IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 8 Ver. 2 (August. 2018), PP 73-82
www.iosrjournals.org

Clinical and Etiological Correlation of Seizures in Children from Birth to 18 Years of Age and Immediate Treatment Outcome

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Abstract: ***Objective****: To find out various causes and their clinical presentations of seizures at different pediatric age groups and to analyze whether clinical and etiological correlation which provides a means to identify seizures that have similar pathophysiological features and to determine the effective medications for specific seizure types and to known the incidence of seizures.* ***Method****: A prospective, descriptive, analytical, cohort study was conducted with a total of 150 patients of 18 years and younger who presented to the Pediatrics emergency department (PED) with the complaints of seizures formed the study population in RIMS Hospital, Kadapa. It was done during a period of August 2017 to January 2018.* ***Results****: Incidence of seizures among total pediatric admissions (TPA) was 3.3% while incidence of seizures among PED was 6.3%. Age wise distribution neonates 74 (49.3%) were more followed by infants and children 55 (36.7%) and adolescents 21 (14%). Gender wise distribution males (59%) were more prone to develop seizures than females (41%). In neonates HIE is major cause for seizures followed by febrile in infants and children and meningitis in adolescents. Most common type of seizures in neonates subtle followed by GTCS in infants & children and adolescents. Among 150 cases seizures are commonly treated with monotherapy i.e., phenobarbitone (pb) in neonates and pb/phenytoin/clobazam in infants & children and phenytoin /Valproic acid in adolescents.* ***Conclusion****: Our study concluded that clinical and etiological correlation of seizures helps for early initiation of appropriate treatment and observed immediate treatment outcomes and the incidence of seizures.*
Key Words: Seizures, etiology, correlation, treatment outcome.

Date of Submission: 25-07-2018 Date Of Acceptance: 10-08-2018

I. Introduction

A seizure represents the clinical expression of abnormal, excessive, synchronous discharges of neurons residing primarily in the cerebral cortex. This abnormal paroxysmal activity is intermittent and usually self-limited, lasting seconds to a few minutes. An individual is considered to have epilepsy when seizures recur over a period of time without obvious precipitants. Epilepsy is not a specific disease, but rather a condition arising from a variety of pathological insults involving the cortex, such as tumors or genetic channelopathies. Serial seizures caused by hypoglycemia, hyponatremia, hypocalcemia, febrile seizures, meningitis, head trauma are not classified as epilepsy unless they become a recurrent process beyond the acute illness[1]. Seizures are one of the most important public health problems in both the developing and developed countries with prevalence of 0.5 to 1% of general population. The age-adjusted prevalence of seizures in developed countries is 4 to 8 per 1,000 populations. An estimated 1 percent of children and adolescents in the United States will experience at least one afebrile seizure by age 14. The incidence is greatest in the first year of life, approximately 120 cases per 100,000 population followed by 40 to 50 cases per 100,000 population until the age of puberty and closer to 10 cases per 100,000 population in the early and mid teens[2]. Fever with seizure is the most common type of seizure in infants and young children. This may be due to febrile seizures or more threatening condition like meningitis. Between 2 and 5% of children experience one or more febrile seizures (FS) by 5 years of age[3]. Between 0.5% and 1% of children and adolescents experience a seizure associated with other acute metabolic or neurologic insults; most of these occur in the neonatal period. Incidence of acute seizures reported from developing countries is o.4% among children of birth to 13 years and 0.9% in children less than 5 years and highest incidence of 1.4% in neonates[4-6]. Diverse medical conditions in the newborn can be associated with neonatal seizures. Hypoxia-ischemia is the most common cause of neonatal seizures[7-8]. Cerebral infarction and stroke the second most common cause of neonatal seizures occurs in otherwise well term infants, without previous risk factors and involves left middle cerebral artery territory and presents with right sided clonic seizures. Intracranial hemorrhage is implicated in 10% to 15% of seizures, and amongst them Intra-ventricular

