

Risk factors of childhood epilepsy in Kerala

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Abstract

Background: We aimed to identify the risk factors for epilepsy in children. **Materials and Methods:** This case-control retrospective study was carried out in the pediatric neurology outpatient service of the Trivandrum Medical College. All children (1–12 years) with epilepsy satisfying the selection criteria were included, after obtaining consent from parents. Those with single seizures or febrile seizures were excluded. Controls were children without epilepsy attending the same hospital. Parents were interviewed and clinical data were obtained from medical records. Statistical analysis included chi-square test, odds ratio (OR), and logistic regression. **Results:** There were 82 cases and 160 controls whose mean age was 6.9 + 3.6 and 5.2 + 3.1, years respectively. On univariate analysis, family history of epilepsy, prolonged labor, cyanosis at birth, delayed cry after birth, admission to newborn intensive care unit, presence of congenital malformations, neurocutaneous markers, incessant cry in the first week, delayed developmental milestones, meningitis, encephalitis, and head trauma were found to be significant. On logistic regression, family history of epilepsy (OR 4.7), newborn distress (OR 8.6), delayed developmental milestones (OR 12.6), and head trauma (OR 5.8) were found to be significant predictors. Infants who had history of newborn distress are likely to manifest epilepsy before 1 year if they are eventually going to have epilepsy (OR 3.4). **Conclusion:** Modifiable factors such as newborn distress and significant head trauma are significant risk factors for childhood epilepsy. Newborn distress is a risk factor for early-onset (<1 year age) epilepsy.

Key Words

Epilepsy, Kerala, risk factor

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*Ann Indian Acad Neurol 2011;14:000-000****

Introduction

Epilepsy is a common neurological disorder that affects nearly 6 lakhs children under 14 years of age in the Kerala state. The incidence of epilepsy is highest at very young age and extreme old age. Epilepsy carries much stigma so that people with epilepsy are unable to lead a normal life. The economic burden of epilepsy is very high. Children with epilepsy often experience the double burden of learning disability, cognitive impairment, and poor scholastic performance. Perinatal insults such as hypoxia, metabolic derangement, and central nervous system (CNS) infections are important modifiable risk factors of epilepsy. Unfortunately there are little data from India on the risk factors for epilepsy in children. There are several methodological limitations for epidemiological studies on epilepsy in developing countries.^[1] Perinatal factors have been suspected to predispose to childhood epilepsy. But

the observations in epidemiological studies had been rather negative or conflicting.^[2] A door to door survey in West Bengal failed to reveal any association between perinatal insult and childhood epilepsy, whereas another similar study in Kerala state supported an association between the two. A population-based survey in Northern district of Kerala state had shown that identification of such risk factors for epilepsy in children would be the first step in the direction of prevention of epilepsy.

It is likely that precise identification of the risk factors for epilepsy would enable us to develop strategies to prevent it. Our objective in this study was to ascertain the risk factors in a hospital cohort of children with epilepsy in comparison to matched control children.

Materials and Methods

This study was carried out in the Departments of Community Medicine and Pediatric Neurology of Government Medical College, Trivandrum. The study period was from November to December 2007. We followed a case-control design in which cases were children with epilepsy and controls were children without epilepsy, both attending to the Medical College Hospital. Informed consent was obtained from the guardians of the children. We included all consecutive children aged 1–12 years attending to the hospital and having two or more

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Quick Response Code: 	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.91950

unprovoked seizures within the previous 5 years. Children with febrile seizures only, those with other major comorbidities (significant mental subnormality, systemic diseases, etc.), and those who were unwilling to participate in the study were excluded. Controls were children aged between 1 and 12 years without epilepsy attending the same hospital.

With regard to the various risk factors, we used the following operational definitions: (a) stay in the new born intensive care unit for 1 or more days as indicator of advanced resuscitation of the newborn; (b) history of significant head trauma: A witnessed or documented head trauma associated with amnesia or loss of consciousness; (c) history of CNS infection: Documented history of meningitis or encephalitis confirmed by CSF examination; (d) neurocutaneous markers: presence of Café-au-lait spots, ash leaf macules, or shagreen patches; (e) newborn distress: Presence of any two of the following: (i) delayed cry after birth, (ii) prolonged labor more than 6 hours, (iii) meconium stained amniotic fluid, (iv) bluish color, (v) incessant cry, and (vi) need for newborn resuscitation.

