Risk Factors of Intractable Epilepsy in Young Children Aged Less than 3-Year old

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Background: Epilepsy is one of the most common serious neurological disorders. Early onset epilepsy associated with significant co-morbidity that affecting a child's behavior, mood, social skills and ability to learn.

Objective: To determine the risk factors of intractable epilepsy in childhood epilepsy among aged less than 3 years old.

Method: This was a retrospective analytical case control study. Patient charts of all 1 - 36 months who had new-onset epilepsy from Bhumibol Adulyadej Hospital, Thailand between 1 January 2008 to 30 June 2019 were reviewed. Children were divided into two groups: Intractable and non intractable epilepsy.

Results: Total epilepsy 233 case. One hundred forty-five case was eliminate from the study (19 febrile convulsions, 126 not epilepsy). Eighty eight cases were included for statistical analysis. Intractable and non-intractable epileptic patients composed of 22 and 66 members, respectively. The cohort consisted of 51.14% (45/88) male, and 48.86% (43/88) female patients. Intractable epilepsy were found development delay at aged diagnostic 100% (22/22), perinatal complication 72% (16/22), preterm labor 18% (4/22), prior febrile seizure 36% (8/22), prior status epilepticus 54% (12/22), generalize epilepsy 63% (14/22), abnormal CT/MRI brain 81% (18/22), abnormal EEG 40% (4/22), first degree family epilepsy 4% (1/22).The 5 statistic significant predictors of intractable epilepsy included developmental delay at diagnosis, perinatal complication, prior status epilepticus, generalized epilepsy, abnormal CT/MRI brain. Multivariable logistic regression indicated that only generalized epilepsy was a predictor of intractable epilepsy.

Conclusion: Twenty five percent epileptic patients of age less than 3 years were medically intractable. A comprehensive risk factors of intractable epilepsy, namely developmental delay at diagnosis, perinatal complication of birth asphyxia, prior status epilepticus, generalize epilepsy, and structural brain abnormality seen as abnormal CT/MRI bran scan.

Keywords: Intractable epilepsy, Epilepsy, Young children

Introduction

Epilepsy is one of the most common serious neurological disorders in children and the highest incidence was found in the younger ages, with rates of 102.4 per 100,000 per year in the first year of life[1]. The World Health Organization and World Federal of Neurology identified epilepsy as the most severe brain disorder[2].In new cases of epilepsy in developed countries were found in babies and the elderly compared to old children and early adults in the developing countries[3]. The cause of this difference was due to different prevalence of disease etiology. Approximately 5–10% of the total population will have an unprovoked seizure[4].

Every year, an estimated of 3.5 million new epilepsy case are diagnosed. Forty percent are pediatric patients younger than 15 years. Epilepsy prevalence in Asia is between 1.5-14 people per 1000 people with high number in newborn and young children.

Prevalence reports of epilepsy in Thailand found higher prevalence of epilepsy yearly in children younger than 12 month[5]. Epileptic risk factors studies found that certain factors, i.e., male patient younger than 12 months, abnormal CT/MRI brain, and delayed developmental at the time of first epilepsy diagnosis were commonly found in epilepsy case[6]. Approximately 70% of Epilepsy patients can control their symptoms with medication. In the event that the patient's seizures do not respond to medication also known as intractable seizure or drug-resistant epilepsy is uncontrollable seizures By using two or more basic antiepileptic drugs at the appropriate dose and duration.

Early onset epilepsy associated with significant co-morbidity and affect a child's behavior, mood, social skills and ability to learn[7]. The importance of early recognition and effective therapy of intractable epilepsy in early childhood. As well as ongoing uncontrolled seizures may result in greater morbidity and mortality due to profound neurodevelopmental delay[8].

Pediatric patients in Bhumibol Adulyadej Hospital was diagnosed in the medical record data related to epilepsy in the past 10 years (2003) up to 370 people.

The goals of this study were to determine the risk factor of medical intractable epilepsy in children with onset of epilepsy before 36 months of age.

Materials and Methods

This was a retrospective analytical case control study. Patient charts of all one to thirty-six months who had new-onset epilepsy before 36 months of age in Bhumibol Adulyadej Hospital (BAH), Thailand between 1 January 2008 and 30 June 2019 were reviewed. The cases were identified by ICD 10 coding G400 - 409. This study protocol was approved by BAH Ethics Committee (IRB no.52/62) on 27 July 2019.

The participating populations were divided into two groups: Intractable epilepsy was case and non-intractable epilepsy was control.