hemorrhage or Periventricular hemorrhagic infarction is the most common Intracranial hemorrhage in preterm infants and constitutes around 45% seizures in preterm[9-12]. CNS infections during intrapartum or postnatal period can be associated with seizures.[13] Biochemical disturbances occur frequently in neonatal seizures either as an underlying cause or as an associated abnormality.[14, 15] Metabolic disturbances could be more commonly transient and rapidly correctable or less commonly inherited as persistent causes. Infants of diabetic mothers (IDM), small for gestational age infants, and infants with birth asphyxia are at more risk of hypoglycemia. Late onset hypocalcaemia due to use of high phosphate infant formula has been cited as common cause of seizures.[16, 17] However commonly hypocalcaemia occurs in infants with trauma, haemolytic disease, asphyxia and IDM and usually coexists with hypoglycemia and hypomagnesaemia and presents at 2-3 days of life.[18] Hypophosphatemia may be caused by ingestion of milk formulas containing high amounts of phosphorous, excessive parenteral administration of phosphorus, impaired renal function, and hypoparathyroidism.[19] Hyponatremia as a result of fluid overload renal compromise and SIADH (syndrome of inappropriate ADH secretion) can be a frequent complication of birth asphyxia and could complicate the management of seizures in this condition. [20] Probability of bacterial meningitis in children with fever with seizure varies from 0.6% to 6.7%. It is essential to exclude underlying meningitis in all children with FS either clinically or if uncertain by lumber puncture (LP) because majority of such cases of meningitis are bacterial in origin and delay in diagnosing meningitis can result in serious neurological morbidity and mortality. Other causes of seizers in this age group were encephalitis, cerebral malaria, tuberculous meningitis and intracranial space occupying leisions. [21-25]In adolescents the common causes of seizures were meningitis, encephalitis, cerebral malaria, secondary hypertension and of late primary hypertension with hypertensive encephalopathy. Most of the children presenting with seizures may never experience recurrence. However, seizure may be the initial presentation of serious medical condition like meningitis / cerebral malaria. Early identification of etiology with clinical correlation and early initiation of treatment is imperative for better outcome. Etiology and clinical presentation varies from place to place and very few such studies have been reported from this region of the country.

II. Aims & Objectives Of The Study:

- The primary objective of the present study is to find out various causes and their clinical presentations of seizures at different pediatric age groups and analyze whether clinical and etiological correlation provided a means to identify seizures that have similar pathophysiological features and to determine which medications are effective for which seizure types.
- The secondary objective of this study is to know the incidence of seizures among paediatric hospital admissions and also to evaluate the immediate treatment outcome.

III. Materials And Methods

The present study was done on children attending to the EM of Pediatrics at RIMS Hospital, Kadapa serving the people coming from poor socioeconomic status. This is a prospective, descriptive, analytical, cohort study. A consecutive 150 pediatric patients of 18 years and younger who presented to the emergency department (ED) of Pediatrics with the complaint of seizures formed the study population and it was carried out during the period of August 2017 to January 2018 at Rajiv Gandhi Institute of Medical Sciences Medical College attached to RIMS Hospital, Kadapa.

Inclusion Critera

All children from birth to 18 years of age with first episode of seizures presented to ED within 24 hours of seizures.

Exclusion Criteria

(1) Age more than 18 years
(2) Children with previous history of seizures
(3) Children with known inborn errors of metabolism
(4) Children with syndromes
(5) Children left against medical advice
(6) Children referred to higher institution.

IV. Method Of Study:

During the study period 150 consecutive patients of 18 years and younger presented to the emergency department (ED) of Pediatrics, RIMS, Kadapa, with the complaint of seizures were enrolled in the study once parents sign informed consent form **(ANNEXURE I)** and the children fulfilled the inclusion and exclusion criteria. A complete history was taken upon hospitalization, and then, a physical examination was performed by the duty resident in charge giving special attention to following factors: age, gender, number and duration of seizures, postictal drowsiness, lethargy, irritability, vomiting, bulging fontanel, neck rigidity, Kernig sign,

