A STUDY ON THE CLINICO-ETIOLOGICAL SPECTRUM IN CHILDREN WITH EPILEPSY AGED 6-15 YEARS

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Abstract:

Aims & Objectives: Epilepsy was defined conceptually as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart with at least one epileptic seizure in the previous 5 years regardless of anti-epileptic drug treatment. The International League Against Epilepsy (ILAE) accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Seizures are one of the most prevalent neurological symptoms and risk factors for hospitalisation among children. This study aims at identifying the aetiology and classification of seizures which is essential for their long-term treatment. This study assessed the clinico-etiological and developmental spectrum among paediatric patients aged 6-15 years. Furthermore, this study also examined the frequently used antiepileptic drugs.

Materials and Methods: A cross-sectional study was conducted on 55 paediatric patients aged 6–15 years admitted from the outpatient department or on regular follow-up at the Neurology OPD in Paediatrics at a tertiary care centre in Western Maharashtra. The complete trial lasted from August 2020 through February 2022. These patients were diagnosed with epilepsy for a duration of at least 6 months. An informed written consent was signed and approved by the primary caregivers of the children included in the study. This transverse study comprised multi-parametric analysis of the patient's clinical condition including seizure type, frequency, duration, and etiology. Electroencephalogram (EEG) and Magnetic Resonance Imaging (MRI) were performed to identify the lateralisation and localization of neuro-functionality.

Results: The study indicated a higher prevalence of epilepsy among male children, with 71% of their corresponding population compared to 29% of female children with epilepsy. Both male and female patients showed their respective peaks at around 8 years of age, which cumulatively consisted of 29% of the total population. However, the developmental profile of epileptic patients demonstrated a comparable proportion of age-appropriate (47.27%) and delayed (50.09%) milestones. Magnetic Resonance Imaging (MRI) findings were not strongly conclusive, as 45.45% of patients had normal reports while 54.54% had abnormalities in their neuroimaging outcomes. Most frequently, EEG is used to diagnose epilepsy, which may generate abnormal readings for epileptic patients. Here, 76.08% of patients showed spikes and sharp waves in their final reports that represent seizure activity, while only 23.91% had normal EEG readings. Furthermore, the type of seizures was analysed, and it was observed that generalised seizures were the most prevalent among patients, accounting for around 72.72%, followed by focal seizures (23.63%) and epileptic seizures (3.63%). In majority of patients, the onset of epilepsy started before the age of two, constituting 30.61%, practically equal to or more than double of any other age group observation. On the therapeutic prevalence, sodium valproate was administered to the maximum number of patients, 31. That constituted 67.39% of the total patients subjected to any medicine. Clobazam and Levetiracetam were the other two frequently administered medicines after sodium valproate with 36.95% and 34.78%, respectively. In this study it was analysed that, multi-drug therapy was more prevalent amongst patients in this age group over monotherapy for both generalized and focal seizures. The etiological spectrum of patients confirmed that structural etiology was found in most patients, with 36.36%, while metabolic etiology constituted 14.54% of the total population. Statistical analysis revealed a statistically significant co-relation between the refractory epilepsy in children aged 6 to 15 years and NICU Admission, Eventful birth history, Developmental delay and abnormal EEG Patterns. There was no statistical co-relation between the abnormal MRI findings and refractory epilepsy.

Conclusion: This study concluded that generalized seizure is the most widespread seizure type that effects the paediatric group aged 6-15 years, where male patients were at a higher risk than females. The onset of seizures was not effectively diagnosed in the early stages. Multidrug therapy was administered and prescribed among the paediatric seizure patients in this age group. EEG and MRI are the most commonly utilised diagnostic tools for Epilepsy.

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1. Introduction

"Seizures" are symptomatic changes driven by the uncontrolled, hypersynchronous activation of neurons. A neurological disorder characterised by persistent seizures that are spontaneous in nature is referred to as "Epilepsy" .It is linked to a variety of neurodegenerative and pathological developments in a localized region of the brain, and it has the potential to expand over the whole cerebral hemisphere[1,2]. It has ramifications on neurobiological, cognitive, physiological, and social aspects[3]. As per the classification guidelines published by the International League Against Epilepsy (ILAE), seizures are classified as (1) focal or partial (2) generalized and (3) epileptic spasms[4,5]. Partial seizures affect the local region of the brain (for eg.one cerebral hemisphere), while the generalised seizure affects the cortical and subcortical structures of the brain with aberrant electric impulses[6,7]. Globally, epilepsy has surpassed 50 million people and is particularly prevalent in rural parts of the developing nations[3,8,9]. The prevalence of epilepsy is highest at the early stage of 12 months–2 years of age, where a direct association with cerebral palsy and mental retardation has been reported [10–13]. It is reported that epilepsy in developed nations has a rate of 0.034% and 0.051% in children aged 8-11 years and 6-12 years, respectively[14,15]. However, these rates increased to 0.1% in developing countries for similar age categories [16]. In the paediatric population, seizure types, such as infantile spasms and epilepsy syndrome, are more diverse, including Lennox Gastaut syndrome, paediatric absence epilepsy, and Dravet syndrome[17,18].