We interviewed the parents of children with a structured questionnaire that was prepared through several discussions and modification after a pilot study. The clinical data of the children were abstracted from their medical records. All the data were exported to an Excel spreadsheet and were analyzed with SPSS for windows version 12.0. Odds ratio (OR) with 95% confidence interval (CI) and chi-square test were used to analyze the univariate factors. *T*-test was used to compare group means. Logistic regression was used to identify the major risk factors.

Results

In this study, we had enrolled 82 children with epilepsy and 160 control children. Cases had a higher mean age 6.9 + 3.6 years (95% confidence interval [CI] 5.2–8.4) when compared with controls where the mean age was 5.2 + 3.1 years (95% CI). The difference in age between the two groups (1.8 years) was significant (95% CI = -2.63 to -0.886; $P < 0.01$). The proportion of boys within the cases (50%) was not statistically significantly different ($P = 0.2$) from that within the control group (59%). The maternal age for the cases (25.2 + 5.2 years) was not significantly different from that of controls (24.3 + 3.3 years). The difference in mean maternal age between cases and controls (1.7 years) was not significantly different (95% CI -2.04 to -0.12; $P = 0.08$). The cases and controls had similar birth weight (2.7 + 0.7 kg and 2.8 + 0.49 kg), and the difference was not statistically significant (95% CI -0.05 to 0.25; $P = 0.2$). The age of onset of epilepsy was 3.3 + 3.2 years [Table 1].

Univariate analysis

In the univariate analysis, family history of epilepsy, history of previous abortions in the mother, prolonged labor, delayed cry at birth, bluish skin at birth, admission to the newborn intensive care unit, newborn distress, presence of CNS malformation, incessant cry in the first week of life, presence of neurocutaneous markers, CNS infections, developmental delay, and significant head trauma were found to have significant association with epilepsy.

We carried out a logistic regression in which these factors were modeled against a dependent variable of presence of active epilepsy.

In this analysis [Table 2], the model explained 40–56% of the variation (Cox and Snell $R^2 = 0.402$, Nagelkerke $R^2 = 0.557$) in outcome. Head trauma, developmental delay, newborn distress, and family history were the only four significant risk factors for epilepsy. The OR for the risk epilepsy and the relative importance of each variable were as follows: Newborn distress 8.6, 26.24, developmental delay 12.69, 22.2, and head trauma 5.8, 10.62 [Table 2].

There was significant association between age of onset of epilepsy and history of newborn distress. There were 30 children with age of onset earlier than 1 year (24 of them had history of newborn distress) and 50 with age of onset later than 1 year (27 of them had history of newborn distress). Those who had onset of epilepsy earlier than 1 year of age had

Table 1: Comparison of children with epilepsy and those without epilepsy

Parameter*	Case	Control	OR	CI	P
Consanguinity	11	31	0.65	0.31–1.36	0.164
Family history of epilepsy	24	15	4.0	1.96–8.16	0.000
Maternal ante natal infection	6	7	1.73	0.56–5.31	0.25
Previous abortions	12	8	3.3	1.27–8.32	0.02
Maternal hypertension	8	11	1.46	0.57–3.80	0.291
Gestational diabetes	5	4	2.53	0.66–9.7	0.149
Antenatal drug exposure	4	3	2.68	0.59–12.23	0.179
Maternal addictions	0	1	0.99	0.98–1.0	0.66
Pre-/postterm delivery	11	12	0.52	0.22–1.24	0.107
Prolonged labor >6 hours	27	10	7.5	3.4–16.52	0.000
Cesarean section	16	41	1.42	0.74–2.72	0.42
Delayed cry	15	5	7.05	2.46–20.18	0.000
Meconium stained amniotic fluid	3	4	1.5	0.33–6.87	0.436
Abnormal fetal presentation	1	7	0.23	0.04–2.50	0.564
Bluish at birth	8	4	4.27	1.25–14.65	0.017
Incessant cry in first week	24	6	11.0	4.27–28.31	0.000
Admission to newborn intensive care unit	23	11	5.38	2.45–11.64	0.000
Newborn distress	52	15	16.76	8.35–33.6	0.000
CNS malformation	9	2	9.67	2.04–45.92	0.001
Developmental delay	40	6	25.0	9.93–63.13	0.000
CNS infection	12	9	2.88	1.16–7.14	0.019
Significant head trauma	17	10	3.92	1.71–9.03	0.001
Head surgery	0	1	0.99	0.98–1.01	0.661
Neurocutaneous markers	9	5	3.99	1.29–12.33	0.014

