e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(9); 251-255

Original Research Article

Clinical Profile of Intractable Epilepsy in Children

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Received: 25-06-2023 / Revised: 28-07-2023 / Accepted: 30-08-2023
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Conflict of interest: Nil

Abstract:

Introduction: Intractable epilepsies constitute a small but a significant proportion of all epilepsies in childhood. In majority of the children epilepsy remains a mild disorder with 60-80% remitting spontaneously or with treatment.. A prompt diagnosis of refractoriness is of paramount importance for consideration of other therapies such as surgery. Early surgical intervention when successful might also prevent or reverse psychosocial consequences and cognitive impairment of uncontrolled seizures during critical periods of development. Based on this aim of our research work is to study the clinical profile of intractable seizures and also to determine the clinical predictors of intractable seizures.

Material & Methodology: Thus study was done as a prospective case control study, for a period of one in a tertiary care teaching hospital in children with intractable seizures aged 1-12 years among both sexes, By case definition Intractable epilepsy is when seizures continue to occur despite maximally itolerated doses of more than two antiepileptics, occurrence of an average of one seizure per month for 18 months with no more than a 3 month seizure free period during these 18 months. Epileptic children who had good control of seizures for the past 1½ Yrs were taken as control and compared. A detailed history was obtained from the parents. History regarding seizure, no of AED, frequency of seizures was obtained. Clinical examination was performed for all the cases.

Results and Conclusions: The following factors were found to be significantly associated with Intractable Epilepsy in our study Age of onset < 1 year, Status epilepticus, Neonatal seizures, Myoclonic seizures, Birth asphyxia, Developmental delay, Abnormal neurological examination, Abnormal EEG, Abnormal MRI scan , Abnormal findings on EEG and MRI must be identified early and referred to a specialist for optimization of pharmacotherapy, considering early surgery in selective cases and trial of the newer modalities of treatment.

Conclusion: Early identification is also important for parental counselling regarding the nature of the disease and importance of compliance to medications. In our study the commonest cause of Intractable Epilepsy was perinatal asphyxia. Perinatal asphyxia can be prevented by good nutrition during pregnancy, regular antenatal check-ups with detection of high risk pregnancy, promoting hospital deliveries and prompt resuscitation of new-born when required.

Keywords: Children, Intractable Epilepsy.

Introduction

Intractable epilepsies constitute a small but a significant proportion of all epilepsies in childhood [1]. Intractable epilepsy is a major health problem in many areas of the world. Chronic uncontrolled epilepsy can have serious medical consequences including an increased risk of mood disorders, physical injuries and sudden unexpected death. Intractable seizures are a major economic burden to the society [2]. In majority of the children epilepsy remains a mild disorder with 60-80% remitting spontaneously or with treatment [3] .Seizure control remains poor in 10 - 20% [4]. A prompt diagnosis of refractoriness is of paramount importance for consideration of other therapies such as surgery. Early surgical intervention when successful might also prevent or reverse psychosocial consequences and cognitive impairment of uncontrolled seizures during critical periods of development [2]. Identification of predictors of intractable epilepsy is important to identify cases early in the course of the disease. The clinical characteristics of intractable seizures are poorly understood and current managements are unsatisfactory. However there are very few studies on intractable seizures. Identification of predictors early in the course of the disease can help in selecting appropriate antiepileptic drugs and select children who are appropriate candidates for surgery. A long term follow up of children with intractable seizures was done by Berget al [5] and

his colleagues [3]. As there is no unifying definition for intractable seizures, we have used Berg et al [5] definition for identification of the cases. Intractability for an individual child is difficult to predict before several years of antiepileptic drug treatment. Intractability appears to decrease with prolonged follow-up, although the burden of this wait and see approach is substantial. Failure of a first antiepileptic drug is a risk factors for intractability but nonetheless many remit6. Based on this aim of our research work is to study the clinical profile of intractable seizures and also to determine the clinical predictors of intractable seizures.

Materials and Methods

Thus study was done as a prospective case control study, for a period of one in a tertiary care teaching hospital in children with intractable seizures aged 1-12 years among both sexes, those children with poor compliance to antiepileptic drug were excluded. By case definition Intractable epilepsy is when seizures continue to occur despite maximally tolerated doses of more than two antiepileptic's, occurrence of an average of one seizure per month for 18 months with no more than a 3 month seizure free period during these 18 months. Epileptic children who had good control of seizures for the past 1½ Yrs were taken as control and compared.

