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LETTER TO THE EDITOR

Drug refractory epilepsy in children: many concerns!

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Dear Editor:

We read with great interest the recently published article by Kharod et al. [1] entitled "Drug-resistant epilepsy in Indian children at a tertiary-care public hospital" in your prestigious journal, and authors concluded that drug refractory epilepsy has early infantile onset. We would like to highlight certain points.

Authors did not arrange references in correct order. They started from number 6 followed by 8. Nowadays, reference management software like Zotero and EndNote are available which can automatically arrange the citation and bibliography.

A recently published systematic review and meta-analysis showed that active point prevalence of epilepsy in children less than 9 years of age was 5.19 and for 10 to 19 years of age was 8.86 per 1000, and active period prevalence for less than 18 years was 4.80 (95% confidence interval, 4.17–5.52) [2]. Authors mentioned epilepsy prevalence of 8–10%, which is high as compared to reported prevalence.

Age at seizure onset and starting of antiepileptic drugs (AEDs) are skewed, probably due to small sample size and cannot be presented as mean and standard deviation; ideally, it should be presented as median and range. According to Table 1, 32 children had structural etiology; however, neuroimaging was abnormal in 31 children. Structural and non-structural etiology can only be ascertained after cranial imaging. How come one patient has normal imaging despite of structural cause?

Authors stated that 36% of children had unknown etiology, and they have mentioned in the footnotes of Table 1 that no patient was in genetic or metabolic categories. Mutation in different genes mainly STXBP1, GRIN2B, ARX, CDKL5,

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[a]	
Structural	32 (64)
Unknown	18 (36)
Comorbidity	
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)
Antiepileptic drugs used[c]	
Valproate[b]	50 (100)
Phenytoin[b]	25 (50)
Phenobarbitone[b]	22 (44)
Clonazepam[b]	20 (40)
Carbamazepine[b]	18 (36)
Levetiracetam	31 (62)
Clobazam	32 (64)
Lamotrigine	15 (30)
Topiramate	5 (10)
Prednisolone/adrenocorticotrophic hormone	4 (08)

[a] Genetic or metabolic categories had no patient

[b] Drugs dispensed from the hospital free-of-charge

[c] Pyridoxine and lacosamide used in 2 and 1 patient, respectively

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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)
Encephalomalacia	03 (6)
Leucoencephalopathy	05 (10)
Leucomalacia	03 (10)
Diffuse cerebral atrophy	08 (16)
Focal gliosis	04 (8)
Meningoencephalitis 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)

KCNQ2, KCNQ3, and KCNT1 genes causes epilepsy or epileptic encephalopathy in infancy or early childhood, and many of these children have developmental delay, behavioral abnormalities, and autistic features [3]. Without doing genetic testing, authors cannot say that 36% of children had unknown etiology. Probably, some of them had underlying genetic etiology.

There are lots of disparity in Tables 1 and 2. Table 1 showed that 31 children had abnormal magnetic resonance imaging (MRI) or computerized tomography (CT) while Table 2 showed that 37 children had abnormal MRI. Table 1 showed that 33 children had abnormal electroencephalography while it is 41 in Table 2. According to EEG abnormalities, 18 children had epileptic encephalopathy including continuous spike-wave in slow sleep, but there was no mention of CSWS or ESES in epilepsy syndromes (instead of this, Dravet syndrome was mentioned). One child had underlying tuberous sclerosis complex; surprisingly, vigabatrin was not tried in spite of drug refractory epilepsy (we know that vigabatrin is not approved by the Government of India, but it is available all over the country).

Lennox-Gastaut syndrome (LGS) is an electro-clinical syndrome, characterized by polymorphic seizures mainly tonic, atonic, and atypical absence, developmental delay, or regression and characteristic EEG pattern [4]. Out of the 50 children, 13 had diagnosis of LGS, but surprisingly only one child had atonic seizure and none of them had atypical absence seizures. Four children had diagnosis of West syndrome, but according to Table 1, none of the children had epileptic spasm.

Hormonal and immunomodulatory therapy have a definitive role in drug refractory infantile or childhood onset epilepsy and epileptic encephalopathies [5]. The current cohort had 18 children with epileptic encephalopathy, but hormonal therapy was tried in only 4 children. Probably, those children were undertreated.

Authors concluded that delayed referral, structural cause, and infrequent use of newer non-pharmacological alternatives were the novel findings in the study. However, this statement was not supported by the data provided. Univariate and multivariate regression analyses would have been better to find out the predictors of drug refractory epilepsy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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