

Early Predictors of Intractable Childhood Epilepsy

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Abstract

Introduction : Intractable epilepsies (IE) contribute to a small but significant component of all epilepsies in childhood. There is paucity of data regarding early predictors and magnitude of IE in Indian children. Early identification and intervention will go a long way in improving their outcome.

Objectives : (1) To study the clinical profile, aetiopathogenesis and outcome of IE (2) To determine the clinical predictors of IE.

Design : Prospective case control study.

Setting : Paediatric Neurology Clinic in a tertiary multidisciplinary hospital.

Material and Methods : Our study comprised total 93 children with epilepsy. Of which 38 children (Group A) met the criteria for intractable epilepsy while remaining 55 had well controlled epilepsy (Group B-well controlled on single anti-epileptic drug (AED). Intractable epilepsy was considered when the children had one or more seizure per month, over a period of 6 months or more and had been tried with at least two (AEDs) with adequate compliance and TDM in therapeutic range. All patients were analyzed by taking detailed history with special reference to perinatal events, development, seizure semiology and detailed antiepileptic therapy taken.

Results : Demographic profile revealed that 90% of children were above 4 years of age and there was a significant male preponderance in both groups. Analysis revealed that 60% subjects had onset of seizures below one year in Group A as compared to only 22% in the well controlled epileptics. Remote symptomatic aetiology was the main aetiology (71%) in Group A with perinatal events contributing to 47% whereas in Group B it was primarily idiopathic (78%). Univariate analysis showed that factors that predicted intractability were early onset seizures, myoclonic, neonatal or mixed seizures, initial high seizure frequency, perinatal asphyxia, neurological impairment, microcephaly, neuroimaging and EEG abnormalities. Multivariate logistic regression analysis revealed that early onset seizures, mixed seizures, neurological impairment and microcephaly had independent predictability.

Conclusions : All children especially those with early onset epilepsy, infantile spasms, mixed seizures, high frequency and those with perinatal risk factors should be closely monitored and evaluated for development of intractable epilepsy.

Introduction

Recent advances in neuroimaging, newer antiepileptic drugs and surgical

interventions for epilepsy have greatly improved the outcome of children with intractable epilepsy (IE), however, the management of few of the IE children still poses a major challenge. Early identification and intervention will go a long way in improving their outcome. Determination of risk factors for intractability may help us to

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understand aetiology and also aids in achieving optimum control of resistant epilepsy. Keeping the above in mind, this study was conducted to determine the clinical predictors of intractable epilepsy in children in a tertiary care centre of Mumbai.

Objectives

- 1) To study the clinical profile, aetiopathogenesis and outcome of IE
- 2) To determine the clinical predictors of IE.
- 3) To estimate outcome and prognosis of children with intractable epilepsy.

Material and Methods

This prospective study was undertaken over period of 2 years in our Paediatric Neurology Clinic at our tertiary referral centre. The study was conducted after getting Institutional Ethical Committee (IEC) clearance. Parents/caretakers consent was taken in all cases prior to enrolment of subjects. It comprised 93 children of which 38 children (Group A- Study cases) had intractable epilepsy and remaining 55 had well-controlled epilepsy (Group B).^{1,2} *Inclusion criteria* consisted of epileptic children below 16 years {Group A} with intractable epilepsy. IE was defined as children having one or more seizure per month, over a period of 6 or more months and tried with at least two anti-epileptic drugs (AEDs) with adequate compliance and with serum AED level in therapeutic range. Control group {Group B} included epileptic children in whom seizures were well controlled for at least 6 months with a single antiepileptic drug.^{1,2} *Exclusion criteria* consisted of children with non compliance to AEDs, acute symptomatic seizures and progressive neurodegenerative disorders.