Cases were diagnosed as intractable epilepsy and ascertained by screening complete diagnostic indexs during inpatient visit as well as at the time of outpatient and emergency room visit at BAH. Data screening by neurological pediatric physicians include1 January 2008 and 30 June 2019 chart followed up included data at least 6 months.

Control were children (1 month –3 years of age) were diagnosed epilepsy.

Definitions for epilepsy to be included in the investigation

Epilepsy was defined as at least two unprovoked seizures occurring greater than 24 hours apart or one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years and Epilepsy syndrome.(Definition of Epilepsy 2014, The International League Against Epilepsy (ILAE)[9].

Intractable epilepsy or Medical epilepsy was defined as: (1) failure of two or more antiepileptic drugs with seizure frequency of more than every 6 months in the year immediately before final follow-up, or (2) having undergone resective epilepsy surgery or callosotomy after failure of two or more antiepileptic agents) (Definition of Epilepsy 2014, The International League Against Epilepsy (ILAE)[9].

Statistic analysis

Estimated sample size for Two-independent proportion Formula.

Power = 0.8, 95% CI (Alpha) = 0.05

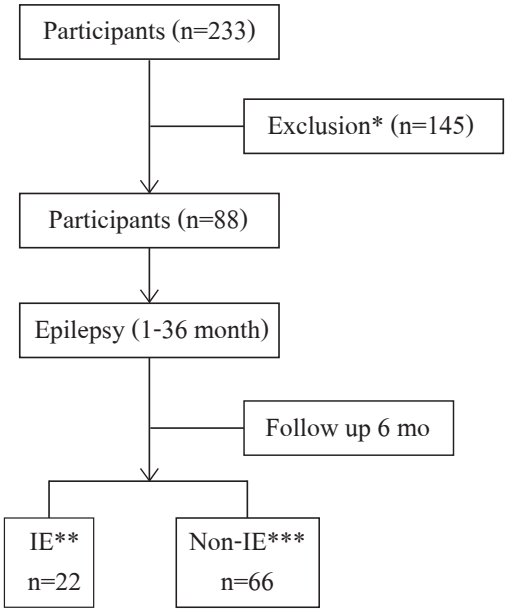
Data was analyzed by using SPSS version 27(IBM Corporation, NY, USA).

Data were described as frequency, and percentage. Children were divided into two groups, based on whether or not they had intractable epilepsy. Potential predictors were assessed by chi-square or odd ratio for categorical variables. The level of significance was set at $p<0.05$. Variables that were significantly associated with intractable epilepsy on univariate analysis were then entered into a logistic regression model.

Results

1. The participants

The total number of patients diagnosed with epilepsy 233 cases. One hundred forty-five cases was eliminated from the study, because 19 were febrile seizure, and 126 were not epilepsy. A total of 88 patients were included into the study after six months of follow-up, with the patients receiving dose and time appropriate medication. Twenty-two patients (25%) met criteria intractable epilepsy and 66 patients (75%) non-intractable epilepsy. The flow diagram was shown in Figure 1.



Figurel: Participant flow diagram

*Exclusion: Febrile convulsion 19, no diagnosis by pediatric neurologist 126

**IE: intractable epilepsy, ***non-IE: non-intractable epilepsy

2. Clinical characteristics

Eighty eight cases diagnosed with epilepsy consisted of 45 (51.14%) male, and 43 (48.86%) female patients. The median age was 9 months. Age at epilepsy diagnosis of 1 and 12 months represented the highest group of 67 patients (77%). We stratified age into ≤12 months versus >12 months. Intractable and non-intractable patients composed of 22 (25%) and 66 (75%) members, respectively.

Among the 22 cases with intractable epilepsy, development delay at aged diagnostic was 22 (100%), perinatal complication 16 (72%), preterm labor 4 (18%), prior febrile seizure 8 (36%), prior status epilepticus 12 (54%), generalize epilepsy 14 (63%), abnormal CT/MRI brain 18 (81%), abnormal EEG 4 (40%), first degree family epilepsy 1 person (4%).

Etiology of epilepsy was mostly structural 18 (81%). Structural brain abnormality were congenital brain anomaly 9 (focal cortical dysplasia 5/9, sturge weber 1/9, holoprosencephaly

2/9, lissencephaly1/9), traumatic brain injury 2 (subdural hemorrhage), birth asphyxia 7.

