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# Predictors of Uncontrolled Seizure in Children Presenting in Tertiary Level Hospital in Nepal: A Prospective Study

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## ABSTRACT

### Introduction

About one third of the children with seizure do not achieve complete seizure control. We aimed to find the predictive factors for uncontrolled seizure in children.

### Methods

This prospective study was conducted from October 2018 to September 2020 at Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Children aged 12 months to 16 years with seizure and who were under regular follow up visits for at least once in past 3 months time were included and followed up for one year. Uncontrolled seizure was defined when seizure frequency was 2 or more in a year during the study period. Various factors were analyzed and when they were significantly different between the groups on bivariate analysis using the Chi square test, they were further analyzed with binary logistic regression model to find out the true predictors.

### Results

Total of 110 children were enrolled. Forty children (36.4%) had their seizure onset before one year of age. About one third of patient had family history of seizure. The most common type of seizure was generalized type (60%). Of the total, 56% had uncontrolled seizure.

Three true predictors of uncontrolled seizure were found. They were (i) age of onset before 12 months of age (OR 2.94; 95% C.I 1.32-6.55), (ii) abnormal findings in neuroimaging (OR 26.5; 95% C.I 8.72-80.07) and (iii) frequency of seizure (OR 40.9; 95% CI 9.05-184.9).

### Conclusion

Seizure onset in infancy, abnormal neuroimaging findings and frequent seizure are predictors for uncontrolled seizure in children. Thus, we suggest that these factors be considered while managing the children with seizure.

**Keywords**
*Children, Kathmandu, predictors, seizure, uncontrolled*

## INTRODUCTION

The lifetime prevalence of epilepsy is 7.60 per 1,000 people. About 4-10% children experience at least one seizure in first 16 years of life.[1,2] The incidence is highest during first year and decreases till teen age.[3]

International League Against Epilepsy (ILAE) has classified epilepsy according to its etiology in six subgroups: genetic, structural, metabolic, immune, infectious, and unknown. Sometimes tuberous sclerosis is classified as a genetic-structural etiology, and Leigh syndrome as a genetic-metabolic subgroup.[4] However, in about half, etiology could not be identified.[3]

Among all the children with seizure about two third achieve seizure free period for longer than 3 to 5 years. In about 10 - 30% of the patients even with appropriate trials of two anti-seizure drugs continue to have seizure, termed as refractory epilepsy.[5,6,7]

Children with refractory seizure are at risk of cognitive decline with behavioral and psychiatric problems, osteoporosis and sudden unexpected deaths.[8,9] Studies have found the association of refractory seizure with age of onset , remote symptomatic seizure, history of status epilepticus, level of intelligence, seizure type/frequency, neurological impairment and neuroimaging and electroencephalographic findings.[10,11,12,13,14] For our study purpose, we have defined seizure to be uncontrolled when seizure frequency was two or more in a year during the study period.

In Nepal, because of lack of trained human resources, limited knowledge of epilepsy, stigmatization, limited medical, surgical and diagnostic options, managing seizure is a challenge.[15] In such scenario, prediction of seizure control would be helpful to (i) plan treatment, (ii) counsel parents regarding duration/effectiveness of anti-epileptic drugs (AEDs) and (iii) find out the cause for non adherence to drugs.

Thus this current study was done with an objective to find out the predictors of uncontrolled seizure in children in a tertiary care hospital in Nepal.

## METHODS

In this cohort study, children were enrolled in a study entitled "Feasibility of telemedicine for the follow up of children with established seizure disorder- A tertiary care center prospective study". The study was set in Neurodevelopmental clinic of Pediatric Department of Tribhuvan University Teaching Hospital (TUTH), Kathmandu. Children aged 12 months to 16 years with seizure were first identified and if they visited for follow up at least once in 3 months time, were then enrolled in the study. Children with febrile convulsion and acute symptomatic seizures; children whose caretakers were not competent to use a smart phone and who were not confident to follow instructions to manage seizure at home according to advice provided by pediatrician through telemedicine were excluded from the study.

Total of 115 children were consecutively enrolled from October 1, 2018 to September 30, 2019. During enrollment, demographic and clinical information of the child and the families were obtained. Investigations such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) of head, Electroencephalography (EEG) and metabolic profile were obtained when indicated. All the children were treated with anti seizure medicines as per the hospital protocol.