CNS: Central nervous system, CI Confidence interval, OR= Odds ratio; $P = P$ value, *Number of subjects who have responded positively to the respective questions only is enumerated. OR with 95% CI and P -value for chi-square tests

Table 2: Logistic regression of selected predictors of childhood epilepsy

	Intercept	Standard error	Wald	df	Significance	Odds ratio
Head trauma	1.758	0.540	10.615	1	0.001	5.800
Developmental delay	2.541	0.539	22.211	1	0.000	12.687
Newborn distress	2.157	0.421	26.237	1	0.000	8.642
Family history	1.567	0.473	10.993	1	0.001	4.791
Constant	-2.372	0.285	69.231	1	0.000	0.093

significantly higher frequency of newborn distress (OR 3.41, 95% CI 1.19–9.77, $P=0.016$).

Discussion

Strength of the study

We adopted a case-control design for this study in order to identify important risk factors for epilepsy in children who attend to hospital for treatment. Case-control design is a convenient technique to identify risk factors wherein risk factors could be examined retrospectively in a well-defined sample of cases. The setting of a major teaching hospital with a large epilepsy cohort provided a wide range of well-characterized epilepsy syndromes to study. Most of the data could be corroborated with the medical records to confirm the accuracy. We examined four broad categories of risk factors for epilepsy, viz (1) familial clustering, (2) maternal factors, (3) perinatal factors, and (4) postnatal factors. In our univariate analysis, we found several factors to have significant association with epilepsy. Nevertheless, on logistic regression analysis, only head trauma, delayed developmental milestones, newborn distress, and family history were the significant risk factors for epilepsy. Together they accounted for 40% of the risk of childhood epilepsy.

The OR for family history of epilepsy as a risk factor of epilepsy was 3.75 in this study. A family history of epilepsy was a risk factor with the least influence ($\beta=1.32$). Most of the syndromes under epilepsy are considered to be a polygenic in etiology. A recent study of genetic liability to epilepsy based on analysis of three-generation pedigree also had shown similar OR for positive family history (3.17 with 95% CI 2.12–4.73).^[3] Neurocutaneous markers are also pointers to phakomatoses, a group of hereditary disorders often associated with epilepsy. There were 13.4% prevalence of consanguinity in the epilepsy group which was comparable to that in the control group ($P=0.164$). According to the National Family Health Survey data, frequency of consanguinity in India ranged from 15.9 to 32.9 (mean 22.2%),^[4] yet its frequency is much less in Kerala state^[5] Consanguinity leads to an increase in the incidence of monogenic recessive disorders including epilepsy.

Maternal factors such as consanguineous marriage, age of the mother at delivery, history of recurrent abortions, maternal infections during pregnancy, hypertension during pregnancy, gestational diabetes mellitus, and history of specific drug intake during pregnancy were not found to be associated with development of epilepsy.

The role of perinatal factors in the pathogenesis of epilepsy remains elusive. These are important risk factors that can be potentially minimized by better antenatal and obstetric care. In Kerala state all births take place under medical supervision