All these patients were analyzed by taking their history, with special emphasis on perinatal events, development, family

history, seizure semiology and detailed antiepileptic drug therapy. Patients underwent thorough CNS and systemic examination. All subjects were appropriately investigated including EEG, BERA, ophthalmology review, AED therapeutic drug monitoring (TDM) and neuroimaging (CT / MRI Brain). Specific investigations were done in indicated patients. Serial TDM levels were done to check AED levels, compliance and toxicity. Parents were advised to maintain seizure diary for record of seizures. On follow up of children, seizure frequency, development of new seizures, side effects, compliance of patients, daily activity and schooling were checked. IE children's response to treatment was categorized into a) **Full response** - A complete or virtually complete response, allowing for an occasional break through seizure, present for at least 3 months of follow up b) **Partial response plus** - reduction in seizures $\geq 50\%$ of the initial frequency c) **Partial response** - reduction in frequency of seizures $\leq 50\%$ and d) **No response** - no change in frequency of seizures or had worsening of seizures.^{1,2}

A computerized analysis of data was performed using SPSS software packages. Data were analyzed separately for univariate comparison. Standard tests of significance, such as Pearson Chi-square test, Likelihood ratio, Continuity correction and Fisher's exact test were used wherever applicable. The odds ratio was used as an approximation of relative risk to indicate magnitude of association between each factor and intractable epilepsy. Multivariate analysis was performed by multiple logistic regression by forward stepwise method to examine the association between intractable epilepsy and predictive factors.

Results

Demographic profile revealed that 90% of

children were above 4 years of age and there was a significant male preponderance in both groups (Male to female ratio, in both groups, was 2.5 : 1 and 1.75 : 1 respectively). Age of onset of seizure was less than 1 year of age in 22 (60%) children with IE (Gr A) as compared to 11 (20%) in well-controlled epileptics (GrB) (Table 1). Generalized seizures were more common than the partial seizures in both groups. Myoclonic / IS seizure type was present in 11 IE children (30%) as compared to a single child in well-controlled epileptics.

Mixed or more than single type of convulsions were noted more often in IE subjects (45% vs 17%). 50% of children with IE had daily seizures, initially, while in Gr B it was only 4%. Status epilepticus (SE) was found in 55% in IE group as compared to only 22% children in well-controlled group. Neonatal seizures and perinatal asphyxia was documented in 21% and 34% of children in-group A and 5% and 15% in-group B respectively. Febrile seizures were documented in 30% and 26% children and family history of seizures in 4% and 9% in

group A and B. Remote symptomatic aetiology was the main aetiology (71%) in Group A with perinatal events contributing to 47% whereas in Group B it was primarily idiopathic (78%) (Table 2). Other causes included neuronal migration disorders, neurocutaneous syndromes and epileptic syndromes like Lennox Gastaut syndrome, West syndrome and Myoclonic epilepsies.

We had studied various neurological factors like neurological impairment (NI) {either mental retardation (MR) or motor disability (MD) or both}, hearing deficit (HD), developmental delay (DD) and microcephaly in both groups (Table 3). We found that almost 66% in study cases had some form of neurological impairment as compared to 16% in Group B. 38% children had both MR and MD in intractable epilepsy group as compared to only 7% in well controlled epileptic. On comparison in both the groups, neurologic impairment, MD, MR, all had statistically significant difference (P < 0.05). The risk of having IE with neurologic impairment was 10 times more as compared to subjects who were normal.

Table 1 : Demographic Profile and Age of Onset of Seizures in Study (Gr A) and Control (Gr B)

Age group	Study Group A -No. (%)			Control Group B- No. (%)		
	Male	Female	Total	Male	Female	Total
0-1	17	5	22 (60)	6	5	11(20)
1-2	5	1	6 (16)	4	5	9 (16)
2-5	3	3	6 (16)	10	3	13 (24)
5-8*	1	1	2 (4)	4	4	8 (15)
8-12*	-	1	1(2)	12	2	14 (25)
12-16*	1	-	1(2)	-	-	-

Between A and B irrespective of gender

Chi-square Test applied	Value	df	P-value	Association
Pearson Chi-Square	16.760	3	0.000792	Significant
Likelihood Ratio	17.576	3	0.000538	Significant

(* Data pooled to apply Chi-square Test)

Table 2 : Aetiology of epilepsy in both groups

	Intractable Epilepsy Group A (n=38) No. (%)	Well Controlled Group B (n=55) No. (%)
<i>Idiopathic</i>	11(29)	43(78)
<i>Remote Symptomatic</i>	27(71)	12(22)
Perinatal Asphyxia	18(47)	7(12)
Ischaemia	1	1
Tuberous Sclerosis	1	-
CC Agenesis	2	-
Pachygyria	2	1
Lissencephaly	1	-
Hydrocephalus	1	-
Precipitating -Reflex –sound	1	-
Precipitating -Fever triggered	-	3
Total	38	45