Several pathological brain abnormalities, including genetic mutations in proteins important for ionic flow, known as channelopathies or neuro transmitter transporters, may induce epilepsy[19]. These pathological brain abnormalities need to be diagnosed and evaluated at the early stage. Electroencephalography (EEG) was chosen as a standard part of diagnostic evaluation[20]. However, neuroimaging techniques for children showing a persistent postictal focal impairment, magnetic resonance imaging (MRI) is the preferred diagnostic technique. While EEG readings assist in classifying the type of seizures, studies suggest that a high percentage of abnormalities were reported in MRI scans for epileptic children, and it should be a part of regular diagnostic examination[21–23].

Epileptologists categorised seizure etiology as structural/metabolic, genetic, or unknown[24]. Structural etiology which is mostly captured in neuroimaging diagnosis refers to the presence of a specific aberrant structural cause in the brain that significantly increases the risk of seizures. The genetic etiology is directly related to genetic inheritance or mutation, with seizure as the primary symptom[25]. The term "metabolic etiology" refers to a known or suspected metabolic disorder, whereas immune etiology relates to immunological disorders[26]. Animal models have long been recognised as important tools in the study of epilepsy, both for research and therapy[27,28].

This study sought to investigate the etiological spectrum and prevalent clinical characteristics of epilepsy cases in children aged 6 to 15 years. A cross sectional study wherein 55 epileptic patients under the given age group were examined for seizure type, frequency, duration, therapy, and etiology. EEG and MRI were used for diagnostic evaluation. This study highlighted the most common type of seizure for paediatric patients aged between 6-15 with the expected age of onset. Overall, a multi-parametric analysis was performed to demonstrate and relate the clinico-etiological factors that were observed about seizures in children.

2. Material & Methods

This cross-sectional study was performed at the Super Speciality Neurology OPD of the Paediatric department at a tertiary care centre in Western Maharashtra. Long-term video EEG/sleep EEG testing, 3-Tesla magnetic resonance imaging (MRI) were included for the diagnostic evaluation. The study was conducted between August 2020 and February 2022, after clearance by the institutional ethics committee.

The study included children aged 6-15 diagnosed with epilepsy for a duration of at least 6 months, seen in out-patient department (OPD), either admitted in paediatric ward of Dr. D.Y. Patil Medical College or on regular follow-up in the neurology speciality OPD. The International League Against Epilepsy (ILAE) defines epilepsy as two or more unprovoked seizures occurring 24 hours apart, with at least one epileptic seizure in the previous 5 years regardless of anti-epileptic drug treatment. Before enrolling the children in the study, their primary caregivers were provided with written consent. A structured Clinical Performa was used to record a detailed medical, developmental, and neurological history as well as the clinical examination and anthropometry. Details including onset age, seizure type, seizure frequency, duration of epilepsy, aetiology, and the number of anti-epileptic medications provided were recorded. The ILAE 2017 classification was used to identify the type of epilepsy and the syndromic classification. A detailed examination including anthropometric parameters, general examination and neurological examination were

performed independently and documented. Participants were classified into two groups: (1) Drug-Reactive Epilepsy and (2) Drug-Resistant Epilepsy, depending on the response to antiepileptic drugs. Drug-resistant epilepsy is the failure of adequate trials of two tolerated, selected, and correctly administered anti-epileptic medicines to produce persistent seizure independence.

