Original article

Utility of neuro-imaging in children with epilepsy and its clinical relevance

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Abstract

Introduction: Epilepsy is one of the most common treatable neurological disorders of the brain. The essential diagnostic evaluation for an unprovoked seizure remains a source of debate. The practice parameter for an afebrile seizure developed by the Quality Standards Subcommittee of the American Academy of Neurology, Child Neurology Society, and American Epilepsy Society recommends electroencephalography (EEG) as a standard part of diagnostic investigation. Neuroimaging is considered as a diagnostic modality in select children.

Objective: To identify the abnormalities on neuroimaging in children with epilepsy and to establish association between clinical characteristics & neuroimaging abnormalities.

Study design: Cross sectional, non-interventional, observational study.

Methods: Children between one month and twelve years of age and diagnosed to have epilepsy were included in our study. Children with acute symptomatic seizures and static encephalopathy were excluded. Neuroimaging was done in each patient and was independently reported by the radiologist. The demographic, clinical and neuroimaging data of all patients were obtained. Pearson Chi-Square test was used to analyze the data.

Results: Of 100 children enrolled, abnormalities on neuroimaging were detected in 63(63%) children. The most common abnormalities on neuroimaging were Ring enhancing lesions (30%) followed by mesial temporal sclerosis (6%) and gliosis /atrophy (6%). A statistically significant correlation was obtained between gender, developmental history, type of seizure, etiology respectively ($p=0.037$, $p=0.002$, $p<0.001$,$p<0.001$) and abnormal neuroimaging.

Conclusion: Neuroimaging should be strongly considered in epileptic children with abnormal development, partial seizures and symptomatic etiology .

Key words: Epilepsy, neuroimaging, children, utility

Introduction

Epilepsy is one of the most common treatable neurological disorders of the brain.(1) It was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. The task force of ILAE has recently proposed that practically epilepsy be considered to be a disease of the brain defined by any of the following conditions: (a) At least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (b) 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; (c) diagnosis of an epilepsy syndrome.(2)

Epilepsy accounts for 1% of the global burden of disease; 80% of the burden of epilepsy is in the

developing world. The overall incidence of childhood epilepsy from birth to 16 years is approximately 40/1,00,000 children per year. The incidence in the first year of life is about 120/1,00,000 population which plateaus between 1 and 10 years of age at 40-50/1,00,000 children(3). An Indian study conducted in Chennai reports crude prevalence rates of 5.35/1000 children. After a correction for heterogeneity due to inter study variation, the overall prevalence per 1000 was 5.33 with urban areas at 5.11and rural areas at 5.47(4). The cumulative lifetime incidence of epilepsy is three percent, more than half the cases begin in childhood. Annual prevalence of epilepsy is lower (0.5 to 1%) because many children outgrow epilepsy (5).

The essential diagnostic evaluation for an unprovoked seizure remains a source of debate. The practice parameter for evaluation of an afebrile seizure developed by the Quality Standards Subcommittee of the American Academy of Neurology, Child Neurology Society, and American Epilepsy Society recommends electroencephalography (EEG) as a standard part of diagnostic investigation.

Neuroimaging is considered optional. Magnetic resonance imaging is the preferred modality and is suggested as an option for children with persistent postictal focal deficits, an abnormal neurologic examination, a focal seizure, or an EEG that shows an abnormality other than patterns characteristic of benign partial epilepsy or idiopathic generalized epilepsy.(6) Neuroimaging guidelines have been published but the use of neuroimaging and the prevalence of detected abnormalities in a clinical setting are unknown. Only a few studies have evaluated the utility of neuroimaging in epilepsy in clinical practice. More research is needed to explore this relationship in order to determine the necessity of neuroimaging in epilepsy. In view of this, we conducted a study to evaluate the usefulness of neuroimaging in children with epilepsy.

Aims and Objectives

1. To identify the abnormalities on neuroimaging in children with epilepsy
2. To establish association between clinical characteristics & abnormal neuroimaging.

Methods and materials:

Our study was a cross sectional, non-interventional, observational study carried out ver a period of 22 months at a large tertiary care centre and teaching hospital .

It enrolled children aged between one month to twelve years and diagnosed with epilepsy. All children with acute symptomatic seizures, static encephalopathy, neonatal seizures and febrile seizures were excluded.