These children were followed up monthly till one year by telephone calls. Children with developmental delays and with comorbid conditions were followed up at 6 and 12 months in hospital. For breakthrough seizures and other health issues, caregivers were advised to call the investigator directly or to bring the child to the hospital.

During monthly follow up calls, participants were asked about seizure recurrence and frequency, seizure semiology along with drug compliance and their adverse effects. Pediatrician, trained in child neurodevelopment performed the enrolment procedure and monthly follow up calls. All the seizures were classified using international classification of epileptic seizures proposed by ILAE.

To compare between controlled and uncontrolled group, the etiology was grouped into a) structural and infectious in one group; and b) genetic, metabolic and unknown into another group. The structural causes include stroke, trauma, cortical dysplasia and infectious cause included central nervous system infections like meningitis, encephalitis, and neurocysticercosis. Generalized genetic seizure, benign epilepsy of centro-temporal spikes, childhood absence epilepsy and epileptic encephalopathy including unknown causes were grouped in genetic seizure.

Uncontrolled seizure was defined when seizure frequency was two or more in a year during the study period. EEG is defined abnormal when the recording showed abnormal basic activities or epileptic discharges.

Decision on selection or continuation of particular AED was made on patient's seizure semiology and epilepsy syndrome. Commonly used AED were sodium valproate, leveteracetam, phenytion and clobazam. The name, dose, frequency, adverse effects of AEDs including plan for breakthrough seizure were written in patient's card. Whenever there was breakthrough seizure, inquiry about adherence was made and drug dose was escalated.

Caregivers were also counseled for hospital visit when necessary. They were also pre-informed to seek medical help in any nearby medical institution as deemed necessary in case of emergency such as status epilepticus. Safety precautions during seizure were also taught during recruitment.

The analysis was done using SPSS 20.0 software (Chicago, IL, USA). The factors that could potentially affect the final outcome were compared between the groups of children who achieved and who did not achieve seizure control. The factors that were significantly different between the groups on bivariate analysis using the Chi square test (P<0.05) were further analyzed with binary logistic regression model to find out the true predictors. P value of 0.05 was taken as cut off for statistical significance. The predictors considered for analysis were - age of onset below one year of age, frequent seizures (2 or more seizure in one year), developmental delay, abnormal neuroimaging, abnormal EEG reading, family history of seizure, etiology of seizure (structural or genetic) of seizure, need of polytherapy (more than one antiepileptic drugs) and type of seizure.

*Table 1. Baseline demographic and clinical characteristics of children*

| Characteristics | Values |
|---|---|
| Mean age in years (SD) | 8.1 (4.3) |
| Age group | |
| 1-5 | 31 (28.2) |
| 6-9 | 36 (32.7) |
| 10-16 | 43 (39.1) |
| Female child (%) | 41 (37.2) |
| Presence of developmental delay | 52 (47.3) |
| Onset of seizure before 1 year of age | 40 (36.4) |
| Seizure onset Type | |
| Focal | 40 (36.4) |
| Generalized | 66 (60) |
| Unclassified | 4 (3.6) |
| Etiology of seizure | |
| Structural | 42 (38.2) |
| Genetic | 45 (40.9) |
| Infectious | 14 (12.8) |
| Metabolic | 2 (1.8) |
| Unknown | 7 (6.3) |
| Abnormal Neuroimaging | 52 (47.3) |
| Abnormal EEG recording | 71 (64.5) |
| Number of AEDs | |
| 1 | 75 (68.2) |
| 2 | 19 (17.3) |
| 3 or more | 16 (14.5) |

The Institutional Review Committee approved the study for maintaining the privacy and confidentiality of telemedicine interaction such as seizure videos, images, chats, text message etc. The telemedicine consultation data were maintained as per American Academy of Pediatrics Telemedicine Act. Written consent was obtained from all the participants before the enrolment. Participants were free to discontinue the tele-consultation any time during the study and were encouraged to follow up in-person at the hospital even if they discontinue.

