

## Original Research Article

# A study of clinical profile of intractable epilepsy in children

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**Received:** 17 December 2019

**Revised:** 02 January 2020

**Accepted:** 28 January 2020

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## ABSTRACT

**Background:** This study was undertaken to find out the prevalence and clinical features of intractable epilepsy (IE) in a tertiary referral center.

**Methods:** Study was conducted in a tertiary care hospital on 60 children with intractable epilepsy. Cases includes intractable epilepsy is when seizures continue to occur despite maximally tolerated 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. Controls: epileptic children who had good control of seizures for the previous 18 months.

**Results:** The prevalence of intractable seizures was 10% with maximum number of children 25 (41.6%) belonged to the 5-12 years. 15 (50%) children had daily seizures. Myoclonic seizures proved to be an important predictor of intractability. 4 children among the cases had history of family seizures, 6 children in cases had history febrile seizure, whereas, 6 children among the controls had history of family seizures, 8 children in controls had history febrile seizure. 23.3% of children presented with *Status epilepticus* in the cases and 16.6% of the children in the controls. Remote symptomatic etiology 12(40%) is the commonest cause of seizure. 13 (43.3%) children in cases and 3 (10%) children among the controls had a history suggestive of birth asphyxia. EEG was abnormal in 17 (56.6%) cases when compared to 11 (36.6%) children in the controls. CT scan was abnormal in 14 (46.6%) cases and 10 (33.3%) controls. MRI was abnormal in 16 (53.3%) children of the cases and 8 (26.6%) children of the controls.

**Conclusions:** 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 newborn when required.

**Keywords:** Birth asphyxia, Cerebral atrophy, Intractable epilepsy, Myoclonic seizures

## INTRODUCTION

Epilepsy is usually a chronic disorder with a varying outcome. There is now general agreement that 70% of patients with newly diagnosed epilepsy can expect one year remission on treatment, but 15-35% of patients develop intractable epilepsy (IE). There are a number of factors which are predictors of poor prognosis. These include organic brain lesion, partial seizures, multiple seizure types, high seizure frequency and abnormal

background EEG activity. Though IE has been extensively studied in the developed countries, there are not many reports of IE from developing countries.

Intractable epilepsies constitute a small but a significant proportion of all epilepsies in childhood.<sup>1</sup> 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.<sup>2</sup>

In majority of the children epilepsy remains a mild disorder with 60-80% remitting spontaneously or with treatment.<sup>3</sup> Seizure control remains poor in 10-20%.<sup>4</sup> 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.

The aim of the study was to study the clinical profile of intractable seizures and to determine the clinical predictors of intractable seizures.

## METHODS

### *Study design*

A Prospective case control study carried out during June 2018-June 2019 at department of pediatrics, Narayana Medical College and hospital, Nellore, Andhra Pradesh, India.

### *Inclusion criteria*

Children aged 1-12 years who met the definition of intractable seizures both sexes.

### *Exclusion criteria*

Children with poor compliance to AED and parents not willing to participate.

### *Cases*

Intractable epilepsy is when seizures continue to occur despite maximally tolerated 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.

### *Controls*

Epileptic children who had good control of seizures for the previous 18 months.

### *Procedure*

Present study had a total of 60 children, 30 cases and 30 controls. A detailed history was obtained from the parents. History regarding seizure semiology, number of AED, frequency of seizures were obtained.

Details regarding age, sex, age of onset of seizures, family history of seizures, history of febrile seizures, history of *status epilepticus*, birth asphyxia,

developmental delay, history of neonatal seizures, were sought from a detailed medical history. Clinical examination was performed for all the cases. Parents were asked to maintain a diary to record the details of daily intake of drugs and to record details regarding occurrence of seizures. Compliance to AED's was assessed by a detailed history and a review of past medical records. Urine for metabolic screening, LFT, RFT and EEG was done for all children. CT scan brain and ophthalmological and ENT evaluation were done.

Data analysis was done using Chi square test. P-value of <0.05 was taken to be significant. The odds ratio was used to indicate the magnitude of association between each parameter and intractable epilepsy.

## RESULTS

During the study period of one year, among seizures, 60 children met the criteria of intractability. In our study, among the seizures, the prevalence of intractable seizures was 10%.

