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ORIGINAL RESEARCH

A study on the clinical profile of drug-resistant epilepsy in children

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Abstract

Epilepsy is a common neurologic disorder with 20-40% remaining drug resistant. Understanding the types and spectrum of drug resistant epilepsy will facilitate targeted investigations and therapy.

Objectives: Study on the clinico-aetiological features of drug resistant epilepsy (DRE) in a cohort of children in a tertiary neurology care facility.

Methods: A descriptive cross-sectional study was conducted at Lady Ridgeway Children's Hospital. Children aged 1 month to 16 years with DRE defined according to the International League Against Epilepsy (ILAE).

Results: The total number of children evaluated was 60 with a mean age of 8.6 years (standard deviation (SD) 4.4). The majority were in the 6-12 year category. The mean age of epilepsy onset was 2.2 years (SD 2.7). However, by age categories, the largest group (40.0%) had onset between 0-6 months. Regarding aetiology, according to the ILAE framework, the majority remained unknown (46.7%). Structural (38.3%), genetic (5%), infections (3.3%), immune (5.0%) and metabolic (1.7%) encompassed the balance.

The commonest epilepsy type across all age groups was focal epilepsy (56.7%). An epilepsy syndrome was diagnosed in 24 (48.0%); Infantile epileptic spasm syndrome was the commonest. The majority were developing normally at seizure onset (62.0%) and of them, 14 subsequently slowed or regressed in development. Of those who presented in status epilepticus as a first presentation (48.3%), close to one third (31.6%) suffered from a neurodevelopmental disorder.

All these children were trialled on multiple anti-seizure medications (ASMs). Some received other modalities of treatment such as immune therapy (30.0%), ketogenic diet (8.3%) and surgery (15.0%).

Significance: The majority of DRE in childhood began in infancy and the majority in this low resource setting remained without identifiable aetiology based on investigations offered. Detailed genetic testing and metabolic screening may aid in establishing the aetiology further.

INTRODUCTION

Epilepsy, one of the most common chronic neurological disorders,[1] is characterised by an enduring predisposition to generate epileptic seizures.[2] Affecting an estimated 50 million people globally, it accounts for a significant proportion of the world's disease burden and over 5 million new cases are diagnosed every year.[3] While the majority of people with epilepsy achieve seizure control through the use of antiseizure medications (ASMs), a substantial subset – between 20-40% – remain resistant to pharmacological treatment, leading to a condition known as drug-resistant epilepsy (DRE).[4,5] DRE is a complex condition characterized by persistent seizures, neurobiochemical alterations, cognitive impairments, and significant psychosocial dysfunction.[6,7] The International League Against Epilepsy (ILAE) defines DRE as the "failure of adequate trials of two tolerated and appropriately chosen and used ASMs (whether as monotherapies or in combination) to achieve sustained seizure freedom".[8]

The global burden of epilepsy is not distributed equally, with nearly 80% of individuals with epilepsy residing in low- and middle-income countries, where both the incidence and prevalence of epilepsy are higher than in high-income countries.[9] In these regions, factors such as limited access to healthcare, the availability of ASMs, and social stigmatisation exacerbate the challenges of managing the disorder. This disparity is even more concerning in the context of DRE, as these patients face not only persistent seizures but also an increased risk of comorbid illnesses[10], psychological dysfunction[11], social stigmatisation[12], reduced quality of life and increased risk of mortality[13] and ultimately a decreased life expectancy.[14] Literature on DRE in children is very limited.

Long-term population-based studies show that up to 70% of individuals with epilepsy can achieve seizure remission, but a significant portion continues to experience refractory seizures despite treatment.[15] These challenges highlight the urgent need for early identification of individuals at risk for DRE, to enable timely intervention with non-pharmacological and precision therapies. These interventions provide meaningful seizure reduction in one-third to one-half of paediatric patients.[16] The integration of these therapeutic strategies into clinical practice holds promise for improving outcomes and quality of life for individuals with DRE, particularly in resource-limited settings, where access to advanced treatments remains limited.

In Sri Lanka, childhood epilepsy is a notable public health concern, with a prevalence of 5.7 per 1,000 children under the age of 16.[17] Given the high prevalence of epilepsy in this population, the proportion of children with DRE is likely substantial, yet studies examining the scope of DRE and its management in Sri Lanka are scarce. This study was conducted at a tertiary care paediatric neurology centre in Sri Lanka to evaluate the spectrum of DRE in children and assess the available management strategies. Ethical approval was obtained from the institutional ethics committee, ensuring adherence to ethical guidelines throughout the research process.

METHODS

This observational, cross-sectional study was conducted at the Neurology Clinic of Lady Ridgeway Hospital, Colombo, Sri Lanka, over a one-year period from November 2019 to December 2020. As the premier children's hospital in the country and a national referral centre, the hospital serves as the epicentre for paediatric neurology care across the island.