Between idiopathic and remote symptomatic totals

Chi-square Test applied	Value	df	P-value	Association
Pearson Chi-Square	22.372	1	2.25E-06	Significant
Likelihood Ratio	23.062	1	1.57E-06	Significant
Odds ratio = 8.779			95 % CI = 3.4 to 22.72	

Table 3 : Various neurological factors for prediction of intractable seizures

	A No. (%)	B No. (%)	P-Value		OR	95% CI
			PC	CC		
Febrile seizure	11(30)	14(26)	0.709	0.892	1.193	0.472- 3.016
Family H/O seizures	2(4)	5(9)	0.565	0.863	0.5556	0.102- 3.027
Status Epilepticus	21(55)	12(22)	0.00092	0.000198	4.0426	1.791- 094
Neonatal seizures	8(21)	3(5)	0.022	0.050	4.622	1.138 – 8.768
Perinatal Asphyxia	13(34)	8(15)	0.026	0.048	3.055	1.117 – 8.352
<i>Neurologic Impairment (NI)</i>	25(66)	9(16)	1.14x10 ⁻⁶	3.38x10 ⁻⁶	9.832	3.69-26.31
Motor Disability (MD)	1(2)	0(0)	—	—	—	—
MR +BI only	10(27)	5(9)	3.55x10 ⁻⁶	1.01x10 ⁻⁵	8.762	3.314 –23.165
MD + MR	14(37)	4(7)				
M D	15(39)	4(7)	0.000153	0.000139	8.315	2.484 –27.832
Hearing Deficit	12(32)	4(7)	0.0027	0.0054	5.885	1.726 – 20.062
Developmental Delay	22(60)	6(11)	1.20x10 ⁻⁶	3.73x10 ⁻⁶	11.229	3.872 – 32.569
Microcephaly	16(42)	4(7)	0.0000584	0.000168	9.200	3.1-29.13

Abnormal EEG was present in 84% of children with intractable epilepsy as compared to 50% in well-controlled seizures. The

various EEG abnormality patterns documented in group A were focal epileptic activity (FEA) (15%), FEA with secondary

generalization (4%), multifocal epileptic activity (MEFA) (11 %), slowing (12 %) generalized epileptic activity (GEA) (16 %) and hypsarrhythmia (8%). In our series, 18 patients in Group A had undergone only MRI while 17 patients in Group A had both CT and MRI scan. In Group B, 43 patients had undergone only MRI, and CT scan was done in 12 children. MRI SPECT was performed in 1 patient in each group

71% of children had abnormal neuroimaging in IE patients as compared to only 29% in Group B. Findings suggestive of perinatal asphyxia (PA) was present in 34% of children with IE. Other abnormalities detected were hippocampal sclerosis, mesial temporal sclerosis, neuronal migration defects, tuberous sclerosis and hydrocephalus.

Most of intractable epileptics (60%) were on 2 AEDs combination and the commonest combination being sodium valproate with either carbamazepine or lamotrigine, clobazam, nitrazepam, phenytoin, phenobarbitone or topiramate and rest of the children were on three or more AEDs (40%). On follow up, the treatment response was evaluated, only 18% IE children had complete seizure control (full response-FR). Remaining 72% had incomplete seizure control (< FR). On comparing the treatment response with number of AEDs used, we found that 73% of IE children on 2 AEDs had less than FR and only 27% achieved full seizure control (FR). Only one child with IE, who was on 3 AEDs combination, achieved complete seizure control.

Statistical evaluation using univariate analysis showed that factors predicting intractability were-early onset seizures, myoclonic, neonatal or mixed seizures, initial high seizure frequency, perinatal asphyxia, neurological impairment, microcephaly,

neuroimaging and EEG abnormalities (Table 4). Multivariate logistic regression analysis revealed that early onset seizures, mixed seizures, neurological impairment and microcephaly had independent predictability.