Brudzinski sign, neurological deficit, prior antibiotic use, laboratory test results (white blood count, C-reactive protein, serum electrolytes, blood sugar and cerebrospinal fluid (CSF) analysis, neuroimaging i.e. cranial CT scan or cranial magnetic resonance imaging (MRI), electroencephalography (EEG), duration of hospital stay, final diagnosis and outcome. The data was documented in a proforma **(ANNEXURE-II)** and transferred to EXCEL software **(ANNEXURE-III)**.Further patients were divided in to 3 groups: 1) Neonates (< Month) 2) Infants and children (> 1 Month to 12 years) 3) Adolescents (13 to 18 years). Variables including age, sex, type of seizure, associated symptoms, developmental history, laboratory test results, neuroimaging examinations, EEG findings, diagnosis, and duration of hospital stay, antiepileptic drugs used and final outcome with follow up **(ANNEXRE IV)** were compared among children of different age groups to analyze clinical & etiological correlation and immediate treatment outcome. Statistical analysis of variables mentioned above was carried out by Chi-square test and P-values. P-value of less than 0.05 was considered as significant statistically.

V. Observations And Results

Incidence:

During the study period a total of 4500 children were admitted in the wards of Pediatric Department of RIMS General Hospital, Kadapa district. Of these 2360 children presented to the pediatric Emergency Department (PED). Among them first acute seizures was the main complaint in 168 children. Of these 18 children were excluded from the study because of various reasons stated in exclusion criteria and 150 were included in the study. Incidence of seizures among total pediatric admissions (TPA) was 3.3% while incidence of seizures among children presented to the PED was 6.3%. **[TABLE-1].**

Table: 1. Incidence Of Seizures In Children

YEAR	STUDY PERIOD	TPA	PED	SEIZURES
2017	August	768	393	23
	September	820	494	22
	October	684	398	35
	November	875	475	23
	December	773	398	23
2018	January	580	302	24
TOTAL	**6 MONTHS**	**4500**	**2360**	**150**

- Incidence of seizures among total pediatric admissions : 3.3%
- Incidence of seizures among cases presenting to PED : 6.3%

Demographic Variables

Age

150 children were divided in to 3 groups: 1) Neonates (< 1 month), 2) Infants and children (1 month to 12 years) and 3) Adolescents (13 to 18 years). Age wise distribution of cases was: neonates 74 (49.3%), infants and children 55 (36.7%) and adolescents 21 (14%). Overall the most common group affected was neonates followed by infants and children and adolescent. **[FIGURE 1]**

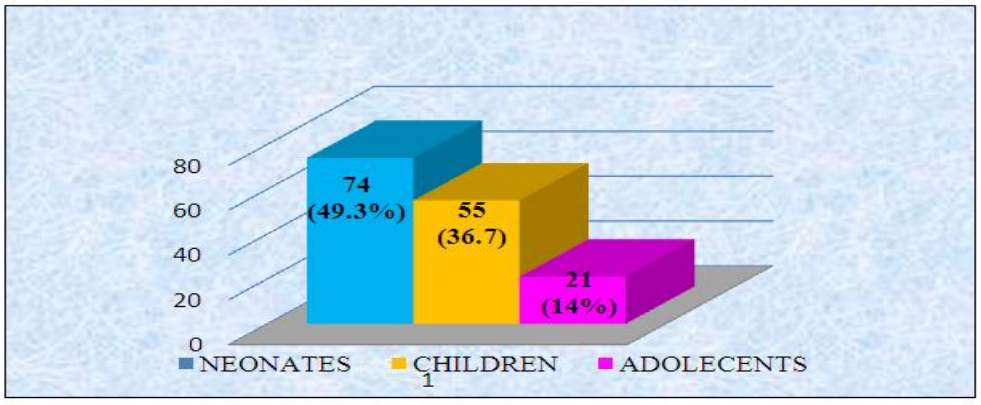

Figure: 1. Age wse distribution

Gender

Out of 150 cases 88 (59%) were male and 62 (41%) females. Overall male to female ratio was 1.4:1. Among the neonates 44 (59%) were males and 30 (41%) females with male to female ratio of 1.5: 1. In

infant/child group males were 31 (56%) and females 24 (44%). Male to female ratio was 1.3: 1. Similarly in adolescent group males were 13 (62%) and females 8 (38%); male to female ratio was 1.6:1.