### *Age distribution of the study population*

Among the 60 children, maximum number of children 25 (41.6%) belonged to the 5-12 years group, 16 (53.4%) in the intractable group and 9 (30%) in the control group. 11 (18.3%) children belonged to the age group 1-2 years with 5 (16.6%) children in the intractable group and 6 (20%) children in the control group. 24 (40%) children were in the 2-5 years group with 9 (30%) in the intractable group and 15(50%) children in the control group.

The total number of males in the study were 39; with 21 (70%) in the case group and 18 (60%) in the control group. There was predominant male preponderance in our study. Male sex was not significantly associated with intractable seizures in our study with a p-value of 0.342.

Children in the intractable seizure group had a higher seizure frequency than compared to the control group. 15 (50%) children had daily seizures, 6 (20%) had more than 1 seizure/week and 9 (30%) children had more than 1 seizure/month in the intractable group. 9 (30%) children had more than 1 seizure/6 months and 21 (70%) children had more than 1 seizure/year in the well control group.

### *Type of seizures*

The commonest seizure in present study was generalized seizures with 23 (76.6%) children in the intractable group and 20 children (66.6%) in the control group. Generalized seizure was not significant in the cases with a p-value of 0.6. Partial seizures were seen in 7 (23.4%) children in the intractable group and 10(33.4%) children in the well-controlled group. Partial seizures were not significantly associated with intractable seizures with a p-value of 0.6.

Among children who had generalized seizures the commonest seizure type was myoclonic seizures in the intractable group. GTCS was the commonest seizure

observed in the control group and intractable group. The commonest type of partial seizures was complex partial seizures in the intractable.

**Table 1: Type of seizures.**

Type of seizures	Cases	Controls	
	Number	Percentage	Number Percentage
Generalized seizures	23	76.6	20 66.6
1 GTCS	9	(30)	13 (43.3)
2 Tonic	3	(10)	5 (16.6)
3 Clonic	2	(6.6)	1 (3.3)
4 Myoclonic	10	(33.3)	1 (3.3)
Partial seizures	7	23.4	10 33.4
1 Simple partial	2	(6.6)	5 (16.6)
2 Complex partial	4	(13.3)	3 (10)
3 Partial seizure with secondary generalization	1	(3.3)	2 (6.6)
Total	30	(100)	30 (100)

#### **Age of onset of seizures <1 year**

There were 15 (50%) children in the cases and 8 (26.6%) children among the controls had age of onset <1 year. 15 (50%) children among the cases and 22 (73.3%) children among the control had age of onset of seizures >1 year. The age of onset <1 year in the cases was significant with p-value of <0.001.

#### **History**

The 4 children among the cases had history of family seizures, 6 children in cases had history febrile seizure, whereas, 6 children among the controls had history of family seizures, 8 children in controls had history febrile seizure. There was no significant difference observed between the groups. 1 child in the cases had history of fever with altered sensorium and cerebrospinal fluid analysis suggestive of central nervous system infection. 15 (50%) children among the cases and 6 (20%) children among the controls had a history of *status epilepticus*. 6 (20%) children among the cases and 3 (10%) children among the controls had history of neonatal seizures.

#### **Birth asphyxia and developmental delay**

A 13 (43.3%) children among the cases and 3 (10%) children among the controls had a history suggestive of birth asphyxia. (P<0.001). 17 (33.3%) children among the cases and 3 (10%) children among the controls had a history of developmental delay (P<0.001).

#### **Neurological examination**

Among the cases 17 (56.6%) children had an abnormal neurological examination when compared to 4 (13.3%) children in the control group (P<0.001).

An 8 (26.6%) children had microcephaly among the cases and 2(6.6%) children had microcephaly in controls (p-value of <0.001).

The 10 (33.3%) children had language delay among the cases and 2(6.6%) children had language delay in controls (p-value of <0.001).

An 8 (26.6%) children had quadriplegia among the cases and 2(6.6%) had quadriplegia in control (p-value of <0.001).

The 4 children in the cases had neurocutaneous markers suggestive of tuberous sclerosis. Other findings were vision abnormalities 4 (6.32%) and hemiplegia 3 (4.7%) among the cases.

