Original Research Article

Risk factors for childhood refractory epilepsy in a tertiary care centre, Chennai, India

Thannoli Gowthami Gowrinathan, Senthil Kumar A.*

Department of paediatrics, Institute of Child Health and Research Center, Madras Medical College, Egmore, Chennai India

Received: 25 May 2019
Accepted: 14 June 2019

*Correspondence:
Dr. Senthil Kumar A.,
E-mail: dr.senthilarul@gmail.com

ABSTRACT

Background: Intractable epilepsy is the pragmatic problem during the treatment of active epilepsy in children. Several risk factors are associated with incidence of intractable/recurrent epilepsy. The current study was done to identify the risk and prognostic factors associated with recurrent epilepsy (RE).

Methods: This descriptive study was conducted on 152 children with idiopathic or symptomatic epilepsy who are on two or more AEDs and who were in follow up in Neurology OPD and inpatients in medical ward at ICH&HC, Chennai. All patients underwent relevant investigations to identify the possible risk factors for incidence of RE in study population. Karyotyping was done for idiopathic cases.

Results: Male preponderance was seen in the study (M:F-2:1). Risk factors such as male sex, age onset of seizures, type of seizures, developmental delay, CNS congenital anomalies, h/o perinatal injury, neuroabnormality, abnormal MRI and EEG was found to have statistically significant association with incidence of RE. No significant association was observed for the factors microcephaly, behavioural abnormalities, h/o febrile seizures and h/o status epilepticus with incidence of RE. No chromosomal abnormalities were detected in idiopathic cases.

Conclusions: Early identification, risk factor analysis and understanding in the dynamics of the disease helps the physician in initiating the appropriate treatment, thereby avoiding the wrong therapy, low dose therapy and infrequent therapy. Above all identification of the risk factors helps in parental counseling and prepare them for expected outcome.

Keywords: Children, Intractable epilepsy, Risk factors

INTRODUCTION

Epilepsy is the most common neurological abnormality in children. Approximately 10.5 million children are diagnosed with active epilepsy that accounts for 25% of the population in the world.1 Ever year about 3.5 million new cases are reported with incidence of epilepsy.2 About 40% of the population affected by epilepsy was below 18 years of age at the time of diagnosis. Of them, 6-14% of children are developing intractable epilepsy.3

Intractable epilepsy (IE) also called as recurrent or refractory epilepsy (RE) can be defined as inadequate seizure control despite appropriate medical therapy with at least two antiepileptic drugs at maximally tolerated doses for more than 18 months, or adequate seizure control with unacceptable drug-related side effects.4
Children with intractable epilepsy will not respond to any antiepileptic drugs and will continue to manifest seizures.

Cognitive and behavioral disturbance are the most common co- morbid conditions of the patients with RE which is usually associated with early onset seizures, severity of seizures, lower socioeconomic class, longer duration etc. Common behavioral symptoms being ADHD, hyperactivity, autistic spectrum disorder (ASD), depression, learning difficulty, low memory, problem solving etc.

Many studies have identified the risk factors associated with RE. The current study was done with the aim not only to identify the risk factors of refractory childhood epilepsy but also to determine the prognosis of seizures in RE and to identify the association of karyotyping analysis in refractoriness.

METHODS

This was a descriptive study done on children with idiopathic or symptomatic epilepsy who are on two or more AEDs and who were in follow up in neurology OPD and inpatients in medical ward at ICH and HC, Chennai during the study period from August 2017 to September 2018. Children of age group from 6 months to 12 years after obtaining written consent from their parents and after counselling for karyotyping were included in the study.

Inclusion criteria were patients on adequate treatment with two AEDs either alone or in combination, with proper compliance and dosage. Exclusion criteria were patients with poor compliance in the form of irregular medication or inadequate dosing.

A pre-structured Questionnaire containing pre-defined variables was filled up, prior to their enrolment in the study. Detailed history of seizures including age of onset, type of seizure, number of seizures at baseline before starting treatment (per day/week/month/year, response to antiepileptic drug(s), longest seizure free interval, any history of status epilepticus (SE) before or as a part of presentation, hospital admissions and treatment, perinatal history, birth history, neonatal history, diet history, development history, associated symptoms (febrile convulsions, head trauma etc), family history of seizure disorder and history of poor scholastic performance, behavioral abnormality and focal motor deficits were collected and CNS infection were taken into account.

Detailed neurological examination is done for all patients that include inspection for neurocutaneous markers, head circumference measurement, assessment of higher functions, examination of cranial nerves, eyes, tone, reflexes, examination of cerebellar system etc. Detailed history of antenatal period and perinatal period was included. The corrected gestational age was calculated for preterms and assessed accordingly. The rate of development, family pattern of development were also taken into consideration.