In all the groups males were more in number but difference is not significant statistically among the groups. (P = 0.8912). **[TABLE 2]**

Table: 2. Age And Gender Wise Distribution Of Cases

AGE GROUP	MALES	FEMALES	TOTAL
Neonates	44 (59%)	30 (41%)	74 (100%)
Infants and children	31 (56%)	24 (44%)	55 (100%)
Adolescents	13 (62%)	08 (38%)	21 (100%)
TOTAL	88 (59%)	62 (41%)	150 (100%)

Etiological Variables

Various etiological causes of seizures observed in this study depending on the age groups are as follows:

Neonatal:

Hypoxic ischemic encephalopathy (HIE) 46 (62%), hypocalcemia 12 (16%), hypoglycemia 6 (8%), hyponatremia 2 (3%), intraventricular hemorrhage (IVH) 2 (3%), meningitis 4 (5%) and septicemia 2 (3%). **[FIGURE- 2]**

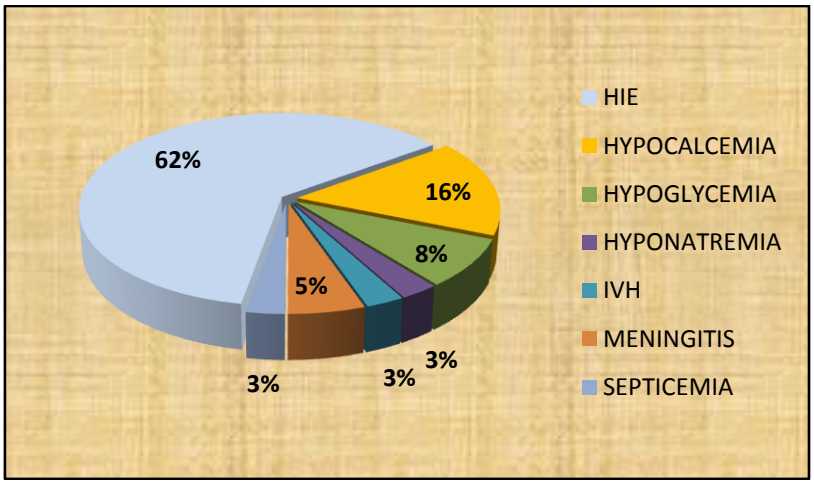

Figure : 2.etiology in neonates

Infants And Children:

Febrile seizures 28 (50%), meningitis 7 (12.7%), encephalitis 5 (9%), cerebral malaria 2 (3.6%), cerebral palsy 2 (3.6%) and un identified etiology 11 (20%)[**FIGURE-3]**

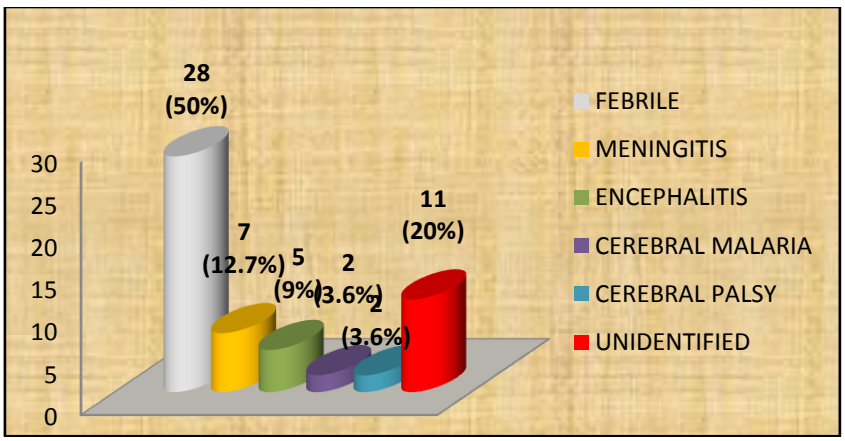

Figure: 3. Etiology of seizures in infants & children

Adolescents:
cerebral malaria 3 (14.2%), secondary hypertension (HTN) 3 (14.2%), primary HTN 1 (4.9%) and unidentified 3 (14.2%). **[FIGURE-4]**

