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ORIGINAL ARTICLE

Drug-resistant epilepsy in Indian children at a tertiary-care public hospital

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Abstract

Background Drug-resistant epilepsy (DRE), a condition in which seizures persist and seizure freedom is unlikely to be attained with further manipulation of anti-epileptic drugs, occurs in around 20% of children with epilepsy. This study was conducted with the aim to study the profile of Indian children with resistant epilepsy, using the new consensus definition of DRE.

Methods All children who had been attending the Pediatric Neurology Clinic regularly for at least 6 months were reviewed between April and September 2015. Children fulfilling the ILAE Commission on Therapeutic Strategies Consensus Proposal definition of DRE were enrolled for the study. After informed consent, the records were reviewed and disease-related data was entered in the study form. The data were analyzed to determine etiological factors and treatment gaps in children with DRE.

Results Fifty children (12 females) with median (range) age of 90 (11–159) months and follow-up of 17.9 (8.5–20) months were enrolled. The mean (standard deviation) age at seizure onset and start of anti-epileptic drugs (AED) were 1.8 (2.11) and 2.1 (2.09) years, respectively. The median (range) number of anti-epileptic drugs that had been tried in these children was 5 (2–9), with drug side effects leading to discontinuation in 8 (16%) patients. Only two patients had tried ketogenic diet; vagal nerve stimulation and epilepsy surgery had not been tried by any family, despite recommendation by the physicians in 7 children.

Conclusions Majority of Indian children with DRE have onset of epilepsy in early infancy, and are infrequently provided access to newer non-pharmacological measures.

Keywords Difficult-to-control epilepsy · Intractable epilepsy · Pharmaco-resistance

Introduction

Epilepsy has a prevalence of approximately 8–10 per 1000, and some of the most difficult-to-control seizure types and epilepsy syndromes occur during childhood, seen both in developed as well as developing countries. Epilepsy, in which seizures persist and seizure freedom is unlikely to be attained with further manipulation of anti-epileptic drug (AED) therapy, is considered as drug-resistant epilepsy (DRE) (also known as pharmaco-resistant epilepsy and intractable epilepsy) [6], and is the main determinant of low quality of life in persons with epilepsy. The proportion of patients whose epilepsy is drug-resistant varies depending on the definition of the condition, the study methods used, and the characteristics of the population being studied [8]. When two AEDs for the correct seizure type and in adequate doses fail, there is only a 5–10% probability of achieving seizure control with a third drug [4].

Although quite a few studies on refractory epilepsy in adults have been reported from India [10], scarce Indian literature is available on DRE in children [2, 12]. Early identification of intractability is important in view of availability of newer modalities of therapy for DRE. A consensus definition for DRE has recently been published, which has led to the adoption of standard terminologies [6]. Therefore, we took up this study to find out the etiological correlates and clinical profile of children with DRE attending a tertiary-care public hospital.

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Methods

This medical record review with patient interviews was carried out between April and September 2015, after institutional ethics committee clearance. Children younger than 14 years and with a follow-up of at least 6 months at the pediatric neurology clinic of our center (a tertiary-care public hospital attached to a medical college), and without seizure freedom (vide infra) were assessed. Children fulfilling a diagnosis of drug-resistant epilepsy were enrolled. Informed written consent from parents, and assent from patients 7 years or older was taken before enrolment.

The diagnosis of DRE was made as per the Ad hoc Task Force of the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies Consensus Proposal [6]: "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom." *Regular follow-up* meant having made at least two visits to the pediatric neurology clinic in the last 6 months. *Seizure freedom* was defined as "freedom from seizures for a minimum of three times the longest pre-intervention inter-seizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer" [2]. *Pseudo-resistance*, in which seizures persist because the underlying disorder has not been adequately or appropriately treated, is ruled out or addressed at our clinic at the time of initial presentation.

A structured form was used to collect the details of the patient, and various disease and treatment characteristics. Relevant details about the age at onset of seizure, age at the time of starting AED, and the total number of antiepileptic drugs received were obtained. Details about etiology of epilepsy, co-morbidities, and adverse effects of antiepileptic therapy (if any) were also obtained from the patients. Parents were interviewed about trial of other modalities of treatment given (Complementary and alternative medicines, Vagal nerve stimulation, etc.). All this information was collected from the medical case records available with the patient, with simultaneous cross-checking from the parent. Parents who did not have all their previous records with them at the time of enrolment were requested to bring them at the next visit, which was usually after 2 weeks in all patients. Children, whose case records were not available, were excluded from the study. Non-availability of case records was considered if these were not available for a period more than 25% of the complete duration of the illness.