#### **EEG**

EEG was abnormal in 17 (56.6%) cases when compared to 11 (36.6%) children in the controls. 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 brain**

CT scan was abnormal in 14 (46.6%) cases and 10 (33.3%) controls. Among the cases, the commonest neurological finding was cerebral atrophy and gliosis. 4 (13.3%) children had cerebral atrophy and 4 (13.3%) children had gliosis among the cases. 1 (3.3%) had cerebral atrophy along with gliosis in the intractable group. 1(3.3%) cases had tubers and calcification on CT scan. 1(3.3%) children had agenesis of corpus callosum,

1 (3.3%) children had features of hydrocephalous. The commonest finding in the control group was ring enhancing lesion (20%).

### **MRI scan**

MRI was abnormal in 16 (53.3%) children of the cases and 8 (26.6%) children of the controls ( $p=0.005$ ).

The commonest finding on MRI was cerebral atrophy which was seen in 8 (26.6%) children. 3 (10%) children had features of gliosis and 1 (3.3%) children had features of cerebral atrophy and gliosis. 2 (6.6%) children in the cases had features of tuberous sclerosis. 1 (3.3%) children each in the cases had features of hippocampal atrophy and agenesis of the corpus callosum. 1 (3.3%) among the cases had features suggestive of neuronal migration disorder. There were 1 case of Polymicrogyria and one case of Lissencephaly. 1 (3.3%) child among the cases had features of hydrocephalous.

### **Etiology of intractable epilepsy**

In 10 (33.3%) children among the cases the etiology was idiopathic and 17 (56.6%) children had remote symptomatic etiology. Remote symptomatic etiology (12(40%)) was significantly associated with intractability ( $p=0.040$ ).

### **Etiology of intractable seizures**

The commonest cause of intractable seizures was perinatal asphyxia 13 (43.3%) followed by tuberous sclerosis 2 (6.6%). Other causes of intractability were neuronal migration disorders 1 (3.3%), corpus callosum agenesis 1 (3.3%), hippocampal atrophy 1 (3.3%), *Postmeningitic sequelae* 1 (3.3%), *Lennox-Gestaut* syndrome 1 (3.3%) cases. Perinatal asphyxia was significantly associated with intractable seizures ( $p$ -value  $<0.001$ ).

## **DISCUSSION**

In general, the prognosis of a newly diagnosed case of epilepsy is good. However, 15-35% patients develop IE i.e. seizure persisting despite treatment. The magnitude of the problem of IE in India is unknown. In present study, the prevalence of intractable seizures was 10%. Radhakrishnan et al estimated 20,000-40,000 patients with IE in India.<sup>5</sup> 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.<sup>6</sup> There are a number of factors which predict poor prognosis. These include organic brain lesions, partial seizures, multiple seizure types, high seizure frequency, seizure onset in infancy and abnormal EEG.

Among 60 children, maximum number of children 25 (41.6%) belonged to the 5-12 years group. 39 children

were males in our study. Malik et al also showed a male preponderance in his study.<sup>7</sup> Same results observed by Akhoundian J et al (76.5%).<sup>8</sup> However male sex was not significantly associated with intractable seizures in present study.

In present study, 15 (50%) children had daily seizures, 6 (20%) had more than 1 seizure/week and 9 (30%) children had more than 1 seizure/month in the intractable group. A similar result was shown by Patil et al in his case group (50%). Akhoundian et al showed the incidence of daily seizures to be 66.7% in his cases.<sup>1,8,9</sup> (30%) children had more than 1 seizure/6 months and 21 (70%) children had more than 1 seizure/ year in the well control group and present results matched well with Patil et al who showed the occurrence of monthly seizures to be 30%.

The commonest seizure in present study was generalized seizures with 23 (76.6%) children in the intractable group and 20 children (66.6%) in the control group. These results were also shown by Chawla et al, Ohtsuka et al and Berg et al in their studies.<sup>10-12</sup>

Among the seizure types myoclonic seizures proved to be an important predictor of intractability in present study. A similar result was shown by Chawla et al, Malik et al and Akhoundian et al in their studies.<sup>7,8,10</sup> Eriksson et al, Udani et al and Berg et al stated that myoclonic seizures/infantile spasms have the poorest seizure control.<sup>12-14</sup>

In present study, 15 (50%) children in the cases and 8 (26.6%) children among the controls had age of onset  $<1$  year. 15 (50%) children among the cases and 22 (73.3%) children among the control had age of onset of seizures  $>1$  year. This compared well with studies of Patil et al (60%) and Chawla et al 66%.<sup>1,10</sup> However Ohtsuka et al in his study stated age of onset of seizures  $<1$  year to be 53%.<sup>11</sup> In present 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.