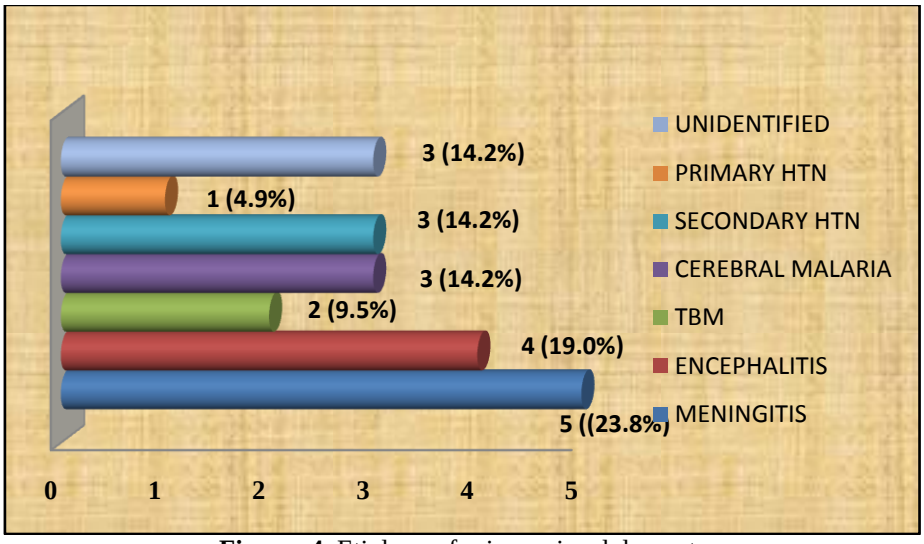

Figure :4. Etiology of seizures in adolescents

Clinical Variables
Type Of Seizures
Neonates
Varied types of seizures noticed in the neonates were subtle seizures 32 (43.2%), focal 18 (24.3%), multifocal 10 (13.5%), clonic 8 (10.8%) and tonic seizures 6 (8.1%). **[TABLE- 3]**

Table: 3. Types Of Seizures In Neonates

TYPE OF SEIZURES	NUMBER	PERCENTAGE
Subtle seizures	32	43.2%
Focal	18	20.3%
Multifocal	10	13.5%
Clonic	08	10.8%
Tonic	06	08.1%
TOTAL	**74**	**100.0%**

Infants And Children
Infants and children presented with generalized tonic clonic (GTCS) 32 (58.2%), simple partial 11 (20%), complex partial 5 (9.1%), myoclonic 3 (5.6%) and absent seizers 4 (7.3%). **[TABLE-4]**

TABLE: 4. TYPES OF SEIZURES IN INFANTS & CHILDREN

TYPE OF SEIZURES	NUMBER	PERCENTAGE
GTCS	32	58.2%
Simple partial	11	20.0%
Complex partial	05	09.1%
Myoclonic	03	05.6%
Absent seizures	04	07.3%
TOTAL	**74**	**100.0%**

Adolescents
In adolescents GTCS were 11 (52.4%) followed by simple partial 4 (19.0%), complex partial 2 (9.5%) and myoclonic 4 (19.0%). **[TABLE- 5]**

Table: 5. Types Of Seizures In Adolescents

TYPE OF SEIZURES	NUMBER	PERCENTAGE
GTCS	11	52.45
Simple partial	04	19.0%
Complex partial	02	09.5%
Myoclonic	04	19.0%
TOTAL	**21**	**100.0%**

Fever

Out of 74 neonates 30 (40.5%) had fever. Similarly 42 of 55 (76.3%) infants & children and 15 of 21 (71%) adolescents had fever. The difference was statistically significant. (P vale – 0.0000)

Symptoms And Signs

The other symptoms observed in the study were: 1) Poor cry 2) Decreased movements 3) Lethargy 4) apnea/tachypnea 5) Fever/hypothermia in neonates; 6) Neck stiffness, 7) Vomiting 8) Head ache and Meningeal signs (Kernig's and Brudgiski's signs) in infants/children/adolescents.