## RESULTS

Total of 115 children were enrolled in the study. Of them, five children lost to follow up thus excluded from the study. The mean age of the children was 8.1 (+ 4.3) years. About 40% were above 10 years of age (Table 2). The male: female ratio was 1.4:1. The mean age of mother and father was 32.2 ( + 8.9) and 37 (+ 9.2) years, respectively. About 37% of the mothers had education of upto Grade V and 54% of the mothers were house-wives. Forty children (36.4%) had their seizure onset before one year of age and 52(36.4%) had developmental delay at presentation. About one third of patient had family history of seizure. The most common type of seizure was generalized type (60%). In children who had structural and infectious etiology, most of them (77%) had controlled seizure and in genetic, metabolic and unknown cause similar proportion (77%) children had uncontrolled seizure. Neuroimaging was not available for 19 (17.3%) children and for those available almost half of children had abnormal findings. Similarly, only 3 (2.7%) children did not have EEG recording and almost two third of them had abnormal EEG recordings. Of the total children, 76 (69%) children were on mono-therapy and 42(67.7%) children

*Table 2. Demographic characteristics of parents*

| Characteristics | Mother | Father |
|---|---|---|
| Mean age in years | 32.2 (8.9) | 37 (9.2) |
| Education | | |
| Till grade 5 | 42 (37.8) | 27 (24.2) |
| Middle School | 24 | 14 (12.6 |
| High School | 33 | 52 (46.8) |
| Immediate or post high school diploma | 11 | 12 (10.8) |
| Graduate or above | 1 | 5 (4.5) |
| Occupation | | |
| Home maker/No Job | 60 (54) | 4 (3.6) |
| Daily wage earner | 2 (1.8) | 13 (11.7) |
| Agriculture | 22 (19.8) | 10 (9) |
| Employee | 26 (23.4) | 72 (64.9) |
| Migrant worker | 0 | 11(9.9) |

*Table 3. Possible risk factors of uncontrolled seizure*

| Factors | Controlled n=48 (%) | Uncontrolled n=62 (%) | Total n=110 |
|---|---|---|---|
| Age of seizure onset | | | |
| < 12 months | 24 (50) | 16 (25.8) | 40 (36.4) |
| > 12 months | 24 (50) | 46 (74.2) | 70 (63.6) |
| Development | | | |
| Normal | 30 (62.5) | 28 (45.2) | 58 (52.7) |
| Delayed | 18 (37.5) | 34 (54.8) | 52 (47.3) |
| Family history of seizure | | | |
| No | 23 (47.9) | 52 (83.9) | 75 (68.2) |
| Yes | 25 (52.1) | 10 (16.1) | 35 (31.8) |
| Type of seizure | | | |
| Focal | 18 (37.5) | 21 (33.9) | 39 (35.5) |
| Generalized | 30 (62.5) | 41 (66.1) | 71 (64.5) |
| Etiology | | | |
| Structural and infectious | 37 (77.1) | 14 (22.6) | 51 (46.4) |
| Genetic, metabolic and unknown | 11 (22.9) | 48 (77.4) | 59 (53.6) |
| Seizure frequency | | | |
| < 1 /year | 45 (93.7) | 22 (35.5) | 67 (60.9) |
| > 2/year | 3 (6.3) | 40 (64.5) | 43 (39.1) |
| Neuroimaging | | | |
| Not available | 4 (8.3) | 15 (24.2) | 19 (17.3) |
| Normal | 37 (77.1) | 7 (11.3) | 44 (40.0) |
| Abnormal | 7 (14.6) | 40 (64.5) | 47 (42.7) |
| EEG | | | |
| Not available | 1 (2.1) | 2 (3.2) | 3 (2.7) |
| Normal | 12 (25) | 21 (33.9) | 33 (30) |
| Abnormal | 35 (72.9) | 39 (62.9) | 74 (67.3) |
| No of AED | | | |
| 1 | 34 (70.8) | 42 (67.7) | 76 (69.1) |
| > 2 | 14 (29.2) | 20 (32.3) | 34 (30.9) |

in mono-therapy had uncontrolled seizure. The potential predicting factors were grouped into controlled and uncontrolled group. Bivariate analysis was performed between these groups and Chi square test was used to test the statistical significance of the difference (Table. 3).

The true predictors of uncontrolled seizure were (a) age of onset before 12 months of age, (b) abnormal findings in neuroimaging and (c) frequency of seizure as shown in Table 3.

Five children died during the study period. Three children had epileptic encephalopathy, one had sequelae of hypoxic ischemic encephalopathy and one had post meningitis sequelae.