All children attending pediatric OPD with seizures were studied. 63 children met the criteria of intractable epilepsy and were included in the case group. Controls were selected by random sampling of children who had good control of seizures for the past 1½ years. Our study had a total of 126 children, 63 cases and 63 controls. The children were enrolled into the study after getting consent from the parents. The study was conducted after Institutional Ethical Committee approval was obtained A detailed history was obtained from the parents. History regarding seizure, no of AED, frequency of seizures was obtained. Details regarding age, sex, age of onset of seizures, family h/o seizures, H/o febrile seizures, H/o of status epilepticus, birth asphyxia, developmental delay, H/o neonatal seizures, were sought from a detailed medical history. Clinical examination was performed for all the cases.

Data was collected and a computerized analysis of data was performed using SPSS Version 24. Data were analyzed separately for univariate comparison. Analysis was done using Chi square test. The Odds ratio was used to indicate the magnitude of association between each parameter and intractable epilepsy.

Results

In our study the prevalence of intractable seizures was 10.53% among all patients attending OPD. A total of 63 children in the intractable seizure group and 63 children in the well-controlled group were studied. Among the 126 children studied, maximum number of children 59 (46.8%) belonged to the 5-12 years group with, 34 (54%) in the intractable group and 25(39.7%) in the well-controlled group.14 (11.1%) children belonged to the age group 1-2 years with 9 (14.3%) children in the intractable group and 5 (7.9%) children in the well-controlled group. 53 (42.1%) children were in the 2-5 years group with 20 (31.7%) in the intractable group and 33(52.4) children in the control group. The total no. of males in the study were 85 with 45 (71.4%) in the case group and 40 (63.5%) in the control group. There was predominant male preponderance in our study. There were 18 (28.6%) females among the cases and 23 (36.5%) females among the controls. Children in the intractable seizure group had a higher seizure frequency when compared to the control group. 32 (50.8%) children had daily seizures, 12 (19%) had more than 1 seizure/week and 19 (30.2%) children had more than 1seizure/month in the intractable group. 19 (30.20%) children had more than 1 seizure/6 months and 44 (69.8%) children had more than 1 seizure/ year in the well-controlled group.

The commonest seizure in our study was generalized seizures with 48 (76.2%) children in the intractable group and 45 children (71.4%) in the control group. Generalized seizure was not significant in the cases with a P value of 0.543. Partial seizures were seen in 15 (23.8%) children in the intractable group and 18 (28.6%) children in the well-controlled group.

Partial seizures were not significantly associated with intractable seizures with a P value of 0.543. 2 children among the cases had more than one type of seizure with mental retardation and slow wave activity on EEG and had features of Lennox-Gastaut syndrome.

Table 1: Type of Seizures

Type of Seizures		**Cases No. %**		**Controls No. %**	
Generalised Seizures		48 (76.2)		45 (71.4)	
1	GTCS	18	(28.5)	30	(47.6)
2	Tonic	7	(11.1)	10	(15.8)
3	Clonic	3	(4.7)	3	(4.7)
4	Myoclonic	20	(31.7)	2	(3.17)
Partial Seizures		15 (23.8)		18 (28.6)	
1	Simple partial	3	(4.7)	10	(15.8)

2	Complex partial	9	(14.3)	5	(7.9)
3	Partial seiz. with sec.generalization	3	(4.7)	3	(4.7)
Total		63	(100)	63	(100)

Among children who had generalized seizures the commonest seizure type was myoclonic seizures in the intractable group.20 children had myoclonic seizures in the intractable group and 2 children in the control group. GTCS was the commonest seizure observed in the control group with 30 children in the control group and 18 children in the intractable group. The commonest type of partial seizures was complex partial seizures with 9 children in the intractable and 5 children in the control group. Myoclonic seizures was significantly associated with intractable seizures in the cases with a p value of <0.001.

Maximum number of children in the cases was on 3 AED whereas maximum number of children in the controls was on 1 AED. All the children in the case group were treated with 3 or more AED. None of the children in the control group were on more than 3 AED.

In our study age of onset was less than one year in 39 (61.9%) children in the cases and 14 (22.2%) children among the controls. 24 (38.1%) children among the cases and 49 (77.8%)children among the control had age of onset of seizures >1 year. The age of onset < 1yr in the cases was significant with P value of <0.001. In our study population, Family H/o seizures were not significant among the cases with a P value of 0.106. 20 children among the cases had H/o febrile seizure with an insignificantp value-0.430.

In our study 2 children in the cases had H/o fever with altered sensorium and cerebrospinal fluid analysis suggestive of Central nervous system infection with an insignificant p value 0.154.

In our study, 32 (50.8%) children among the cases and 12 (19%) children among the controls had a history status epilepticus. 31 (49.2%) children among the cases and 51(81%) children among the controls did not have history of status epilepticus. Children with intractable seizures had a higher incidence of status epilepticus with a significant P value of <0.001.