A written informed consent of the parents and assent of the subject (>7 years) were obtained prior to participation. An approval was obtained from the Institutional Ethics Committee.

The data was collected by asking history as well as reviewing the medical records of each subject. The demographic data, birth, developmental , family and treatment histories were recorded in a predesigned performa.

The clinical details like age of onset of epilepsy, duration of epilepsy, seizure type and frequency of seizures as 2, 3-5, 5-10 and multiple (>10) episodes were charted. The findings of general and systemic examination of all the subjects were obtained. All children underwent neuroimaging and to avoid bias, all imagings were reported independently by a single radiologist who has extensive experience in epilepsy imaging. International League against Epilepsy (ILAE) 1981 classification was used to classify seizure type. The etiology of epilepsy was classified according to the 1989 ILAE Classification & 2001 ILAE proposal. Treatment

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outcome was classified as remission (no seizures without drug treatment), conditional remission (no seizures under treatment) and treatment resistance (seizures even on 2 or more appropriate antiepileptic drugs).

For data analysis, neuroimaging was grossly divided into normal and abnormal imaging. Data collected was analysed to identify neuroimaging abnormalities and even to associate the various clinical features with abnormal neuroimaging .The data collected was predominantly non parametric and thus Pearson Chi Square test was applied to find the correlation. The statistical tool used was SPSS version 20. $P < 0.05$ was taken as significant in all the statistical analysis.

Results:

Demographic and clinical data :

A total of 100 [54 (54%) boys] children aged 1.5 months to 12 years and diagnosed with epilepsy were enrolled in the study. Table 1 depicts the demographic and clinical characteristics of the study population. The highest number of children (79%) were more than 5 years and only few (8 %) children were less than 2 years of age. The mean (SD) age of onset of epilepsy was 5.5 (3.2) year and median was 5.7 years. More than half of (52%) children had their onset of epilepsy after 5 years of age .The mean (SD,range) duration of epilepsy at enrolment was 2.2 (2.4, 1month -10 years) year. In our study, abnormal birth history in the form of prematurity, low birth weight, neonatal seizures,IUGR,and/or birth asphyxia was recorded , the most common amongst these was history of low birth weight. The outcome in our study was grouped as remission (no seizures without treatment), conditional remission (no seizures under treatment) and refractory to treatment (seizures on 2 or more anti epileptic drugs). (Table 1)

Neuroimaging data :

All enrolled children underwent a brain scan; MRI done in 82(82%) children, MRI with MRI SPECT in 16 children and CT Scan brain in 2 children. Abnormalities were detected in 63 (63%) children amongst whom 55 had atleast one abnormality and 8 children revealed two or more abnormalities(Table 2). The most commonly detected abnormality was ring enhancing lesions in 30 (30%) children predominantly due to neurocysticercosis (24) and remaining due to tuberculoma . The less common abnormalities identified were hippocampal sclerosis (6%) and gliosis/atrophy (6%). Other lesions identified were calcification in 4 children, choroid cyst in 3 children, tumors in 2 children and vascular abnormalities in 5% of children. Vascular abnormalities were in the form of multiple cavernous angiomas(2),infarcts (2) and angiomatosis with calcifications (1). Polymicrogyria and pachy gyria were found in 4 children and tubers were noticed in 2 children.

Clinical characteristics in relation to neuroimaging abnormalities:

We observed that girls had a higher possibility of having an abnormal neuroimaging as compared to boys ,the association between the gender and abnormalities on neuroimaging being statistically significant (p=0.037). Our study verified that children with symptomatic epilepsy and partial seizures had a demonstrable high frequency of abnormalities on neuroimaging. In the present study, 58 children had symptomatic epilepsy and all 58 (100%) had abnormalities on neuroimaging where as only 5 out of 42 children (11.9%) with idiopathic seizures had abnormalities on neuroimaging, proving that the association between etiology of seizure and an abnormal neuroimaging was stastically significant. ($p<0.001$) . This may imply that children with

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symptomatic etiology have a very high rate of abnormal neuroimaging.