*Table 4. True predictor of uncontrolled seizure in 110 participant children*

| Predictor | Odds ratio | p-value | 95% CI |
|---|---|---|---|
| Seizure onset before 1 year of age | 2.94 | 0.05 | 1.32 - 6.55 |
| Abnormal neuroimaging | 26.50 | <0.001 | 8.72 - 80.07 |
| Frequency of seizure | 40.91 | <0.001 | 9.05 - 184.98 |
| Etiology | 11.77 | 0.22 | 4.79 - 28.89 |
| Developmental delay | 1.95 | 0.35 | 0.91 - 4.20 |
| Family history of seizure | 0.17 | 0.29 | 0.07 - 0.42 |
| Number of AEDs | 1.21 | 0.89 | 0.54 - 2.74 |
| Abnormal EEG | 0.57 | 0.34 | 0.24 - 1.34 |
| Type of seizure | 1.20 | 0.37 | 0.55 - 2.63 |

## DISCUSSION

The current study explored the risk factors for uncontrolled seizure in children aged 12 months to 16 years of age in a tertiary level hospital in Nepal. Of total 110 children, 62 (56.3%) of the children had uncontrolled seizure at the end of one year follow up. The age of onset of seizure, abnormal neuroimaging findings and frequency of seizure were found to be the predictors of uncontrolled seizure. In our study, the proportion of uncontrolled seizure is high. This might be because there is no unanimous definition for uncontrolled seizure and at times uncontrolled and intractable seizure are used as synonyms. In our study we have defined uncontrolled seizure as two or more seizure during the study period of one year irrespective of number of AEDs the child is receiving.

Berg et al, in their study had defined intractable seizure when children had average of one seizure or more average of one seizure or more a month over a 2-year period and who, during that time, had failed trials of at least three different AEDs.[16] Similarly, Chawla et al had defined intractable seizure when children had one or more seizures per month over a period of 6 or more months and who had experienced trials of at least two different AEDs with adequate compliance.[13]

In our study, age of onset of seizure before one year of age was found to be one of predictors for uncontrolled seizure. Similar finding was reported by other studies where they have also found poor control of seizure when onset was during infancy.[17,18] In developing countries, perinatal asphyxia and infections like meningitis are common which might result in seizure.[19,20] In our study also, children who developed seizure before 12 months of age, many of them had asphyxia at the time of birth. Another independent risk factor was abnormal neuroimaging findings. There were almost equal number of children with normal and abnormal neuroimaging finding; however children with abnormal neuroimaging findings were found to have 26 times odds of having uncontrolled seizure. The most common pathological finding in our study was encephalomalatic changes, cortical dysplasia and mesial temporal sclerosis. Neuroimaging is important to find the etiology of seizure and also helps to plan the management and counsel the parents regarding the outcome of the seizure. The international guideline also recommends MRI for children whose seizure onset is before 2 years of age regardless of neurologic examination or seizure semiology except for simple febrile seizures.[21]

Among the total of 62 children with uncontrolled seizure, almost 70 % of children were on monotherapy. The finding is in contrast to the finding by Paudel et al, in which they have found that 70% of the children responded to monotherapy.[22] In our study, whenever parents reported uncontrolled seizure, the dose of the medicine was either increased or second drug was added or switched to the drug that was not used before. As drug level was not obtained for these medicines, it is difficult to say that uncontrolled seizures were drug resistant. There is also chance that the patient might be receiving wrong AED or suboptimal dose.[23] Another factors for uncontrolled seizure might be poor adherence. The poor adherence to the medication in epilepsy is common.[24] In our experience, we found parents have tendency to stop the medicines when seizure is controlled for sometime. Another reason for poor adherence might be because of unavailability of the medicine in their home- town and parents have to travel to cities. When the study was being conducted there was four months long lockdown due first wave of COVID 19 pandemic and children had missed their medications.

Family history of seizure, presence of developmental delay, type and etiology of seizure, EEG finding and number of AEDs did not predict the seizure control at one year follow up.

The strength of our study is that it is a prospective study and had tried to explore the potential risk factors for uncontrolled seizure and was able to find out the true risk factors for uncontrolled seizure. All the children were followed up every month via a telephone call. However, children were not assessed clinically for follow up. In cases where seizure were not controlled, dose of AEDs were increased and at times changed to other medications but whether parents understood the instructions or followed it is not known. To add to this the study had not explored whether children received optimal doses of the AEDs or not, the adherence to the drugs and drug level of AEDs is also not available before they can be labeled as refractory seizure.

## CONCLUSION

The true predictors of uncontrolled seizure in children are onset before one year of age, frequent seizure and abnormal neuroimaging findings. Thus, we suggest to consider these risk factors while managing and counseling the parents.

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## CONFLICT OF INTEREST

The author(s) declare that they do not have any conflicts of interest with respect to the research, authorship, and/or publication of this article.

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