Also in our study 13 (20.6%) children among the cases and 5 (7.9%) children among the controls had H/o neonatal seizures in the past. 50 (79.4%) children among the cases and 58 (92.1%) children among the controls did not have a history of neonatal seizures. H/o neonatal seizure was a risk factor for intractable seizures with a significant P value- 0.042. In our study 29 (46%) children among the cases and 9 (14.3%) children among the controls had a history suggestive of birth asphyxia. 34 (54%) children among the cases and 54 (85.7%) children among the controls did not have a history of birth asphyxia. H/o birth asphyxia in the cases was significant with a P value of <0.001.

Also in our study, 34 (54%) children among the cases and 6 (9.5%) children among the controls had a history of developmental delay. 29 (46%) children among the cases and 57 (90.5%) children among the controls were developmentally normal. H/o developmental delay is significant in the cases with a P value of <0.001.

Among the cases 41 (65.1%) children had an abnormal neurological examination when compared to only 9 (14.3%) children in the control group. 22(34.9%) children among the cases and 54 (85.7%) among the controls were neurologically normal.

EEG was abnormal in 53 (84.1%) cases when compared to 30 (47.6%) children in the controls. 10 (15.9%) children among the cases and 33 (52.4%) children among the controls had a normal EEG. The abnormality noted in most of the children was bilateral sharp wave discharges and multifocal sharp waves. Abnormal EEG in the intractable group was significant in the cases with a P value of <0.001.

CT scan was done in all the children enrolled in the study. CT scan was abnormal in 28 (44.4%) cases and 21 (33.3%) controls. 35 (55.6%) children among the cases and 42(66.7%) children among the controls had a normal CT scan. Abnormal CT scan in the cases was not significant with a p value of 0.201. In our study 35 (55.6%) children among the cases and 42 (66.7%) children among the controls had a normal CT scan. 28 (44.4%) children among the cases and 21 (33.3%)had abnormal findings on CT scan.

Among the cases the commonest neurological finding was cerebral atrophy and gliosis. 9 (14.3%) children had cerebral atrophy and 9 (14.3%) children had gliosis among the cases. 2 (3.17%) had cerebral atrophy along with gliosis in the intractable group. 4(6.34%) cases had tubers and calcification on CT scan. 2(3.17%) children had agenesis of corpus callosum, 2 (3.17%) children had features of hydrocephalous. The commonest finding in the control group was ring enhancing lesion (17.4%). MRI was not done in 9 cases and 21 controls. MRI was abnormal in 35 (55.6%) children of the cases and 12 (19.04%) children of the controls. Abnormal MRI was significant in the cases with a P value of 0.005. MRI Scan was not taken in 9 cases and 21 controls that had a lesion on CT scan. The commonest finding on MRI

was cerebral atrophy which was seen in11 (20.37%) children. 9 (11.1%) children had features of gliosis and 3 (5.5%) children had features of cerebral atrophy and gliosis. 4 (7.40%) children in the cases had features of tuberous sclerosis. 2 (3.70%) children each in the cases had features of hippocampal atrophy and agenesis of the corpus callosum. 3 (5.5%) among the cases had features suggestive of neuronal migration disorders. In 19 (30.15%) children among the cases the etiology was idiopathic and 44(69.8%) children had remote symptomatic etiology. Remote symptomatic etiology was significantly associated with intractabilitywith a P value of 0.044.

Table 2: Etiology of Intractable Seizures among the Cases

Etiology	Cases No.	%	ODDS Ratio	P Value
Perinatal Asphyxia	29	(46)	5.118	<0.001
Tuberous Sclerosis	4	(6.34)	1.641	0.170
Neuronal migrationdisorders	3	(4.76)	-	0.080
Corpus callosum agenesis	2	(3.17)	-	0.154
Hippocampal atrophy	2	(3.17)	-	0.154
Postmeningitic sequelae	2	(3.17)	-	0.154
Lennox-Gastaut syndrome	2	(3.17)	-	0.154

The commonest cause of intractable seizures was perinatal asphyxia 29 (46%) followed by tuberous sclerosis 4 (6.34%). Other causes of intractability are neuronal migration disorders 3 (4.76%), corpus callosum agenesis 2 (3.17), hippocampal atrophy 2 (3.17%), Postmeningitic sequelae 2 (3.17%), Lennox- Gestaut syndrome 2 (3.17%) cases. Perinatal asphyxia was significantly associated with intractable seizures with a significant P value <0.001.

Discussion

The prevalence of intractable seizures was 10.53% in our study. Camfield et al [7] showed the prevalence of intractable seizures to be 8% in his studies. Sillanpaa in his study showed the prevalence of intractable seizures to be 22%. Medically intractable seizures is estimated to develop in 10- 20% of children with epilepsy [8].