Another clinical criterion that influenced the rate of abnormalities detected on neuroimaging was the type of seizure. Out of 54 children with generalised seizures 24 (44.4%) had an abnormal neuroimaging. As opposed to this, 39 out of 46 (84.8%) children with partial seizures had abnormal brain scans. This distinctly showed that association between type of seizure and abnormal neuroimaging was highly significant (p<0.001). A significant correlation was obtained between development of the child and having an abnormality on neuroimaging as in our case all the 14 children (100%) with delayed development had an abnormal neuroimaging (*p=0.002*).

In our study, 4 children had history of neonatal seizures and all had an abnormal neuroimaging however the correlation between the two was statistically insignificant (p = 0.294). Neuroimaging was abnormal in 9 of 11 children with abnormal birth history and 54 out of 89 children with normal birth history had abnormal neuroimaging but the correlation was statistically insignificant (*p*=0.171).

The age of onset of epilepsy, frequency of seizures, family history of epilepsy, and type of therapy did not show any association with abnormalities on neuroimaging. Out of 63 children with abnormal neuroimaging, 53 (84.1%) children were in remission and 10 children (15.9 %) had refractory seizures.

Whereas out of 37 children with normal neuro-imaging, 35(94.6%) children were in remission and 2 children (5.4 %) had refractory seizures. (p= 0.06). Refractoriness to treatment was linked to abnormal neuroimaging but was not stastically significant.

Table : 1 Demographic & Clinical characteristics of the subjects (*n=100*)

Characteristic	**Number**	**Mean (Sd) or %**
Age		7.7year (3.02)
Gender (males)	54	54%
Abnormal birth history	11	11%
Delayed development	14	14%
h/o epilepsy in 1º relative	08	8%
h/o neonatal seizure	04	4%
Age of Onset of epilepsy		5.5 year (3.19)
Duration of epilepsy		2.2years (2.4)
Seizure type		
Generalised	54	54%
Partial	40	40%
Partial with secondary generalisation	06	06%
Treatment Outcome		
Conditional Remission	82	82%
Remission	06	06%
Refractory	12	12%

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Table 2: Distribution of neuroimaging abnormalities in study population (n=100)

Lesions on Neuroimaging	**Frequency**	**Percentage (%)**
Normal	37	37
Abnormal	63	63
1 abnormality	*55*	*87.3*
>/=2 abnormalities	*08*	*12.7*
Ring enhancing lesion(NCC /tuberculoma)	30 (24/06)	30
Hippocampal sclerosis	06	06
Gliosis & Atrophy	06	06
Encephalomalacia	04	04
Calcification	04	04
Cortical Malformation	04	04
Choroidal cyst/ Tumor / Tuber	03/02/02	07
Vascular Malformation	03	03
Infarcts	02	02

Table 3: Association between clinical characteristics of epilepsy and neuroimaging

Clinical Characteristic	Frequency	Abnormal Neuroimaging	p value
Gender (Female)	46	34	0.04
Age of onset of epilepsy			0.15
< 2 years	24	19	
2 – 5 year >/=	24	13	
5 years	52	31	
Seizure type			
Generalised	54	24	< 0.001
Partial	46	39	
Etiology			< 0.001
Symptomatic	58	58	
Idiopathic	42	05	
Multiple Seizure (frequency >10)	40	28	0.42
H/o focal neurologic deficits	02	02	0.53
H/o neonatal Seizures	04	04	0.30

Family history of seizures	08	07	0.25
Abnormal birth history	11	09	0.17
Delayed Development	14	14	0.002
Outcome			0.06
Remission	07	02	
Controlled remission	81	51	
Refractory	12	10	

Discussion

Epilepsy is a chronic disease characterized by recurrent seizures which affects 2% of the population. (7) The Child Neurology Society and the American Epilepsy Society recommend a routine EEG for all children with epilepsy and an urgent neuroimaging for children with persistent postictal focal neurologic deficits. Strong consideration is recommended for nonurgent neuroimaging in

certain clinical circumstances, including cognitive or motor impairment of uncertain etiology, unexplained abnormalities on neurologic examination, abnormal EEGs not representing a benign syndrome, seizures of partial onset, or in children under the age of 1 year. (6,8) Most studies have

recommended neuroimaging only in selected patients, but definitive risk factors for abnormal neuroimaging findings cannot always be found.