The 4 children among the cases had history of family seizures, 6 children in cases had history febrile seizure, whereas, 6 children among the controls had history of family seizures, 8 children in controls had history febrile seizure. Family history of seizure was not significantly associated with intractable epilepsy in our study. These results go along with Patil et al and Akhoundian et al.<sup>1,8</sup>

Febrile seizure is a known risk factor for epilepsy the probable risk factor being hippocampal damage due to hyperthermia.<sup>15</sup> History of febrile seizure was not significantly associated with intractable seizures in present study. These results were comparable with Patil et al.<sup>1</sup> 23.3% of children presented with *status epilepticus* in the cases and 16.6% of the children in the controls. Similar results were stated by Patil et al (55%).<sup>1</sup> However



Akhoundian et al showed only 11.8% of the cases to have status epilepticus.<sup>8</sup> History of *status epilepticus* was significantly associated with intractable epilepsy in present study. These results went well with Berg et al and Patil et al.<sup>1,12</sup> However in Akhoundian et al study there was no significant association between *status epilepticus* and intractable seizures.<sup>8</sup> The explanation would be cause of an insult to the growing brain.

In present study, 13 (43.3%) children among the cases and 3 (10%) children among the controls had a history suggestive of birth asphyxia ( $P < 0.001$ ). 17 (33.3%) children among the cases and 3 (10%) children among the controls had a history of developmental delay. ( $P < 0.001$ ). Similar results were shown by Atlunbasak et al and Patil et al.<sup>1,9</sup>

History of developmental delay was significantly associated with intractable epilepsy in our study. Similar results were shown by Aithala et al in his study.

The 8 (26.6%) children had microcephaly among the cases and 2 (6.6%) children had micricephaly in controls (p-value of  $< 0.001$ ). Berg et al, Chawla et al and Patil et al also showed similar results.<sup>1,10,12</sup>

Abnormal neurological examination was a predictor of intractable epilepsy in present study. 10 (33.3%) children had language delay among the cases and 2 (6.6%) children had language delay in controls. 8 (26.6%) children had microcephaly among the cases and 2 (6.6%) children had micricephaly in controls (p-value of  $< 0.001$ ). Chawla et al, Akhoundian et al and Atlunbasak et al also showed similar results.<sup>8-10</sup> 40% of the children had microcephaly, 30% children had language delay and 25% had quadriplegia.

EEG was abnormal in 17 (56.6%) cases when compared to 11 (36.6%) children in the controls. The abnormality noted in most of the children was bilateral sharp wave discharges and multifocal sharp waves. Atlunbasak et al and Singhvi et al (69%) also showed the same results in their study.<sup>9,16</sup>

CT scan was abnormal in 14 (46.6%) cases and 10 (33.3%) controls. Among the cases, the commonest neurological finding was cerebral atrophy and gliosis. Singhvi et al reported 41% of abnormal CT scan among his cases.<sup>16</sup> Abnormal CT scan among the cases was not significantly associated with intractable epilepsy in present study. However Akhoundian et al and Singhvi et al showed association between abnormal CT and intractable epilepsy.<sup>8,16</sup>

MRI was abnormal in 16 (53.3%) children of the cases and 8 (26.6%) children of the controls. The commonest finding on MRI was cerebral atrophy which was seen in 8 (26.6%) children. Patil et al stated abnormal neuroimaging was associated with intractable seizures in his study.<sup>1</sup>

The commonest cause of seizure in the cases was remote symptomatology in present study. Similar results were shown by Atlunbasak et al, Berg et al and Patil et al in their studies.<sup>1,9,12</sup>

## CONCLUSION

In present 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.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Sree CB, Belavadi GB. A study of clinical profile of intractable epilepsy in children. *Int J Contemp Pediatr* 2020;7:664-9.