Anticonvulsants

Neonates

From among 74 neonates with convulsions 20 (27%) neonates required no anticonvulsant; 35 (47%) needed monotherapy with phenobarbitone; 19 (26%) had to be treated with dual therapy with phenobarbitone plus phenytoin sodium for control of seizures. **[FIGURE- 5]**

Infants And Children

In this age group 29 (53%) children were treated with monotherapy with clobazem/phenobarbitone /phenytoin, while 26 (47%) required dual therapy with phenobarbitone plus phenytoin. **[FIGURE -6]**

Adolescents

Among the adolescents 16 (76%) required monotherapy with phenytoin / sodium valproate; 5 (24%) needed dual therapy. **[FIGURE- 7]**

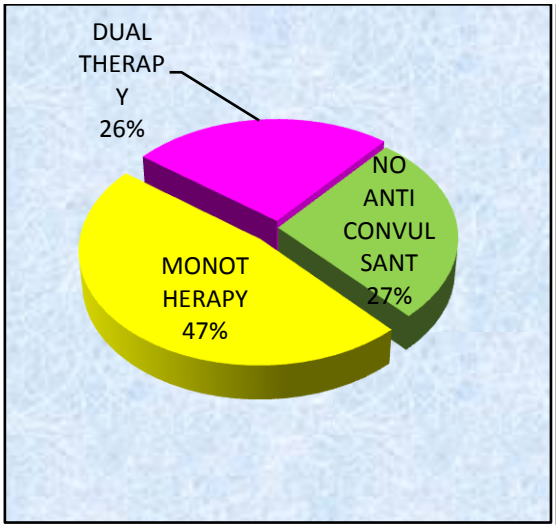

Figure:5.neonates-no .of. Anticonvulsants Needed

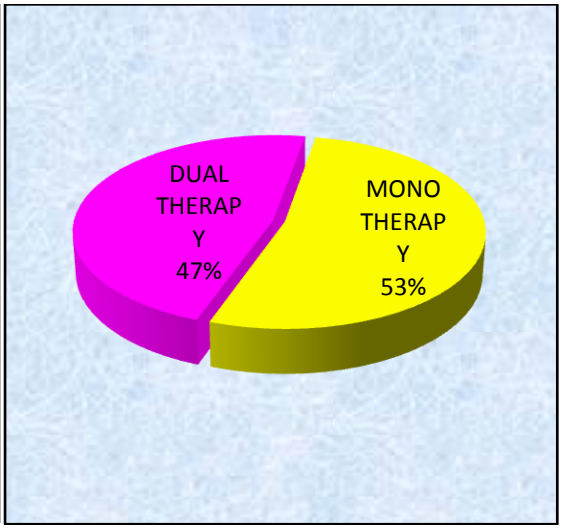

Figure: 6.infants &children-no.of. anticonvulsants needed

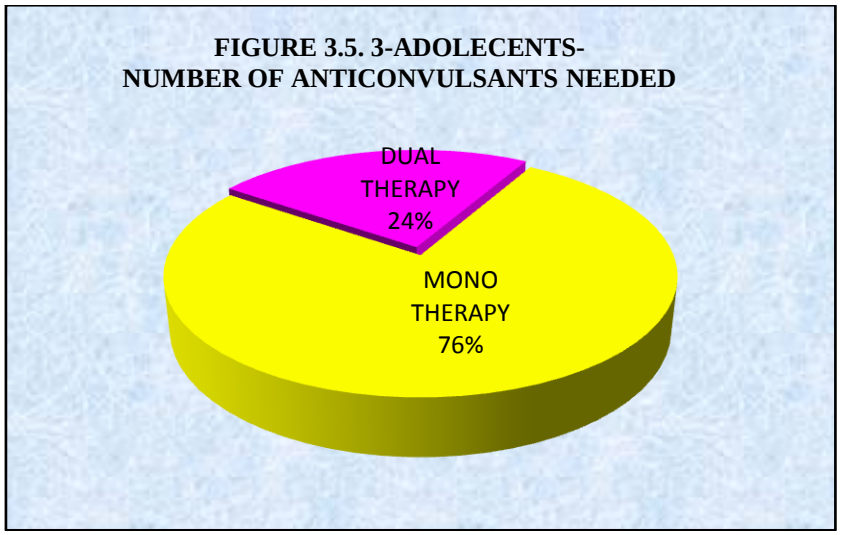

Figure:7. Adolescents-no. of anticonvulsants needed

Out Come

At Discharge At the time of discharge 68 (91.9%) neonates, 28 (50.9%) infants and children and 12 (57.1%) of adolescents needed no anticonvulsant; 6 (8.1%) of neonates, 19 (34.5%) of infants and children and 4 (19.0%) adolescents required monotherapy while 8 (14.5%) infants and children and 5 (23.8%) of adolescents needed dual therapy. **[TABLE- 6]**

TABLE:6. DUAL TO MONO / NIL CONVERSION

AGE GROUP	NIL	MONO	DUAL
Neonates	*68 (91.9%)	6 (8.10%)	0 (0.0%)
Infants and children	*28 50.9%)	19 (34.5%)	8 (14.5%)
Adolescents	12 (57.1%)	4 (19.0%	5 (23.8%)
TOTAL	**108**	**29**	**13**

*Including13 deaths in neonates & 1 in infants and children

At The End Of Follow Up