Children aged 1 month to 16 years diagnosed with drug-resistant epilepsy (DRE) were invited to participate in the study. DRE was defined according to the ILAE as the "failure of adequate trials of two tolerated and appropriately chosen ASM regimens (whether as monotherapy or in combination) to achieve sustained seizure freedom." Patients who had defaulted on treatment or had not received the optimal combination of two ASMs were excluded from the study.

Eligible children were evaluated through face-to-face interviews conducted during clinic visits or hospital admissions. Clinical history was meticulously reviewed, with a focus on seizure onset, frequency, type, epilepsy classification at onset and over time, aetiology, family history, and the presence of comorbid conditions. Investigations included serial electroencephalograms (EEG), video EEG (if available), neuroimaging, metabolic profiles, and genetic testing where accessible. Comprehensive general and systemic examinations were performed to identify neurological abnormalities, syndromic features, neurocutaneous markers, and associated illnesses. Details of previous treatments and their outcomes were systematically recorded, along with current therapeutic regimens.

All data were entered into an electronic database and analysed using statistical methods with SPSS software version 20.

RESULTS

A total of 60 children (38 males), with a mean age of 8.6 years (standard deviation (SD) 4.4) were enrolled. Majority of these children were in the age group of 6-12 years at time of interview (Table 1). The mean age at epilepsy onset was 2.2 years (SD 2.7), but the median age was 10 months. The youngest at onset was five days of life and oldest at onset was 11 years. Very early onset (during the first six months

of life) was seen in 24 cases. The majority of these children were described as developing age appropriately at the time of onset of epilepsy. However, a large proportion of them (55%) lagged behind in development at the time of evaluation. This retardation was noticed after the onset of epilepsy (Table 1).

The most common type of epilepsy at the last evaluation was focal (56.7%). A definite epilepsy syndrome was diagnosed in 41.6% of children as contributory to their DRE; Infantile Epileptic Spasm syndrome (15%) being the commonest. Other epilepsy syndromes in this group of DRE included atypical benign partial epilepsy of childhood, Lennox-Gastaut syndrome, temporal lobe epilepsy, epileptic encephalopathy with spike-wave activation in sleep, Rasmussen syndrome and Ohtahara syndrome (Table 2).

When looked at underlying aetiology, a large portion accounted for unknown aetiology (46.7%) (Table 3).

All these children were trialed on best antiseizure medication combination regimens recommended for their underlying epilepsy type. Some benefited from other modalities of therapy used for drug resistant epilepsy, likewise nine children underwent epilepsy surgery, five received the ketogenic diet and 18 received immune therapy and are being continued to date. The number of ASM given to a patient ranged between 1 and 4. The maximum number of drugs given as combination therapy of ASM at a given time was four drugs. All these children were trialed on the best combinations of ASM regimens (Table 4). Other treatment options such as vagus nerve stimulation had not been offered due to unavailability of services.

TABLE 1 Characteristics of children with DRE (n=60)

Characteristic	No (%)
Sex	
Male	38 (63.3)
Female	22 (36.7)
Mean age (years)	8.6
Mean duration of follow up (years)	6.3
Age at onset of epilepsy (m=months; y=years)	
0-6 m	24 (40)
7-12 m	12 (20)
1-2 y	5 (8.3)
3-5 y	7 (11.7)
6-10 y	11 (18.3)
11-16 y	1 (1.7)
Development at onset of epilepsy	
Age appropriate	34 (56.7)
Delayed	25 (41.7)
Regression	1 (1.7)
Current developmental status	
Age appropriate	20 (33.3)
Delayed	33 (55)
Regressed	7 (11.7)
Family history of epilepsy	6 (10)

TABLE 2 Characteristics of the drug resistant epilepsy group

Characteristic	Number (%)
Presentation in status epilepticus	29 (48.3)
Type of epilepsy	
Focal	34 (56.7)
Generalized	13 (21.7)
Focal and generalized	9 (15)
Unknown	4 (6.7)
Epilepsy syndrome	25 (41.6)
Atypical benign partial epilepsy of childhood	1 (1.7)
Infantile epileptic spasm syndrome	9 (15)
Lennox Gastout syndrome	7 (11.7)
Temporal Lobe epilepsy	4 (6.7)
Otahara syndrome	1 (1.7)
Epileptic encephalopathy with spike-wave activation in sleep	2 (3.3)
Rasmussen syndrome	1 (1.7)
Neurological deficit at onset of epilepsy	28 (46.7)
Abnormal EEG at onset of epilepsy	50 (83.3)
Brain imaging	
Normal	21 (35.0)
Structural abnormality	21 (35.0)
Ischemic insult	5 (8.3)
Infection	2 (3.3)
Non specific abnormality	11 (18.3)