Engels seizure burden score was estimated to detail the seizure frequency and disability. Score of 6-12 is associated with disability and intractability. Newborns Denver score (0-6 years) was employed to assess the neurological developmental history. Global developmental delay implies a delay that is more than 2 standard deviation below the mean for chronological age in 2 or more than two developmental domains, in children <5 years of age.

Relevant investigations was done like CSF analysis, metabolic screenings for urine and serum samples to identify inborn errors of metabolism, EEG, cerebral imaging like MRI and CT scan of brain were done in the patients. During the study period, 31 patients with idiopathic cause of refractory seizures with normal and abnormal phenotype were randomly selected and subjected to karyotyping which was done by collecting the venous blood in aseptic manner after informed consent (Confirm the number of idiopathic cases).

The collected data was entered in MS Office Excel spread sheet and were analyzed by using SPSS- version 20.0. P values less than 0.001 were considered as statistically significant.

RESULTS

A total of 152 patients with incidence of refractory epilepsy were included in the study. Male dominance was observed in the study. Children of age less than 3 years were the major proportion with refractory epilepsy in our study. 27 (17.8%) children were under the age of 6 months-1 year, 39 (25.7) were under 1-3 years, 37 (24%) were under the age group of 3-6 years and 6-10 years each and 14 were under >10 years.

Table 1 presents the demographic and possible etiological factors associated with recurrent seizures. In this study age of onset of seizures was found to be more in children of age group less than 1 year (54.6%) and the difference compared to other age groups was found to be highly significant (p<0.001). Generalized seizure type (48%) was the most frequent type, followed by focal seizures (40%). Multiple seizures was the third most common type (38%) followed by myoclonic seizures (28%) and infantile seizures (11%). 100 (69.79%) patients had seizures irrespective of the time. Diurnal occurrence was noted in 26 (17.11%) patients and 25 (16.45) were nocturnal. Out of the total 152 children with recurrent epilepsy, 64 showed significant behavioral disturbance. Out of 64 patients 33 had ADHD, 31 were found to have hyperactivity, ASD and stereotypic behavior. Of the total 152, 104 (68.4%) patients were found to have global developmental delay, with onset prior to starting of AED’s.
Table 1: Demographic characteristics and risk factors determining recurrent epilepsy among study population (n=152).

| Variables                          | Number of patients (N) | Percentage (%) |
|-----------------------------------|------------------------|----------------|
| **Sex**                           |                        |                |
| Males                             | 102                    | 67             |
| Females                           | 50                     | 33             |
| **Age in years**                  |                        |                |
| 6 months - 1 year                 | 27                     | 17.8           |
| 1-3 years                         | 39                     | 25.7           |
| 3-6 years                         | 37                     | 24             |
| 6-10 years                        | 37                     | 24.3           |
| >10 years                         | 14                     | 9.2            |
| **Age of onset of recurrent seizures** |                    |                |
| <1 year                           | 83                     | 54.6           |
| 1-5 years                         | 45                     | 29.6           |
| >5 years                          | 24                     | 15.8           |
| **Type of seizure**               |                        |                |
| Idiopathic                        | 31                     | 20.3           |
| Secondary                         | 121                    | 79.6           |
| **Seizure semiology**             |                        |                |
| Multiple seizures                 | 58                     | 38             |
| Infantile                         | 16                     | 11             |
| Myoclonic                         | 42                     | 28             |
| Generalized                       | 73                     | 48             |
| Focal                             | 60                     | 40             |
| **Timing of seizures**            |                        |                |
| Nocturnal                         | 25                     | 16.45          |
| Diurnal                           | 26                     | 17.11          |
| Any time                          | 101                    | 66.4           |
| **Behavioural disturbance**       |                        |                |
| Present                           | 64                     | 42.2           |
| Absent                            | 88                     | 57.8           |
| **Developmental delay**           |                        |                |
| Present                           | 104                    | 68             |
| Absent                            | 48                     | 32             |
| **Febrile seizures**              |                        |                |
| Present                           | 55                     | 36.2           |
| Absent                            | 97                     | 63.8           |
| **Status epilepticus**            |                        |                |
| Present                           | 69                     | 45             |
| Absent                            | 83                     | 55             |
| **Neuroabnormality**              |                        |                |
| Present                           | 100                    | 66             |
| Absent                            | 52                     | 34             |
| **Microcephaly**                  |                        |                |
| Present                           | 58                     | 38             |
| Absent                            | 94                     | 62             |
| **EEG**                           |                        |                |
| Abnormal                          | 126                    | 83             |
| Normal                            | 26                     | 17             |
| **CT scan brain**                 |                        |                |
| Abnormal                          | 82                     | 53.9           |
| Normal                            | 70                     | 46.05          |
| **MRI**                           |                        |                |
| Abnormal                          | 106                    | 69.7           |
| Normal                            | 46                     | 30.2           |
Febrile seizures were documented in 55 (36.2%) children. Status epilepticus was found in 69 (45.4%) patients. Most common neuroabnormalities noticed were quadriplegia, hemiplegia and paraparesis/paraplegia (37) followed by visual disturbance (20), hearing disturbance (11), aphasia/speech disturbance (18), movement disorder (12), and hypotonia (17) (Figure 1).