At the end of 2 weeks of follow up 71 (95.9%) neonates, 28 (50.9%) infants and children and 12 (57.1%) adolescents required no anticonvulsants; 3 (4.1%) neonates, 23 (41.8%) infants and children and 8 (38.1%) adolescents needed monotherapy; 4 (7.3%) infants and children and 1 (4.8%) adolescents required dual therapy. **[TABLE -7]**

Table: 7. Dual To Mono / Nil Conversion

AGE GROUP	NIL	MONO	DUAL
Neonates	71 (95.9%)	3 (4.1%)	0 (0.0%)
Infants and children	28 (50.9%)	23 (41.8%)	4 (7.3%)
Adolescents	12 (57.1%)	8 (38.1%)	1 (4.8%)
TOTAL	**111**	**34**	**5**

*Including 13 deaths in neonates & 1 in infants and children

VI. Discussion

Incidence of seizures among total pediatric admissions (TPA) was 3.3% while incidence of seizures among children presented to the PED was 6.3%. Our findings are in correlation with those of Saleem Hussain et al who reported an incidence of 7.84%.[49]

Seizures were predominantly observed in neonates (49 %) followed by infants and children (37%) and adolescents (14%). Overall the incidence of seizures decreased with increase in age. Rupa Dalmia et al, Nagendra Choudari et al and Sameer Kumar Jain et al noticed similar findings. [44, 51, 39]

Out of 150 cases 59% were male and 41% females. Overall male to female ratio was 1.4:1. Among the neonates 59% were males and 41% females with male to female ratio of 1.5: 1. In infant/child group males were 56% and females 44%. Male to female ratio was 1.3; 1. Similarly in adolescent group males were 62% and females 38% with male to female ratio of 1.6:1. In all the groups males were more in number but difference is not significant statistically among the groups. Shetty K et al, Jan Muzafar et al , Shahzad Najeed et al and others noticed more number of males getting seizures and the findings are in correlation with those of present study. [48, 40, 33]