(98.5% attended by a doctor).^[6] Several community-based studies have failed to demonstrate any causal relationship between perinatal insult and occurrence of epilepsy. The national collaborative perinatal project that followed up more than 54,000 children for 2 years indicated that congenital malformations of the fetus (cerebral and noncerebral) rather than perinatal insult are risk factors for nonfebrile seizures in children. According to this study, prenatal, labor, and delivery factors appeared to contribute very little to childhood seizure disorders.^[7] The Rochester study also had shown similar findings.^[8] According to a cohort study in United Kingdom^[9] (17,414 children followed up until 23 years of age), the etiology was birth trauma for 2% of cases. The other important causes were congenital malformations (9%), CNS infections (6%), and head injury (9%). In our study, higher proportion of children had these etiological factors: Congenital defects (11%), CNS infections (14.6%), and head injury (20.7%). Nevertheless, several hospital-based case-control studies and smaller community-based studies suggest that perinatal insult to brain may be a risk factor for epilepsy. According to a hospital-based case-control study in Turkey, neurological impairment, history of atypical febrile seizures, severe head injury, and a low Apgar score were the most important risk factors for epilepsy in children.^[10] On the contrary, a study from Chandigarh, India,^[11] did not confirm reproductive factors as risk factors for epilepsy. A case-control study from Germany^[12] showed that elderly mother, previous abortions, eclampsia, low birth weight, asphyxia, and post maturity were associated with epilepsy. An Italian follow-up study^[13] recognizes asphyxia and neurological syndromes to be important in developing epilepsy in children. Another incident case-control study from Sweden^[14] had shown that maternal hypertension (OR 4.8), Apgar score <6 (OR 3.8), abnormal gestational age (OR 6.7), and caesarean section (OR 18) were associated with childhood epilepsy. Our study, however, did not find maternal hypertension, abnormal gestational age, and caesarean section to be associated with epilepsy.

The setting of this study to a tertiary referral center and the relatively small sample size are limitations of this study. The differences in the observations between large population-based prospective studies and smaller hospital-based case-control studies could be partly be due to methodological issues and differences in samples. Further, societies with higher medical services where optimal antenatal and obstetric care are prevalent for several decades, it is likely that perinatal factors may not contribute significantly to childhood epilepsy. In contrast to this, societies with low socioeconomic background and poor antenatal and obstetric care are likely to experience more perinatal damage leading to epilepsy. In a Chinese study,^[15] perinatal factors were the most frequently found cause of epilepsy. A population-based survey in a Northern district of Kerala state^[16] showed that a history of perinatal complications,

low body mass index, and recent physical symptoms were independently associated with active epilepsy in children of 8–12 years of age.

We found that newborn distress had significant association with age of onset of epilepsy. The risk of newborn distress was 3.4 times higher in those with early onset (before 1 year of age) epilepsy. This can be a very useful clinical measure. A survey in Delhi^[17] showed that one third of infantile spasms were due to perinatal causes. In a Saudi Arabian study,^[18] perinatal factors accounted for 40% of etiology for those with epilepsy onset less than 5 years.

We found that head trauma is a significant, potentially preventable risk factor for childhood epilepsy. Positive family history for epilepsy, head trauma, febrile convulsions, and abnormal perinatal history were found to be risk factors for childhood epilepsy in a case–control study in Jordan.^[19] Severity of head trauma had been identified as an important predictor of future development of epilepsy.^[20]

Intrauterine infections, especially cytomegalo virus, were associated with epilepsy and cortical malformation.^[21] In our study, maternal infections were not found as a risk factor.

Conclusion

There are several limitations for this study that should be taken into consideration while interpreting the results. This was a hospital-based study with case–control design. A community-based case–control study is the ideal design to identify risk factors. There are several practical difficulties in undertaking such studies within a short period of time in India. Because this is a retrospective study, there is always a potential for recall bias.

In this study, we observed significant association between developmental delay, newborn distress, significant head trauma, and family history and childhood epilepsy. Those infants who had newborn distress are likely to manifest with epilepsy before one year of age if they are eventually going to have epilepsy. Conversely, newborn distress is an importance risk factor when the age of onset of epilepsy was less than 1 year.

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How to cite this article: Attumalil TV, Sundaram A, Varghese VO, Vijayakumar K, Mohammed Kunju PA. Risk factors of childhood epilepsy in Kerala. *Ann Indian Acad Neurol* 2011;14:283-6.

Received: 23-12-10, **Revised:** 08-03-11, **Accepted:** 16-05-11

Source of Support: Nil, **Conflict of Interest:** Nil