The results of our study showed that neuroim-aging in children with epilepsy was found to be abnormal in 63 (63%) children. Of these 63 children, 55 had at least one neuroimaging abnormality and 8 children had two or more abnormalities. The most common neuroimaging abnormality found in our study was ring enhancing lesions (30%); three-fourth of which were due to neurocysticercosis and remaining due to tuberculoma., The very high prevalence and incidence of neuro-infections particularly neurocysticercosis (the most common CNS parasitic infection) followed by tuberculosis in developing countries could be the reason for such large number of ring enhancing lesions being reported in our study. The other common abnormalities observed were hippocampal sclerosis (06%), gliosis and atrophy (06%) and encephalomalacia(04%).

Other abnormalities found were cortical malformations (4%) , vascular malformations (3%),calcification (03%), choroidal cyst (03%), tumour(02%), infarcts (02%), tubers (02%), subdural hygroma (01%) . U C Wieshmann *et al* in their study reported abnormal neuroimaging in 51% of patients which is comparable to our study. The most commonly detected abnormality in their study was hippocampal sclerosis, followed by non-specific abnormalities, vascular abnormalities, tumours, brain damage, malformations of cortical development (9). In another study by Sanjib Sinha et at. neuroimaging abnormality found was around

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53%(10). In the study conducted by LM Li et al. 74% of the neuroimaging were abnormal and 7% patients had more than one lesion. Their principal MRI diagnoses were hippocampal asymmetry, cortical dysgenesis, tumour, and vascular malformation(11). Where as in a study conducted by Amirsalari et al in 2011, abnormal MRI was seen in 28.5% patients and consisted of brain atrophy (10%), increasing white matter signal intensity in T2-weighted images (8%), benign cysts (5%), brain tumors (4%) and vascular abnormalities (1.5%) (12).

Andrew J. Kalnin et al mentioned an abnormal MRI in 31% of subjects and the common findings among them were ventricular enlargement (51%), leukomalacia/gliosis (23%), gray matter lesions like heterotopias and cortical dysplasia (12%), volume loss (12%), other white matter lesions (9%), and encephalomalacia(6%)(13). I J Craven et al reported an abnormality of neuroimaging in 20.2% patients, with mesial temporal sclerosis being the most common abnormality in 11.5% of diagnosed patients(14). Neuroimaging abnormalities in most studies conducted worldwide range from 20.2% to 74%.Results of most studies on neuroimaging abnormalities in epilepsy are comparable to our study. The feature common to all the above studies is that hippocampal sclerosis is the most common abnormality on neuroimaging in developed countries and second most common to ring enhancing lesions in developing countries.

Another striking finding of our study, was that history of partial seizures, delayed development, etiology of epilepsy (symptomatic vs idiopathic) and female sex greatly increased the likelihood of getting an abnormal neuroimaging. Of 54 patients with generalised seizure, only 24 (44.5%) had an abnormal neuroimaging, whereas of 46 children with partial seizures 39 (84.7%) had an abnormal neuroimaging. This difference was statistically significant ($p< 0.001$). More over this finding was consistent with other similar studies . Sujit Sharma and his colleagues in their study identified 2 criteria associated with high risk for clinically significant abnormal neuroimaging (15) ; the presence of a predisposing condition, and focal seizure . Of the high-risk patients, 26% had clinically significant abnormal neuroimaging compared with 2% in the low-risk group(15). Khodapanahandeh et al too found a significant relationship between abnormal neuroimaging and focal seizure ($p < 0.001$) in their study(16). It may be appropriate to put that partial seizures are highly associated with a higher diagnostic yield on neuroimaging.

In our study, the association of neuroimaging with etiology of seizure (symptomatic vs idiopathic) was statistically significant ($p<0.001$). Those children with symptomatic epilepsy had a high probability of finding an clinically relevant abnormality on neuroimaging. Berg et al. found in their multiple logistic regression analysis of all imaged patients, the type of epilepsy (idiopathic versus nonidiopathic) had the strongest predictors of having a positive MRI scan(17).

This finding is consistent with our study.

We also found that abnormalities on neuroimaging were found in all fourteen (100%) children with delayed developmental milestones .Whereas 49 of 86 normally developed children had neuroimaging abnormality.(56.9%) Commonly observed neuroimaging abnormalities in these children were gliosis, encephalomalacia and atrophy,. The relation between developmental delay and abnormalities identified on neuroimaging was statistically significant ($p=0.002$).