Most common cause of seizures in neonates was HIE (62%) followed by hypocalcemia (16%) hypoglycemia (8%) hyponatremia (3%), IVH (3%), meningitis (5%) and septicemia (3%). Sameer Kumar Jain et al , Rabindran et al were also of the openion that HIE was the leading cause of seizures in neonates. [39, 54] Among the infants and children Febrile seizures was in first place (50%) followed by meningitis (12.7%) encephalitis (9%), cerebral malaria (3.6%), cerebral palsy (3.6%) and unidentified etiology (20%). Ohja AR et al and Emestina EM et al from their studies concluded that febrile seizures were most common cause among infants and children. [32, 45].In adolescent age group common etiological cases in the decreasing order of frequency were Meningitis (23.8%), encephalitis (19%), TBM (9.5%), cerebral malaria (14.2%) secondary HTN (14.2%), primary HTN (4.9%) and unidentified (14.2%). Rupa Dalmia et al study opined that Central nervous system (CNS) infections followed by Intra cranial space occupying leisions (ICSOL) as common causes of seizures among adolescents. These findings are similar to our studies. [44,]

Among the neonates subtle seizures were most commonly observed (43.2%) followed by focal (24%) multifocal (13.5%) clonic (10.8%) and tonic seizures (8.1%). Shahzad Najeeb et al reported similar observations. [33]In infants and children GTCS were (58.2%); next in the order noticed were simple partial (20%) complex partial (9.1%), myoclonic (5.6%) and absent seizers (7.3%). Arpit Gogoi et al and Tauhid Iqbali noticed GTCS to be the commonest type in this age group. [46, 43] In adolescents GTCS were (52.4%) followed by simple partial (19.0%), complex partial (9.5%) and myoclonic (19%). Shetty KS et al reported GTCS as most common type.[48]

Out of 74 neonates (40.5%) had fever. Similarly (76.3%) infants & children and (71%) adolescents had fever. The difference was statistically significant.

The other symptoms observed in the study were: 1) Poor cry 2) Decreased movements 3) Lethargy 4) apnea/tachypnea 5) Fever/hypothermia in neonates; 6) Neck stiffness, 7) Vomiting 8) Head ache and Meningeal signs (Kernig's and Brudgiski's signs) in infants/children/adolescents.

From among 74 neonates with convulsions 27% neonates required no anticonvulsant; 47% needed monotherapy with phenobarbitone; 26% required dual therapy with phenobarbitone plus phenytoin sodium for control of seizures. Rabindran et al study results are in concordance with our results. [54] In this age group 29 (53%) children were treated with monotherapy with clobazem/phenobarbitone /phenytoin, while 26 (47%) required dual therapy with phenobarbitone plus phenytoin. The findings are in correlation with Rabindran et al study. [54] Among the adolescents 16 (76%) required monotherapy with phenytoin / sodium valproate; 5 (24%) needed dual therapy. Gosaye MT et al study results are going together with our study.

At the time of discharge 92% neonates, 51% infants and children and 57% of adolescents needed no anticonvulsant; 8% of neonates, 35% of infants and children and 19% adolescents required monotherapy while 15% infants and children and 5 24% of adolescents needed dual therapy. Results are in correlation with Gosaye MT et al study results. [53]

At the end of follow up 96% neonates, 51% infants and children and 57% adolescents required no anticonvulsants; 4% neonates, 42% infants and children and 38% adolescents needed monotherapy; 7% infants and children and 5% of adolescents required dual therapy. Results are in correlation with Gosaye MT et al study results. [53]

VII. Conclusions

After conducting the study and analyzing the results following conclusions were drawn:

1) Seizures are still a common presentation in Pediatric emergency department in both developing and developed countries.
2) Children presenting with seizures needs immediate initiation of anticonvulsant therapy.
3) Based on clinical presentation etiological cause can be identified to a large extent and we can correlate both and identify the best anticonvulsant suited to individual patient.
4) Our study results proved beyond doubt that clinical and etiological correlation of seizures definitely helps early initiation of appropriate treatment and the research question is answered.

VIII. Limitations Of The Present Study

Following Are The Limitations Of The Present Study:

1) Due to the relatively short period of the study only 150 patients were enrolled in the present study. The small sample was a limiting factor in statistically analyzing the data to draw reasonable conclusions.
2) Selection of participants from a single medical center limited the generalization of our results to the entire population of patients with acute seizures.
3) Patients were not followed up to find out the long term sequelae like permanent neurological damage, effect on scholastic performance, drug compliance and drug complications.

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