-estimation of the size of the epileptogenic zone. Thus, the limitations of all data used to identify the epileptogenic zone need to be kept in mind. Better tools are required to enable the clinician to counsel families with regard to anticipated post-operative neuropsychological or cognitive deficits.

Conclusion Epilepsy remains the most common neurological disorder in childhood, but children with epilepsy remain underserved in many regions of the world. With accurate

diagnosis and appropriate treatment, outcomes can be optimised. Much work however is still required, in enhancing recognition and in improving long-term outcomes of the DEE phenotypes .

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Legends for figures:

Figure 1: Current classification of seizure and epilepsy subtypes in neonates and childhood

Figure 2: Age-specific epilepsy syndromes (DEE-developmental & epileptic encephalopathies, GGE-genetic generalized epilepsy, CAE-childhood absence epilepsy, SeLECTS Self Limited Epilepsy with Centro Temporal Spikes, SeLEAS Self Limited Epilepsy with Autonomic Seizures, COVE Childhood Occipital Visual Epilepsy, POLE Photosensitive Occipital Lobe Epilepsy. Blocks represent range for age of onset of epilepsy.

Figure 3- Epileptogenic substrates in surgically remediable syndromes as apparent on MRI (highlighted in arrow): A) multiple cortical tubers of TSC; B) left hippocampal sclerosis; C) left medial temporal dysembryoplastic neuroepithelial tumor; D) dual pathology- right insular cavernoma with hippocampal sclerosis; E) right parietal focal cortical thickening with loss of grey white differentiation and 'transmantle sign' suggestive of focal cortical dysplasia; F) left hemimegalencephaly in a child with TSC; G) left posterior cortex gliosis with ulegyria secondary to hypoglycaemic injury in neonatal period; H) left hemispheric gliosis and atrophy as a sequel of hemiplegia-hemiconvulsion-epilepsy syndrome; I) right frontal and caudate atrophy with gliosis and early right hemiatrophy due to Rasmussen encephalitis; J) hypothalamic hamartoma

Figure S1- to be reproduced with permission from Cross JH, Reilly C, Gutierrez Delicado E, Smith ML, Malmgren K Epilepsy surgery for children and adolescents: evidence-based but underused. *Lancet Child Adolesc Health 2022 Jul;6(7):484-494*

The MDT (multidisciplinary team) should include a paediatric neurologist or paediatric epileptologist, a paediatric neurophysiologist, a paediatric neurosurgeon, a paediatric neuroradiologist, a paediatric neuropsychologist and paediatric neuropsychiatrist. EEG= electroencephalogram. ESI=electrical source imaging. fMRI=functional MRI. MEG=magnetoencephalography. MSI= magnetic source imaging. SPECT = single photon emission computed tomography. TMS=transcranial magnetic stimulation. 3D=three dimensional.

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