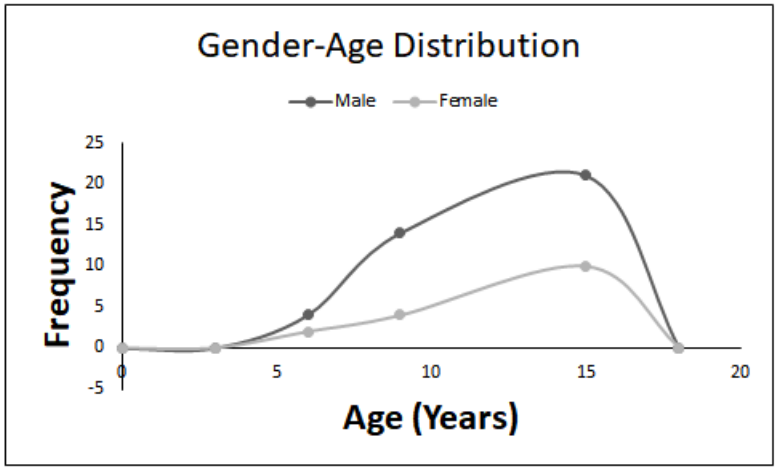
Majority of children were evaluated with routine EEG in the sleep state for 30 minutes and video EEG was performed in the indicated cases. The EEG was done within the three months of enrolment, interpreted, and reported by a paediatric neurologist. Majority of children underwent neuroimaging with 3 Tesla MRI along with epilepsy protocol. Neuroimaging findings as well as other indicated investigations related to epilepsy work-up, such as metabolic screening and genetic testing were documented.

3. Results

This study illustrated the observation of 55 paediatric patients aged 6-15 years. Generalized seizures were observed in 40 patients that accounted for 72.72% while focal seizures in 13 (23.63%) and epileptic seizures in only 2 (3.63%) of the patients that were classified for the seizure type. Table 1 shows the categorization of seizure types in the patient population.

Table 1. Distribution of the patients on the basis of Seizure Classification

Type of seizures	Cases	Percentage
Generalised seizures	40	72.72%
Focal seizures	13	23.63%
Epileptic seizures	2	3.63%



This study recorded the gender of the patient group, which consisted of 39 (71%) male and 16 (29%) female patients. The gender distribution, 39:16, signifies that epilepsy is more common in the male gender as compared to the female. The age distribution of male and female patients is depicted in Figure 1. Both male and female patients showed their corresponding peaks at around 8 years of age, with 21 (53.8%) and 10 (62.5%). The clinico-demographic data (Table 2) showed the maximum number of patients were in the age group of 8 to 13 years, comprising 59.8% of the total population.

Electroencephalogram (EEG) and Magnetic resonance imaging (MRI) were performed on 44 patients. It was found, 11 of them (23.91%) had normal EEG findings while 35 (76.08%) had abnormal EEG readings. In MRI imaging, 20 (45.45%) patients had normal MRI findings while 24 patients (54.54%) had abnormal MRI reports. Based on a comprehensive developmental history, age appropriate and delayed milestones were seen in 26 (47.27%) and 28 (50.09%) cases in both categories, respectively. However, only one case was observed under the neuro-regression category. In the pool of 55 patients, age of onset was available for 49 patients. In the remaining cases, reliable informants were absent or ambiguous history of patients was detected. Age of onset data (Table 3) shows that 15 patients (30.6%) had an onset age of 0-2 years. In addition, 2 to 4 years, 4 to 6 years, 6 to 8 years, and 8 to 10 years of age were all common onset ages, and each interval had 6 to 8 patients, constituting 14-16%. The statistics support early medical intervention as the preferred measure to control epilepsy. This data also supports the genetic rationale of epilepsy or a

neurological disorder presenting at birth/antenatally. However, spontaneous mutation at the genetic level can also result in epilepsy regardless of the patient's age.

Table 2. Demographic and Clinical data of the study group

Categories		**Total**	**Percentage (%)**
Age	6-7	13	23.63%
	8-10	16	29.09%
	11-13	16	29.09%
	14-15	10	18.18%
Gender	Male: Female	39:16	71%, 29%
Developmental milestones	Age Appropriate	26	47.27%
	Delayed	28	50.09%
	Neuro-regression	1	1.81%
MRI finding	Normal	20	45.45%
	Abnormal	24	54.54%
EEG findings	Normal	11	23.91%
	Abnormal	35	76.08%

Treatment modalities include medications (antiepileptic drugs), surgical interventions, and special dietary interventions (ketogenic diet). Table 4 shows that greater utilisation of multi-drug therapy for better seizure control.

Table 3. Patient's distribution based on Age of onset

Age of Onset (Years)	**Patient Count**
0-2	15
2-4	7
4-6	8
6-8	8
8-10	6
10-12	3
12-14	2

Out of 34 cases of generalized seizures, 21 of them were prescribed with multidrug therapy, while 19 were on mono drug treatment. In contrast, in focal seizure, 12 patients out of 13 were on multidrug therapy and only one was on mono-drug therapy. Lastly, epileptic seizures had 2 cases in the data set, and both were on mono drug therapy.