Discussion

Medically intractable epilepsy is estimated to develop in 10-20% of children with epilepsy.³ IE has deleterious effects on child's health and quality of life and is a heavy burden on the caretaker and society.⁴ Therefore identification of predictors of intractability, early in the course of disease, can help to target rational combination AED therapy and surgery. Recent progress in epilepsy surgery has led to dramatic improvement in prognosis for some children with medically refractory seizures.⁵

On analyzing our series we noted that nearly 60% of IE children had onset of seizures early in infancy as compared to only 20% with well-controlled epilepsy. This compared well with other studies like Chawla *et al*⁶ (66%), Yoko Ohtsuka *et al*⁶ (53%) who also documented early onset of seizures in 60%. The probable explanation for early onset seizures is related to the underlying aetiopathogenesis like perinatal asphyxia, West syndrome, myoclonic epilepsies, cortical developmental abnormalities, intrauterine infections and the propensity of acquired infections leading to symptomatic epilepsy. 71% of our intractable epileptic children had remote symptomatic epilepsy while only 29% were idiopathic in nature. Amongst the former aetiologies, perinatal asphyxia constituted almost 50% children of intractable seizures and was an important predictor for intractability. Our findings were corroborative with those of Chawla *et al*⁶ and Sillanpaa *et al*.⁷ Also we observed that due to the above aetiologies there was initial high seizure frequency and the presentation with more

Table 4 : Univariate comparison in both groups

	Group A No. (%)	Group B No. (%)	Odds Ratio	95% CI	P-value
Age of onset < 1 yr	22(60)	11(20)	5.5	1.69-9.94	0.0009
Initial seizure frequency					
Daily	19(50)	3(4)	17.333	4.6-65.309	6.31x10 ⁻¹²
> 1/week	8(20)	2(5)	7.067	1.408-35.47	2.96x10 ⁻¹⁵
1-4/mo	11(30)	9(16)	2.082	0.765-5.667	<0.05
< 1/mo	-	41(75)	0.0045	0.0002-0.079	0.06
Sex					
Male children	27 (71)	35(64)	-	-	0.047
Female children	11 (29)	20(36)	-	-	0.644
Seizure type					
Partial convulsions	9 (24)	13(24)	1.003	0.379-2.653	1.003
Generalized convulsions	15 (40)	36(65)	0.3442	0.1463 -0.8100	0.013
Myoclonic / IS	11 (30)	1(2)	22.000	2.696 -179.50	0.000125
H/o Neonatal seizure	8 (21)	3(5)	4.622	1.138-18.768	0.022
H/o Febrile seizures	11 (30)	14(26)	1.193	0.4720 -3.016	0.709
H/o StatusEpilepticus	21(55)	12(22)	4.426	1.791 -10.940	0.000921
Family H/o seizures	2 (4)	5(9)	0.5556	0.1020 -3.027	0.565
Neurologic impairment (MD+MR)	25 (66)	9(16)	9.8	3.6-26.0	1.14x10 ⁻⁰⁶
Motor disability	15 (39)	4(7)	8.315	2.484 -27.832	0.000153
Mental Retardation	24 (63)	9(16)	8.762	3.314 -23.165	3.55x10 ⁻⁰⁶
EEG abnormality	32 (84)	28(51)	5.538	1.26-15.78	0.000969
Abnormal Neuroimaging	27 (71)	16(29)	5.982	2.46-21.165	6.61x10 ⁻⁰⁵
Mixed seizures	17 (45)	6(11)	6.611	2.286 -19.123	0.000202
Remote symptomatic epilepsy	28 (71)	12 (22)	8.799	3.4-22.72	2.25x10 ⁻⁰⁶
Microcephaly	16 (42)	4 (7)	9.200	3.1-29.13	0.0000584

than one type of seizures in children with IE. The above conditions also led to significantly higher episodes of status epilepticus in the IE group as compared to the well-controlled epileptic children. Status epilepticus in these was possibly as a result of primary or secondary brain damage.

Among the different seizure types, myoclonic seizures proved to be important predictor of IE in our study, on univariate comparison: but multivariate analysis did not prove it to be a significant marker. This predictability of myoclonic seizure was also noted by Chawla *et al*² study on multivariate

analysis. However, Berg *et al*,⁸ Udani *et al*⁷ and Huttenlocher *et al*,⁹ did not find correlation between initial seizure types and intractability. Eriksson *et al*¹⁰ and other studies^{1,8,9} stated that mixed seizures and myoclonic/ infantile spasms have the poorest seizure control. In Singhvi *et al*¹¹ study conducted on adult epileptics, partial seizure was a poor prognostic factor. However, most of the studies^{2,6,8} found GTC as major seizure type, and our study revealed it too. Febrile seizure is a known risk factor for epilepsy, the probable mechanism being that hippocampal damage can occur due to hyperthermia.¹² In our study, on analyzing

history of febrile seizures, we didn't find any statistical correlation with intractability and this was also observed in other studies.^{1,2,4-8,11}