The results were comparable to the similar studies conducted. In a study conducted by Carol Camfield et al, abnormality in neuroimaging was more commonly identified in those with

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severe/profound developmentally delayed children compared to normal children (p=0.001)(18). Al-Rumayyan AR et al in their study found a statistically significant association between developmental delay (p<0.01) and neuroimaging(19). What could not be explained in our study was a significant association obtained between the female sex and abnormal neuroimaging (p=0.037). This might be a mere co -incidence. No other related studies have observed any such correlation.

In the current study, we did not find any link between age of onset of epilepsy and increased chance of abnormal neuroimaging (p =0.153). Sanjib Sinha et al. observed no significant relation (p = 0.38) when they compared age of onset with the neuroimaging findings. Even though their study was mainly done in adults the findings were comparable with our study. However,Khodapanahandeh et al found a significant relationship between abnormal neuroimaging and age under 2 years (p < 0.002) (16). This is possibly not consistent with our study because their study population included children who were admitted with a first afebrile seizure and also the incidence of epilepsy is high in this age group. Schrader et al. observed in their study that early age of seizure onset was the best predictor of abnormal MR imaging in children with epilepsy with occipital features(20). Our study revealed that history of neonatal seizures, positive family history of epilepsy , abnormal birth history ,and seizure frequency did not raise the possibility of abnormal neuroimaging. Although neuroimaging was found abnormal in all the 4 children with history of neonatal seizures, the number was too small to comment. Amirsalari, et al in their study reported abnormal MRI findings in 31.4% of patients with positive family history of epilepsy and in 14.9% of patient without this history ; the difference was meaningful(12). In the present study, rate of abnormalities detected on neuroimaging in children (9 of 11 children) with a significant birth history was high nevertheless this correlation was statistically insignificant (p=0.171) which implies that abnormal birth history is practically not always associated with high possibility of finding an abnormality on neuroimaging.

Neuroimaging abnormalities were independent of seizure frequency in our study (p=0.422) though U C Wieshmann in his study found that the yield of neuroimaging (18%) was lower in patients with single epileptic seizures(9). This could be explained on the basis that our study did not include many patients with isolated single seizure. Patients with single seizure may have a more benign form of epilepsy that may be less likely to be associated with structural abnormalities, moreover such patients often have only CT imaging and subtle abnormalities may have been overlooked and some structural abnormalities such as atrophy may only develop after the onset of epilepsy. Similar result was published by King et al who found 38 lesions in 300 patients with single attacks(21).Another factor that we correlated with neuroimaging abnormalities was focal neurological deficits.

There were only two children with persistent focal neurologic deficits and both had abnormal neuroimaging; but the number was too small to comment. Al-Rumayyan AR et al had found a statistically significant association between neuroimaging and the presence of new focal neurological findings (p<0.01) in their study(19). This is not comparable to our study possibly their study involved children presenting to the emergency department with a new-onset seizure. Our study showed that outcome did not bear any correlation with neuroimaging (p=0.06).. In a study by Spooner et al , all children with lesions on MRI

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were non seizure free ($p < 0.001$)(22). This is not comparable with our study probably as they included only patients with temporal lobe epilepsy in their study which is usually associated with refractory epilepsy There were few limitations to our study. There may be referral biases as our study was conducted at an urban tertiary referral centre. Sample size was small. Our data are also dependent upon parental and witness recollection. Larger studies are necessary which would provide unbiased results.

Conclusions

Ring enhancing lesions, hippocampal sclerosis and gliosis /atrophy were the common abnormalities identified on neuroimaging in children with epilepsy. Partial seizures, symptomatic epilepsy and \ or history of delayed development were highly associated with abnormalities on neuroimaging.

We conclude from our study that neuroimaging is indispensable in children with partial seizures, symptomatic epilepsy and delayed development.

Acknowledgements:

1. The authors thank Dr. Avinash N. Supe, Director (M E & M H) and Dean of Seth GS Medical College and KEM Hospital for granting permission to publish the paper.
2. The authors thank Dr. Shilpa Sankhe, Assistant Professor, Department of Radiology of Seth GS Medical College and KEM Hospital for giving expert opinion on neuroimaging in our study.

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