Data thus obtained were entered in Excel spreadsheets in an anonymized format and statistical analysis done using Microsoft Excel program. Continuous data were summarized as mean (standard deviation) or median (range), and categorical data represented as percentages.

Results

A total of 53 children with DRE were identified during the study period, of which three did not have complete records. None refused consent. Thus, 50 children (12 females) with median (range) age of 90 (11–159) months and follow-up of 34.2 (8.5–68) months [follow-up at our institution, 17.9 (8.5–20) months] were enrolled. The mean (SD) age at seizure onset and start of AED were 1.8 (2.11) and 2.1 (2.09) years, respectively. The total number of AED that had been tried in these children varied from 2 to 9 (median 5), with drug side effects leading to discontinuation occurring in 8 (16%) patients in the previous 1 year. Complementary and alternative medicines had been tried in the last 1 year by seven families.

Table 1 Clinical profile of children with drug-resistant epilepsy ($N = 50$)

Characteristic	No. (%)
> 1 type of seizures	30 (60)
Predominant seizure type	
Generalized	43 (86)
Tonic-clonic	25 (50)
Myoclonic	12(24)
Tonic	04(08)
Atonic	01(02)
Absence	01(02)
Focal	07 (14)
Etiologic diagnosis[1]	
Structural	32 (64)
Unknown	18 (36)
Co-morbidity	
Global developmental delay/Intellectual disability	26 (52)
Cerebral palsy	11(22)
Autism	04 (08)
Isolated microcephaly	04 (08)
Others	05 (10)
Abnormal electroencephalography	33 (66)
Abnormal neuroimaging (CT/MRI)	31 (62)
Anti-epileptic drugs used[3]	
Valproate[2]	50 (100)
Phenytoin[2]	25 (50)
Phenobarbitone[2]	22 (44)
Clonazepam[2]	20 (40)
Carbamazepine[2]	18 (36)
Levetiracetam	31 (62)
Clobazam	32 (64)
Lamotrigine	15 (30)
Topiramate	5 (10)
Prednisolone/adrenocorticotrophic hormone	4 (08)

[1] Genetic or metabolic categories had no patient; [2] drugs dispensed from the hospital free-of-charge; [3] pyridoxine and lacosamide used in 2 patients and 1 patient, respectively

Only two patients had tried ketogenic diet; vagal nerve stimulation and epilepsy surgery had not been suggested to any family, though 7 patients were considered suitable candidates during evaluation at our center. Additional participant details are shown in Table 1. Table 2 shows the results of the investigations in these patients.

Discussion

The current study was conducted on 50 consecutive children with drug-resistant epilepsy, attending the pediatric neurology clinic at a tertiary-care public hospital in India. Majority had onset before the age of 2 years, were under treatment for mean 34.2 months, and receiving from 2 to 9 (median 5) drugs. Non-pharmacological measures for seizure control were infrequently explored.

In previous studies in adults [1, 5, 10, 11], the predictors of medically refractory epilepsy included age of onset before 14 years, partial seizures, presence of neurological deficits, perinatal insult, delayed milestones, history of central nervous system (CNS) infection, and abnormal brain imaging. A previous Indian study among children [2], although not using the current DRE definition, also reported perinatal problems and sequelae of CNS infection in nearly three-fourth of the children. In the current study, these were found in only 30% of the children. One of the reasons could be that children with sequelae of perinatal insult are usually under management of the child development clinic of our hospital, and they were not included in the study. We also observed an early age of onset of seizures (1.8 year) in these patients, with 44% having seizure onset in early infancy (< 1 year). We found that in our group of patients, generalized tonic-clonic seizures were the most common type of seizures, either present alone or along with other types of seizures. Chawla et al. [2] also did not find partial seizures to be more common in DRE in this region. Similar to previous studies, EEG abnormalities were found in around two-thirds patients [10]. Abnormal neuroimaging findings (computed tomography, CT or magnetic resonance imaging, MRI) have been found to be associated with intractability in almost 40% of the patients [10]; whereas, we had 90% patients with DRE having an MRI abnormality.

Despite the documented financial and seizure-control benefits [7], and longer life span [9] associated with epilepsy surgery in surgically-eligible candidates, none of the children had been evaluated for the same during their management at previous centers. Moreover, despite the large number of AED being used, no efforts had been made to optimize drugs being used despite evidence being available that this does not lead to an increase in seizures [3].