Microcephaly was seen in about 38%, which was associated with cerebral atrophy in the CT scan and MRI reports. Abnormal EEG was seen in 83% of the patients which is a consistent predictor of refractory epilepsy. Abnormal CT and MRI brain scan was found in 70% patients.

History of perinatal injury (64), multiple risk factors (57) and neonatal seizures (53) were identified as predominant risk factors (p<0.001) (Figure 2).

Table 2: Analysis of risk factors determining the variables among study population (n=152).

| Variables                                | Number of patients (N) | Percentage |
|------------------------------------------|------------------------|------------|
| Malesex                                  | 104                    | 67.1       |
| H/o age of onset <1year                  | 83                     | 54.6       |
| Type of these seizures                   |                        |            |
| Generalised                               | 71                     | 46.7       |
| Myoclonic                                 | 43                     | 28.3       |
| Infantilepsams                            | 17                     | 11.2       |
| Developmental delay                      | 107                    | 70.4       |
| H/operinatal injury                      | 64                     | 42.1       |
| Neonatal seizures                        | 53                     | 34.9       |
| Multiplerisk factors                     | 58                     | 38.15      |
| CN S congenital anomalies                | 19                     | 12.5       |
| Degenerative disorders/ IEM              | 19                     | 12.5       |
| Microcephaly                             | 58                     | 38.2       |
| Neuro abnormality                        | 100                    | 68.4       |
| EEG (abnormal)                           | 129                    | 84.9       |
| MRI (abnormal)                           | 106                    | 69.7       |
| Seizurescore (>1-3/day)                  | 31                     | 20.4       |
| Behavioral disturbance                   | 65                     | 42.8       |
| H/febrileseizures                        | 59                     | 38.8       |
| H/ostatusepilepticus                     | 65                     | 42.8       |

In this study the differentiation in sex distribution, age of onset of seizures, type of seizures; incidence of developmental delay, risk factors, neuro-abnormalities, and prevalence of abnormal EEG, MRI, and seizure scores (>1-3/day) was found to be statistically significant.
with incidence of recurrent epilepsy in the study population. No significant association was observed between occurrence of recurrent epilepsy and Presence of behavioral abnormalities, history of febrile seizures and status epilepticus among the study population (Table 2).

Engel’s seizure score was also obtained from the questionnaire and this showed the association of high seizure score with RE. Seizure score of 5 and 9 were commonly observed. Seizure score of 9, 10, 11 were associated with myoclonic and infantile spasms (Figure 3).

In this study, out of 31 patients, who underwent karyotyping, leucocyte for analysis could not be cultured in 3 patients as there was contamination and hence repeated. All the other 28 patients had a normal karyotyping. One had short Y (46XY a) chromosome which was a normal variant. (Confirm number of patients who underwent Karyotyping).

**DISCUSSION**

The assessment of the risk factors plays an important role in the diagnosis, which is the first step in the management of refractory seizures. The factors that determine the outcome of RE are varied age of onset, seizure type, ictal, post-ictal phenomena etc. The patients affected by drug resistant epilepsy have an increased frequency of co-morbid conditions, psychological dysfunction, stigmatization, poor quality of life and high risk of mortality and finally, reduced life expectancy.7

The basic factor that determines the prognosis is the underlying aetiology. Identification of the risk factors helps in proper management and prognostications. So it is important to ascertain the type of seizures, localization of the epileptogenic zone, sequence of event, age of onset, sex, perinatal insults, history of status epilepticus etc. Investigations like EEG, MRI, CT scan, TMS, UMS, karyotyping to aid the same. This serves as an important tool in the management of RE.