TABLE 3 Aetiology

Aetiology	Number (%)
Structural	23 (38.3)
Developmental malformation	15 (25)
Focal cortical dysplasia	13 (21.6)
Polymicrogyria	2 (3.3)
Hypoxic ischemic brain injury – gliotic changes	5 (8.3)
Hippocampal sclerosis	3 (5)
Infection	2 (3.3)
TORCH	1 (1.6)
Meningitis – sequelae	1 (1.6)
Immune	3 (5)
Rasmussen encephalitis	1 (1.6)
Autoimmune Epilepsy	2 (3.3)
Genetic	3 (5)
Tuberous sclerosis	2 (3.3)
SCN8A association	1 (1.6)
Metabolic	
Glut-1 deficiency syndrome	1 (1.6)
Unknown	28 (46.7)

TABLE 4 Treatment received

Treatment	Number (%)
Only ASMs	28 (46.6)
Surgery	9 (15)
Ketogenic diet	5 (8.3)
Immune	18 (30)
IVMP	19 (31.7)
Oral prednisolone	19 (31.7)
PLEX	1 (1.7)
MMF	12 (20)
Rituximab	5 (8.3)
Currently used number of ASMs	
2 drugs	11 (18.3)
3 drugs	37 (61.7)
4 drugs	12 (20.0)
ASMs currently used	
Sodium valproate	25 (41.7)
Clobazam	25 (45.0)
Carbamazepine	25 (41.7)
Levetiracetam	31 (51.7)
Clonazepam	12 (20.0)
Lamotrigine	6 (10.0)
Topiramate	30 (50.0)
Oxcarbazepine	6 (10.0)
Vigabatrin	8 (13.3)
Gabapentin	2 (3.3)
Phenytoin	4 (6.7)
Ethosuximide	3 (5.0)
Acetazolamide	2 (3.3)

ASMs – Anti Seizure Medications
IVMP – Intravenous methyl prednisolone
PLEX – Plasma exchange
MMF – Mycophenolate mofetil

DISCUSSION

Though most newly diagnosed epilepsy patients have a favourable outcome, about 30% develop pharmaco-resistance, requiring aggressive management strategies. Early identification of pharmacoresistance is important in view of alternative modalities of therapy. Literature on DRE in children is limited. This study on DRE in children from Sri Lanka identified that the majority had an onset in infancy, infantile epileptic spasm syndrome (IESS) was the commonest underlying epilepsy syndrome, and the DRE resulted in an epileptic and/or developmental and epileptic encephalopathy in the majority.

Previous studies on DRE in children have consistently highlighted the predominance of certain epilepsy types and syndromes particularly focal epilepsy, which is the most frequently reported type of epilepsy in DRE cases. Focal epilepsy often arises from structural brain abnormalities, such as malformations of cortical development, mesial temporal sclerosis, or perinatal brain injuries.[16] This was the case in our patients as well. This aligns with our findings, as the majority of our patients presented with focal epilepsy, consistent with previous research suggesting a strong correlation between structural aetiologies and DRE.

In addition to focal epilepsy, generalised epilepsy syndromes like Lennox-Gastaut syndrome (LGS) and Dravet syndrome are commonly seen in children with DRE. These syndromes, often associated with genetic or developmental aetiologies, contribute to the challenges of treating drug resistant seizures.[18] Similar to our findings, these syndromes are frequently diagnosed in children with DRE, further emphasising the importance of early genetic and developmental evaluations in managing these complex cases.

A striking feature noted in our study and echoed in other research is the early onset of epilepsy as a predictive factor for the development of DRE. Several studies have observed that epilepsy starting in infancy or early childhood is a significant predictor of intractability.[19,20,21] This trend was evident in our cohort, where the majority of children with DRE had an early onset of seizures, highlighting the need for early, proactive management and close monitoring for signs of intractability.

Interestingly, as in our study, many children with DRE did not have an identifiable aetiology despite extensive testing. Fine & Wirrell (2020)[22] and Tsang et al. (2019)[23] have pointed out that a significant proportion of paediatric DRE cases remain idiopathic, which could be attributed to the limitations in the availability of advanced diagnostic tools, especially in resource-limited settings. In our context, the lack of access to certain investigations may have contributed to the inability to identify underlying causes in many patients. However, among those with an established diagnosis, structural aetiologies were most common, consistent with findings by Wirrell et al. (2012)[24], who observed a similar trend in young children with intractable epilepsy. This emphasizes the importance of comprehensive imaging and genetic testing to identify potential causes and guide treatment options.