Table 4. Drug Therapy Specifications in the study group

Types of seizures	**Single drug therapy**	**Multi drug therapy**
Generalised seizures	19	21
Focal seizures	1	12
Epileptic seizures	2	0

Further, the etiology of patients was determined using various diagnostic modalities, including EEG, 3T MRI, blood investigations, genetic testing, and neurological examination. According to a cumulative diagnosis from these, the clinical aetiology of 20 patients (36.36%) was categorised as structural, 8 patients (14.54%) were classed as metabolic, 9 patients (16.36%) were classified as genetic/idiopathic, and 18 patients (32.72%) were classified as unknown. Table 5 shows the data for the clinical aetiology of patients. This indicates that children with structural abnormalities are at a greater risk of developing Epilepsy.

Table 5. Patient's distribution based on Aetiological Spectrum

Etiology	**Cases**	**Percentage**
Structural	20	36.36%
Metabolic	8	14.54%
Genetic	9	16.36%
Unknown	18	32.72%
Total	55	100%

Later, MRI reporting data was paired with EEG reports; 44 patients underwent both EEG and MRI, whereas 11 patients either the diagnostic modalities were not undertaken due to varied reasons or sufficient data was unavailable. EEG reporting revealed 11 patients with normal findings while 7 of them were detected as abnormal by MRI. Similarly, 15 of the 19 patients whose MRI scans showed no abnormalities had aberrant EEG results. A statistical chi-square test was performed on the data shown in Table 6 at a 95% confidence level. The p-value was calculated as 0.59, which confirms the statistical independence between EEG and MRI findings.

Table 6. Relationship between MRI findings and EEG findings.

	MRI Findings		
EEG Findings	**Normal**	**Abnormal**	**Total**
Normal	4	7	11
Abnormal	15	18	33
Total	19	25	44

In the current study, a total of 48 patients were on medication, and 7 of them did not receive any regular medicine. Figure 2 shows the name of the drug and the number of patients prescribed with it. Sodium valproate is the most common drug prescribed to 30 patients, indicated by 62.5% of patients consuming sodium valproate alone or in conjunction with other medications. It is administered intravenously or is also available in tablet form to facilitate administration. However, various side effects of sodium valproate were also identified, including nausea, vomiting, drowsiness, and dry mouth; in rare cases, liver failure was also recorded. This drug is used for patients with absence of seizures, partial seizures, and generalised seizures. In this study, 19 of 34 patients with generalised seizures were prescribed sodium valproate. 9 out of 13 focal seizure patients and both epileptic seizure patients were administered this medication. Clobazam and Phosphenytoin were two other medications frequently prescribed following sodium valproate. Clobazam was used in 17 cases (35.4%) while Phosphenytoin was used in 16 cases (33.3%).

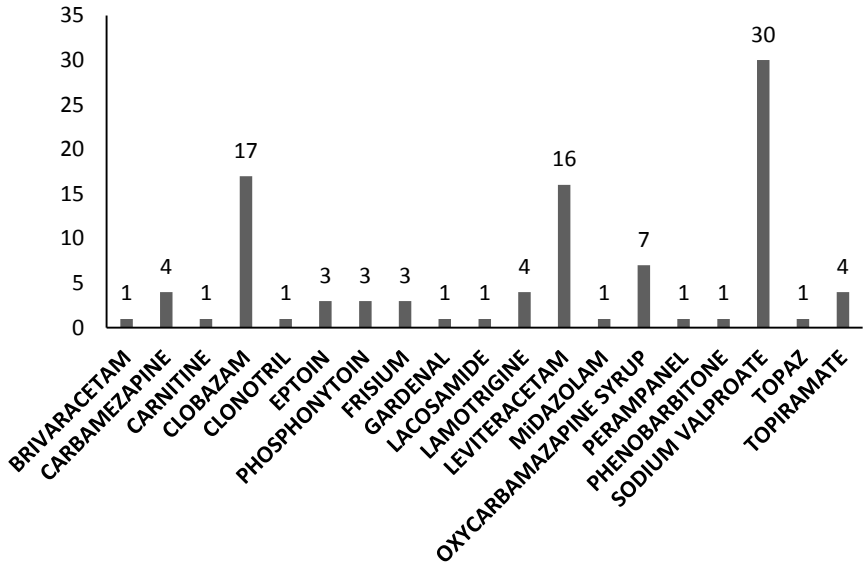


Figure 2. Antiepileptic drugs used in children aged 6-15.