In this study, male gender was predominantly affected (67.1%) which is in agreement with Akhoundian et al.9 The age of onset of seizures were observed predominantly in infants (54.6%) and in children aged 1-5 years (29.6%). This was similar to Berg et al and Malik et al.9,10

In this series, motor phenomena in the form of generalized tonic-clonic seizures was documented in 48 patients, tonic posturing and versive head-turning in about 23 patients, myoclonic in 43 and infantile spasm in 17 patients. Generalized seizure type had the worst prognosis which was similar to Berg et al study.9

In this study, developmental delay was noticed in 68% patients. This was in accordance with previous studies of Udhani et al.11 P value in this study was significant <0.001, which proves its association with refractory epilepsy.

In this series, out of the 152 children studied, 64 patients had behavioral disturbances. Majority (33) had ADHD and another set of patients (31) had hyperactivity, autism and stereotypic behaviors. Children from 6 months to 1 year (27) children were not assessed (17.8%) and 61 patient had no behavioral symptoms. Prevalence of behavioral disturbances is more in male patients and almost all female children seen with behavioral disorder were associated with ADHD. But in this study, no signification association was seen with the behavioural abnormality and the incidence of RE. This was similar to the studies of Datta et al.12

Febrile seizures were present in 55 patients (36.2%) in this study. The association of febrile seizures with refractoriness is controversial according to Tripathy et al.13 They observed febrile seizures as an independent factor. Status epilepticus was found in 68 patients (44.7%) but no significant association was observed with RE. This was in accordance with studies Malik et al.10

In this study, perinatal insult (64) multiple risk factor (58), neonatal seizures (53) were the identified as the major association factors with RE. Perinatal insult was the predominant independent risk factor followed by neonatal seizures. These observations were in association with the studies of Hauser et al.14

Microcephaly was seen in 58 (76%) of the patients with RE with no significant association with incidence of RE (p<0.04). Abnormal neuro examination was seen in 100 patients with no deficits in 52 patients presenting a strong association with RE (p<0.001). This was accepted by Berg et al, Udani et al and Tripathi et al.9,11,13

Abnormal EEG was associated with poor outcome which was seen in 126 patients (84%, p value <0.001). This was in association with previous studies.9,11

Multiple seizure frequency is a red flag sign for the treating physician. In this study, Engel’s seizure score was also taken as a parameter, to study the burden of RE. In this study, all the patients presented with high seizure score; out of which seizure score >10/day without status epilepticus were associated with cluster of spasms and is also the worst prognosticating factor. p value showed significance value <.01. This is similar to the study of Berg et al.9

Karyotyping helps in identification of rare and common copy number changes associated with different diseases. Large and recurrent microdeletions at 15q13.3, 16p13.11 and 15q11.2 genes can be considered as substantial risk factors for epilepsy.15 In the current study karyotyping was done for all patients with idiopathic cause of RE with normal phenotype and with dysmorphism. Karyotyping was done in 31 patients. No abnormalities in chromosomes were detected in the study (Confirm the number of idiopathic cases).
CONCLUSION

The assessment of the risk factors plays an important role in the diagnosis, which is the first step in the management of refractory seizures. The factors that determine the outcome of RE are varied age of onset, seizure type, ictal, post-ictal phenomena etc. The patients affected by drug resistant epilepsy have an increased frequency of co-morbid conditions, psychological dysfunction, stigmatization, poor quality of life and high risk of mortality and finally, reduced life expectancy.7

The basic factor that determines the prognosis is the underlying aetiology. Identification of the risk factors helps in proper management and prognostication. So it is important to ascertain the type of seizures, localization of the epileptogenic zone, sequence of event, age of onset, sex, perinatal insults, history of status epilepticus etc. Investigations like EEG, MRI, CT scan, TMS, UMS, karyotyping to aid the same. This serves as an important tool in the management of RE.

In this study, male gender was predominantly affected (67.1%) which is in agreement with Akhoundian et al.5 The age of onset of seizures were observed predominantly in infants (54.6%) and in children aged 1-5 years (29.6%). This was similar to Berg et al and Malik et al.9,10

In this series, motor phenomena in the form of generalized tonic-clonic seizures was documented in 48 patients, tonic posturing and versive head-turning in about 23 patients, myoclonic in 43 and infantile spasm in 17 patients. Generalized seizure type had the worst prognosis which was similar to Berg et al study.9

In this study, developmental delay was noticed in 68% patients. This was in accordance with previous studies of Udhani et al.11 P value in this study was significant <0.001, which proves its association with refractory epilepsy.