The early markers of intractability included history of perinatal asphyxia, neonatal seizures and more than one type of seizures, remote symptomatic epilepsy and epileptic syndromes in patients in our series. Mental retardation and subnormality and developmental delay were significantly more noticed in the IE group and there was a likelihood of developing resistant seizures. Our study also depicted similar results and we found that MR was an independent indicator for prediction of intractability (done by Multivariate regression analysis). Microcephaly has been reported to be associated with adverse developmental outcomes in subpopulation of epileptic children.^{2,8} It was found to be strong predictor for intractability in our study unlike Chawla *et al*² and Berg *et al*⁸ case-control study.

Epilepsy syndromes that carry high intractability are Ohtahara syndrome in neonates, West syndrome, and severe myoclonic epilepsy in infancy, Lennox-Gastaut syndrome and Rasmussen encephalitis.^{10,13} These catastrophic epilepsies are generally associated with poor outcome and therefore early identification and intervention helps to achieve adequate seizure control.

In our study, 84% children with IE had abnormal findings on EEG and these ranged from focal epileptic activity (FEA), multifocal epileptic activity (MFEA), generalized epileptic activity (GEA) to hypsarrhythmia. This was found to have statistical significance only on univariate comparison. Our finding was supported by various Indian studies^{1, 11} and foreign authors.⁶

Latest advances in neuroimaging (MRI SPECT, PET) has made it possible to detect

underlying aetiology, are helpful in categorization and improve management of children especially with resistant seizures. MRI volumetric measurement aids to the diagnosis of mesial temporal sclerosis (MTS) early in childhood. In our cohort of children MRI was utilized as imaging modality in most of patients for better characterization of epilepsy early in course. It revealed that in 71% children with IE had neuroimaging abnormality with major share of findings suggestive of perinatal asphyxia (≈50%) followed by neuronal migration disorders. Similar findings were noted by Singhvi *et al*,¹¹ Semah *et al*¹⁴ and Udani *et al*¹ in their series.

Most of our children with IE were on 2 or 3 drugs polytherapy (60% and 34%). On 3 months follow-up we observed that 6 children had full Response (FR) were on 2AEDs while only one child having FR was on 3AEDs combination. This was a significant finding. The above results were in accordance with other studies in literature.^{6,11} Addition of third AED in patients with IE controlled seizures only in 10-15% cases.^{8,11,13} Like Singhvi *et al*,¹¹ we also noted that seizure control with more than 2 AED's was no better than using 2 primary drugs and infact may lead to more toxicities. Therefore addition of newer AEDs like Vigabatrin, Topiramate, and Clobazam should be considered.¹⁵

An important aspect in the management of intractable epileptic children is social impact on the child and the family.¹² Such children often need to be taken care of and require special schooling. In our series, 34% children could not attend school due to mental retardation or intractable epilepsy and about 32% were getting training in special school. Since our study sample was small, the associations of these factors need to be validated by further large sample longitudinal follow up and case control study. Other

limitations of our study were that it had a male bias and being a tertiary centre it had a highly selected group of IE children

In conclusion our study outlines the various predictive factors in relation to IE; following were significantly related to intractability on univariate comparison: -age of onset < 1 year, initial high frequency, myoclonic/IS seizure type, mixed seizures, history of neonatal seizures, history of status epilepticus, neurological impairment, mental retardation, microcephaly, EEG and neuroimaging abnormality. This was in agreement in various studies.^{1,2,4-8,11,14} When we applied multiple logistic regression analysis, to the significant factors, we found only 1) age of onset less than 1 year, 2) mixed seizures, 3) neurological impairment 4) microcephaly as independent predictors for intractability. Thus, all children with epilepsy having above-mentioned factors should be followed up regularly for early recognition of intractable epilepsy.

Key Messages

1. Early onset seizures, myoclonic or infantile spasms, more than one seizure type, high initial seizure frequency and presence of neurological impairment are important early predictors of intractability.
2. Remote symptomatic aetiology, especially perinatal asphyxia / HIE was the leading cause of intractable seizures in our series.

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