In our study 67.5% of the children were males. There was a significant male preponderance in both the groups. Similar results were seen by Javad Abhondian et al [9] (76.5%). Mallik et al also showed a male preponderance in his study. However male sex was not significantly associated with intractable seizures in our study.

In our study the incidence of daily seizures was 50.8% in the case group. A similar result was shown by Manoj et al [1] in his case group (50%). Javad et al [9] showed the incidence of daily seizures to be 66.7% in his cases. The occurrence of weekly seizures in our study was 19% and these matched well with Manoj et al [1] studies (20%). 30.2% of our cases had monthly seizures and our results matched well with Manoj et al [1] who showed the occurrence of monthly seizures to be 30%. The commonest seizure type in our study was generalized seizures. These results were also shown by Chawla et al [11], Ohtsuka et al [12] and Berg et al [5] in their studies. Among the seizure types Myoclonic seizures proved to be an important predictor of intractability in our study. A similar result was shown by Chawla et al [11], Malik et al [10] and Javad et al [9] in their studies. Eriksson et al [13] and Berg et al [5] stated that myoclonic seizures/infantile spasms have the poorest seizure control. 82.5% of the cases were on 3 AED's, 11.1% on 4 AED's and 6.3% on 5 AED. 4.8% of the controls were on 3 AED's. None of the children in the control group was on more than 3 AED.

In our study 61.9% of the children with intractable seizures had age of onset < 1 year. This compared well with studies of Manoj et al [1] (60%) and Chawla et al [11] 66%. However Ohtsuka et al [12] in his study stated age of onset of seizures <1 year to be 53%. In our study age of onset of seizures was a predictor of intractable epilepsy. The reasons for early onset of seizures are due to the etiologies like perinatal asphyxia, Tuberous sclerosis.

In our study 12.7% of our cases had a family history of seizures. Family H/o seizure was not significantly associated with intractable epilepsy in our study. These results go along with Manoj et al [1] and Javad et al [9].

Febrile seizure is a known risk factor for epilepsy the probable risk factor being hippocampal damage due to hyperthermia [14]. H/o febrile seizure was not significantly associated with intractable seizures in our study. These results were comparable with Manoj et al [1]. H/o fever with altered sensorium was not significantly associated with intractable seizures in our study.

50.8% children presented with status epilepticus in the cases and when compared to 19% of the children in the controls. Similar results were stated by Manoj et al [1] (55%). However Javad et al [9] showed only 11.8% of the cases to have status epilepticus. H/o status epilepticus was significantly associated with intractable epilepsy in our study. These results went well with Berg et al [5] and Manoj et al [1]. However in Javad et al [9] study there was no significant association between status epilepticus and intractable seizures. The

explanation would be cause of an insult to the growing brain.

There were 46% of children with H/o perinatal asphyxia among the cases. Chawla et al [11] showed 50% of his cases with perinatal problems. Perinatal asphyxia was a predictor of intractable epilepsy. Similar results were shown by Atlunbasak et al [15] and Manoj et al [1]. H/o developmental delay was significantly associated with intractable epilepsy in our study. Similar results were shown by Aithala et al [16] in his study.

Microcephaly among the cases (39.7%) was significantly associated with intractable seizures in our study. Berg et al [5], Chawla et al [11] and Manoj et al [1] also showed similar results. Abnormal neurological examination was a predictor of intractable epilepsy in our study. Chawla et al [11], Javad et al [9] and Atlunbasak et al [16] also showed similar results. 40% of the children had microcephaly, 30 % children had language delay and 25% had quadriplegia. Abnormal EEG among the cases was significantly associated with intractable seizures in our study. Atlunbasak et al [15] and Singhvi et al [17] (69%) also showed the same results in their study.

Abnormal CT scan was seen in 44.4% of our cases. Singhvi et al [17] reported 41% of abnormal CT scan among his cases. Abnormal CT scan among the cases was not significantly associated with intractable epilepsy in our study. However Javad et al [9] and Singhvi et al [17] showed association between abnormal CT and intractable epilepsy. Abnormal MRI scan among the cases was associated with intractable seizures in our study. Manoj et al [1] stated abnormal neuroimaging was associated with intractable seizures in his study.

Conclusion

In our study the commonest cause of Intractable Epilepsy was perinatal asphyxia. Perinatal asphyxia can be prevented by good nutrition during pregnancy, regular antenatal checkups with detection of high risk pregnancy, promoting hospital deliveries and prompt resuscitation of newborn when required. Status epilepticus is also a significant risk factor for Intractable Epilepsy. It must be prevented by counselling mothers regarding compliance to drugs and to seek medical facilities for early intervention when seizures occur.

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