In this series, out of the 152 children studied, 64 patients had behavioral disturbances. Majority (33) had ADHD and another set of patients (31) had hyperactivity, autism and stereotypic behaviors. Children from 6 months to 1 year (27) children were not assessed (17.8%) and 61 patient had no behavioral symptoms. Prevalence of behavioral disturbances is more in male patients and almost all female children seen with behavioral disorder were associated with ADHD. But in this study, no significant association was seen with the behavioural abnormality and the incidence of RE. This was similar to the studies of Datta et al.12

Febrile seizures were present in 55 patients (36.2%) in this study. The association of febrile seizures with refractoriness is controversial according to Tripathi et al.13 They observed febrile seizures as an independent factor. Status epilepticus was found in 68 patients (44.7%) but no significant association was observed with RE. This was in accordance with studies Malik et al.10

In this study, perinatal insult (64) multiple risk factor (58), neonatal seizures (53) were the identified as the major association factors with RE. Perinatal insult was the predominant independent risk factor followed by neonatal seizures. These observations were in association with the studies of Hauser et al.14

Microcephaly was seen in 58 (76%) of the patients with RE with no significant association with incidence of RE (p<0.04). Abnormal neuro examination was seen in 100 patients with no deficits in 52 patients presenting a strong association with RE (p<0.001). This was accepted by Berg et al, Udani et al and Tripathi et al.9,11,13

Abnormal EEG was associated with poor outcome which was seen in 126 patients (84%, p value <0.001). This was in association with previous studies.9,11

Multiple seizure frequency is a red flag sign for the treating physician. In this study, Engel’s seizure score was also taken as a parameter, to study the burden of RE. In this study, all the patients presented with high seizure score; out of which seizure score >10/day without status epilepticus were associated with cluster of spasms and is also the worst prognosticating factor. p value showed significance value <.01. This is similar to the study of Berg et al.9

Karyotyping helps in identification of rare and common copy number changes associated with different diseases. Large and recurrent microdeletions at 15q13.3, 16p13.11 and 15q11.2 genes can be considered as substantial risk factors for epilepsy.15 In the current study karyotyping was done for all patients with idiopathic cause of RE with normal phenotype and with dysmorphism. Karyotyping was done in 31 patients. No abnormalities in chromosomes were detected in the study (Confirm the number of idiopathic cases).

Funding: No funding sources
Conflicting interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Forsgren L. Incidence and prevalence. In: Wallace SJ, Farrell K, Eds. Epilepsy in children. 2nd Ed. Arnold, London;2004:21-25.
2. Yilmaz BS, Okuyaz C, Komur M. Predictors of Intractable Childhood Epilepsy. Paediatr Neurol. 2013;48(1):52-5.
3. Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch Study of Epilepsy in Childhood. Brain. 2004;127(Pt 8):1774-84.
4. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rappaport S, Beckerman B. Early development of
intractable epilepsy in children: A prospective study. Neurology. 2001;56:1445-52.
5. Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: A case-control study. Epilepsia. 1996;37:24-30.
6. Ohtsuka Y, Yoshinaga H, Kobayashi K. Refractory childhood epilepsy and factors related to refractoriness. Epilepsia. 2000;41:147.
7. Dalic L, Cook MJ. Managing drug-resistant epilepsy: challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:2605-16.
8. Akhondian J, Heydarian F, Jafari SA. Predictive factors of pediatric intractable seizures. Arch Iran Med. 2006;9:236-9.
9. Berg AT, Levy SR, Testa FM, Shinnar S. Treatment of newly diagnosed pediatric epilepsy: a community-based study Arch pediatr Adolesc Med. 1999;153:1267-71.
10. Malik MA, Hamid MH, Ahmed TM, Ali Q. Predictors of Intractable Childhood Epilepsy. J College Phy Surg Pak. 2008;18(3):158-62.
11. Udhani V. Paediatric Epilepsy- An Indian Perspective. Indian J Paeditr. 2005;72:309-13.
12. Datta SS, Premkumar TS, Chandy S, Kumar S, Kirubakaran C, Gnanamuthu C, et al. Behaviour problems in children and adolescents with seizure disorder: Associations and risk factors. Seizure. 2005;14:190-7.
13. Tripathi M, Vibha D, Bhatia R, Srivastava MVP, Singh MB, et al. Predictors of refractory epilepsy in North India: A case–control study. Seizure. 2011;20(10):779-83.
14. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia. 1994;35(2):1-6.
15. Mulley JC, Mefford HC. Epilepsy and the new cytogenetics. Epilepsia. 2011;52(3):423-32.

Cite this article as: Gowrinathan TG, Kumar SA. Risk factors for childhood refractory epilepsy in a tertiary care centre, Chennai, India. Int J Contemp Pediatr 2019;6:1432-8.