In line with other studies, we found that abnormal EEG patterns, neurological deficits at the time of epilepsy onset, and abnormal imaging findings as predictors of DRE in children.[25,26] These clinical markers are valuable in identifying children at high risk for refractory seizures, enabling earlier intervention and potentially improving outcomes. The early recognition of these risk factors could be crucial in implementing timely therapeutic strategies, such as the consideration of non-pharmacological treatments or the use of precision medicine approaches.

For children with pharmacoresistent epilepsy, other therapeutic options exist, and at times can be very effective. In select cases, with an identified, surgically remediable focus, targeted resection is a viable option, with up to 60-70% achieving seizure freedom. Dietary therapy with the ketogenic diet may result in seizure freedom in 10-15%, and worthwhile seizure reduction in more than half of cases. Palliative surgeries may also markedly reduce seizure burden. Callosotomy is often effective for children with drop seizures, who are not candidates for focal resection. Vagus nerve stimulation results in meaningful seizure reduction in one third to one half of children.[16] In our cohort all had received a trial of best antiseizure medication combination regimens recommended for their underlying epilepsy type. Some benefited from other modalities of therapy used in DRE, such as immune therapy (30.0%), ketogenic diet (8.3%) and surgery (15.0%). Other treatment options such as vagus nerve stimulation had not been offered due to unavailability.

Developmental and epileptic encephalopathies, which represent the most severe group of epilepsies, are characterised by seizures and frequent epileptiform activity that result in developmental slowing or regression. These conditions typically manifest in infancy or early childhood and include several well-known epilepsy syndromes. Patients with DEEs often experience a wide range of comorbidities including intellectual disability, psychiatric features, such as autism spectrum disorder and behavioural problems, movement and musculoskeletal disorders and gastrointestinal and sleep problems. Additionally, DEEs are associated with an increased mortality rate, placing substantial psychosocial burdens on families and caregivers. Professor Shunsuke Ohtahara proposed that these epileptic encephalopathies exist on an age-dependent electroclinical spectrum with clinical and electroencephalographic features that are influenced by the maturation of the nervous system. These include early infantile developmental epileptic encephalopathy (EIDEE) formally known as Ohtahara syndrome, infantile epileptic spasm syndrome (IESS) formally known as West syndrome, and Lennox-Gastaut syndrome (LGS).[27] Advances in next-generation sequencing have enabled the identification of genetic causes in more than 50% of patients.[28] In line with this, our study identified several syndromes, with IESS (15%) being the most common contributory syndrome in our cohort. Other identified syndromes included Atypical Benign Partial Epilepsy of Childhood, Epileptic Encephalopathy with Spike-Wave Activation in Sleep (EE-SWAS), Lennox-Gastaut Syndrome (LGS), Temporal Lobe Epilepsy, Rasmussen Syndrome, and Ohtahara Syndrome.

The finding that 55% of children in this cohort experienced developmental regression after epilepsy onset highlights the significant impact epilepsy can have on cognitive and developmental outcomes. While many children were developing normally before seizure onset, the regression reflects the debilitating effects of ongoing seizures, especially in pharmacoresistent cases. This aligns with other studies showing that epilepsy can lead to cognitive and developmental delays.[29] The result underscores the need for early, effective seizure management and multidisciplinary care to minimize developmental regression and improve long-term outcomes

LIMITATIONS

It is important to note that a significant portion of the study cohort had an unknown aetiology for their condition. This could potentially be due to the lack of advanced diagnostic techniques available for evaluating focal epilepsies. Focal epilepsies, which originate in a specific area of the brain, can often present with subtle or variable features that are difficult to detect using conventional imaging methods. The absence of sophisticated diagnostic tools such as high-resolution functional imaging, magnetoencephalography (MEG), or detailed structural imaging could contribute to this uncertainty in determining the underlying cause.

Additionally, the absence of genetic studies in this cohort may have further hindered the ability to identify underlying genetic factors that could contribute to the development of epilepsy. Genetic testing is becoming increasingly important for understanding the aetiology of epilepsy, especially in cases where conventional diagnostic approaches fail to reveal clear causes. The lack of these diagnostic resources may explain the high number of cases with indeterminate causes, highlighting the need for more sophisticated tools and genetic testing to better inform diagnosis and treatment strategies.

Clinical relevance

Drug-resistant epilepsy in children often begins in early life, with significant adverse effects on their development and quality of life. Identifying the underlying aetiology and the specific epilepsy syndrome is crucial, as it directly influences the management plan and allows for the timely

consideration of alternative therapeutic regimens. Early intervention with appropriate treatments can significantly improve seizure control and, consequently, the quality of life for these children. This study highlights the importance of diagnostic advancements and the need for broader access to innovative treatment options, particularly in resource-limited settings, to ensure optimal care for children with DRE.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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