Table 2 Epilepsy syndromes and investigation details in children with drug-resistant epilepsy (N = 50)

Characteristic	No. (%)
Epilepsy syndrome	18 (36)
Lennox-Gastaut syndrome	13 (26)
West syndrome	04 (8)
Dravet syndrome	01 (2)
Magnetic resonance imaging abnormalities ($n = 41$)	
Periventricular leucomalacia	03 (6)
Encephlaomalacia	03 (6)
Leucoencephalopathy	05 (10)
Leucomalacia	03 (10)
Diffuse cerebral atrophy	08 (16)
Focal gliosis	04 (8)
Meningo-encephalitis sequelae	03 (6)
Sub-arachnoid hemorrhage (past)	01 (2)
Focal calcification (NCC)	01 (2)
Structural defects (migration defect-3, Corpus callosal agenesis-2, Tuberous sclerosis-1)	06 (12)
Normal	04 (8)
EEG abnormalities ($n = 49$)	
Generalized discharges	12 (24)
Focal discharges	11 (22)
Epileptic encephalopathy (continuous spike-wave in slow sleep, hypsarrhythmia, Lennox-Gastaut syndrome)	18 (36)
Normal	8 (16)

This is possibly one of the first pediatric studies from India applying the recent consensus definition to study drug-resistant epilepsy in children [6]. The small number of subjects and lack of a control group were the major limitations of this study. The retrospective nature of labelling DRE is another limitation; a prospective study may give further insights into the timeline and predictors of developing DRE.

Drug-resistant epilepsy is a significant problem and most of the affected patients have onset in pediatric age. The use of a consensus definition is likely to make research and comparison across groups easier. Certain factors have been identified associated with drug resistance and knowledge of these helps the treating clinicians refer them timely to specialized centers, and parents appropriately counseled.

Conclusions

Delayed referral, neuroimaging abnormalities in the majority, and infrequent use of newer non-pharmacological alternatives among Indian children with DRE were the novel findings in this study. Further multi-centric prospective studies may assist in delineating the associated factors and outcome of DRE in Indian children.

Author contributions PKP: assisted in clinically managing the patients and study design, compiled the data, and prepared the initial draft of the manuscript. DM: designed and initiated the study, clinically managed the patients, did the statistical analysis, prepared the final draft of the manuscript, and would be the guarantor. MJ: provided important intellectual inputs in the study design, conduct, and manuscript preparation. All authors approved the final manuscript for submission.

Compliance with ethical standards

Conflict of interest All authors declare that there were no conflict of interest.

References

1. Berg AT, Levy SL, Testa FM, D'Souza R (2009) Remission of epilepsy after two drug failures in children: a prospective study. Ann Neurol 65:510–519
2. Chawla S, Aneja S, Kashyap R, Mallika V (2002) Etiology and clinical predictors of intractable epilepsy. Pediatr Neurol 27:186–191
3. Dash D, Aggarwal V, Joshi R, Padma MV, Tripathi M (2015) Effect of reduction of antiepileptic drugs in patients with drug-refractory epilepsy. Seizure 27:25–29
4. Go C, Snead OC (2008) Pharmacologically intractable epilepsy in children: diagnosis and preoperative evaluation. Neurosurg Focus 25:2
5. Gururaj A, Sztriha L, Hertecant J, Eapen V (2006) Clinical predictors of intractable childhood epilepsy. J Psychosom Res 61:343–347
6. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G et al (2010) Definition of drug-resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51:1069–1077
7. Oldham MS, Horn PS, Tsevat J, Standridge S (2015) Costs and clinical outcomes of epilepsy surgery in children with drug-resistant epilepsy. Pediatr Neurol 53:216–220
8. Perucca E (2005) Can drug-resistance in epilepsy be minimized? Challenging commonly held beliefs. Epileptic Disord 7:14–21
9. Sánchez Fernández I, An S, Loddenkemper T (2015) Pediatric refractory epilepsy: a decision analysis comparing medical versus surgical treatment. Epilepsia 56:263–272
10. Singhvi JP, Sawhney IMS, Lal V, Pathak A, Prabhakar S (2000) Profile of intractable epilepsy in a tertiary referral center. Neurol India 48:351–356
11. Tripathi M, Padhy UP, Vibha D, Bhatia R, Padma Srivastava MV, Singh MB, Prasad K, Chandra SP (2011) Predictors of refractory epilepsy in North India: a case-control study. Seizure 20:779–783
12. Udani VP, Dharnidharka V, Nair A, Oka M (1993) Difficult to control epilepsy in childhood–a long term study of 123 cases. Indian Pediatr 30:1199–1206