Table 7. Relationship of parameters controlling refractory and non-refractory epilepsy

Risk factor	Non Refractory (N=26)	Refractory (N=30)	Odd ratio	P
NICU Admission	7(26.9)	18(60)	4.071	0.01*
Eventful Birth History	6(23.1)	16(53.3)	3.81	0.021*
Developmental Delay	1(3.8)	5(16.7)	4	0.014*
MRI (Abnormal)	23(88.5)	24(80)	0.522	0.39
EEG (Abnormal)	3(11.5)	6(20)	3.25	0.007*

Lastly, the refractory and non-refractory case analysis was performed with the NICU Admission, Eventful birth history, Delayed developmental milestones presentation, abnormal MRI, and EEG findings (Table 7). Statistical analysis revealed a statistically significant co-relation between the refractory epilepsy in children aged 6 to 15 years and NICU Admission (p value- 0.01), Eventful birth history (p value- 0.021) , Developmental delay (p value- 0.014) and abnormal EEG Patterns (p value- 0.007) . There was no statistical co-relation between the abnormal MRI findings and refractory epilepsy.

4. Discussion

Epilepsy is the most prevalent neurological condition among adolescence[29,30]. In addition, it can be associated with other infectious diseases[31]. Both prevalence and incidence rates are elevated in developing nations[3,8,9]. Effective epilepsy management and treatment rely on early disease diagnosis[32,33]. The aim of this study was to investigate the clinico-etiological spectrum in 6 to 15-year-old children.

This study observed that male children were at higher risk compared to female, out of 55 patients, 39 (71%) were male and 16 (21%) were female. This observation is consistent with various other studies conducted earlier. A study conducted by a multi-institutional, collaborative network of 27 academic epilepsy institutions revealed that males (mean age = 22.3 Years) reported seizures much more frequently than females (mean age = 25.9 Years)[34]. Another study suggested that marginally lower incidences of seizures were reported for female in contrast to males [35]. It was also reported that Febrile seizures were more common in boys than girls (age:5 Years)[36].

This study indicated that generalised seizures are the most prevalent kind of seizure among youngsters, accounting for 72.72% of the overall population. A similar study was performed at Zhongnan Hospital of Wuhan University, China on 200 children and generalized seizure was found in 98% of patients [37]. A retrospective study was carried out at Department of Paediatrics, Manipal Teaching Hospital, Pokhara that also confirmed the higher prevalence of generalized seizures

(69.9%) amongst 551 admitted children[38]. Similarly other studies also advocated for the similar conclusion on the prevalence of type of seizure[8,39].

EEG and MRI reporting analysis revealed that EEG reporting showed abnormalities in 76.08% of the cases while MRI detected the same in 54.54%. In a 2016 study conducted at the Al-Zahra and Kashani Hospitals in Isfahan, Iran, abnormal findings were recorded in 62.3% of instances using EEG among 199 seizure patients, compared to 25.6% in MRI scans[40]. A recent study in 2020 on 112 on patients aged 1-6 years showed that EEG had a higher ratio of abnormal reports with 75.9% compared to 24.1% of MRI findings[41]. This study also indicated that there is no direct correlation between the MRI and EEG finding the same was also observed in our study.

In addition, our findings showed that developmental milestones for children with seizures did not differ significantly between age-appropriate and delayed. It proposed that developmental milestone is not the robust marker for seizure/epilepsy. Onset age for seizure in this study was found maximum (30.6%) in the age interval of 0-2 years indicating the early onset of seizure. This may indicate to neurological disorder presenting at birth/antenatally. In earlier investigations, an association between developmental delay and the significant birth history was demonstrated[42,43].

Finally, our study examined the medicinal and therapeutic elements interventions for seizures and showed that multidrug therapy was prescribed twice as often as monodrug therapy. In addition, sodium valproate was shown to be the most prescribed medicine to epilepsy patients in this study. Combination of two antiepileptic drug has shown successful results in the cases where either the tolerance for first drug has been developed or the evidence of adverse reaction were shown[44,45]. However, monotherapy remains the treatment of choice for newly diagnosed seizures[46,47].

5. Conclusion

Children aged 6-15 diagnosed with seizures are generally prone to have generalized seizures with structural aetiology where male children are at higher risk than female. Early onset of seizures is prevalent and therefore requires early medical intervention using appropriate diagnostic methods. Statistical analysis revealed a statistically significant co-relation between the refractory epilepsy in children aged 6 to 15 years and NICU Admission, Eventful birth history, Developmental delay, and abnormal EEG Patterns. There was no statistical co-relation between the abnormal MRI findings and refractory epilepsy.

Combination of antiepileptic drug therapy is the most adopted choice of treatment where sodium valproate, clobazam and phosphenytoin are the three most frequently prescribed drugs.

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