The group of one to twelve months, there were 18 (81%) and 49 (74%) intractable and non-intractable patients, respectively. The clinical data is shown in Table 1.

Table 1 Clinical characteristics (n=88)

Variable	Intractable epilepsy (n=22)*	Non-intractable epilepsy (n=66)*
Male	12(45)	33(50)
Age (mo)		
1-12	18(81)	49(74)
13-36	4(19)	17(26)
Developmental delay	22(100)	30(45)
Perinatal complication	16(72)	24(36)
Preterm labor	4(18)	13(19)
Prior febrile seizure	8(36)	20(30)
Prior status epilepticus	12(54)	6(9)
Generalize epilepsy	14(63)	60(90)
Etiology		
Structural	18(81)	20(43)
Genetic	2(9)	7(9)
Unknown	2(9)	39(48)
CT**/MRI*** brain		
Abnormal	18(81)	20(43)
Not done	2(9)	26(45)
EEG****		
Abnormal	4(40)	11(39)
Not done	12(54)	26(40)
Firstdegree family epilepsy	1(4)	10(15)

*n(%), **CT: computer Tomography, ***MRI: magnetic resonance imaging, ****EEG: electroencephalography

3. Potential risk factors for intractable epilepsy

Predictive Factors for medical intractability on univariate analysis from this study were shown in Table 2.

The five statistic significant predictors of intractable epilepsy included developmental delay at diagnosis (odd ratio 0.58, 95% confidence interval [CI] 0.46, 0.73, p = 0.03), perinatal complication (odd ratio 4.67, 95% confidence interval [CI] 1.61, 13.52, p = 0.03), prior status epilepticus (odd ratio 12, 95% confidence interval [CI] 3.67, 39.32, p = 0.01), generalized epilepsy (odd ratio 0.17, 95% confidence interval [CI] 0.05, 0.58, p = 0.02), and abnormal CT/MRI brain (odd ratio 13.00, 95% confidence interval [CI] 3.56, 33.25, p = 0.01). All five factors were entered into a multiple logistic regression model, the only one significant factor was generalized epilepsy (p = 0.02).

Table 2 Predictors of medical intractability (N=88)

Variable	Odds ratio (95%CI)	*p*-value	Multivariable logistic regression	
			Odds ratio (95%CI)	*p*-value
Male gender	1.20 (0.46,3.16	0.71		
Aged<12mo	1.46 (0.43,4.98)	0.537		
Developmental delayed	0.58 (0.46,0.73)	0.03	0.23 (0.02,4.33)	0.99
Perinatal complication	4.67 (1.61,13.52)	0.03	0.43 (0.03,5.73)	0.53
Preterm labor	0.90 (0.262,3.14)	1.00		
Prior febrile seizure	1.31 (0.48,3.63)	0.58		
Prior status epilepticus	12.00 (3.67,39.32)	0.01	0.53 (0.05,4.80)	0.57
Generalize epilepsy	0.17 (0.05,0.58)	0.02	21.11 (1.51,295.25)	0.02
Etiology	1.30 (0.46,3.89)	0.02		
Abnormal CT*/MRI** brain	13.00 (3.56,33.25)	0.01	0.13 (0.01,1.35)	0.99
Abnormal EEG***	1.20 (0.46,3.16)	0.97		
family history epilepsy	0.27 (0.03,2.21)	0.27		

*CT: Computer Tomography, **MRI: Magnetic Resonance Imaging (MRI), ***EEG: Electroencephalography

Discussion

Previous studies on epilepsy in children younger than 3 years old were relatively rare, including intractable epilepsy. There was small number of study in Thailand. Most of them were released to determine risk factors for intractable epilepsy in children less than 3 years old. It was difficult to compare to previously published literatures in Thailand. Therefore, we had to compare to study published from abroad which might be related to racial differences.

The present study showed that 25 percent (18/22) of cases who presented with epilepsy before 36 months would be intractable epilepsy. This was less than the Wirrell's report that reporting at 33 percent [1]. The low incidence of the present study might be the small numbers of cases that less than Wirrell's study (88 vs 127 cases).

This investigation revealed developmental delay at diagnosis (mainly global delayed development), perinatal complication (such as birth asphyxia), prior status epilepticus, being generalized epilepsy, and abnormal CT/MRI brain especially structural brain abnormality were major risk factors of intractable epilepsy.

Development delay at aged of diagnostic was reported at 100 percentin present study while only 54 percent was reported in Wirrell'sstudy[1]. Structural brain anomaly was reported as the etiology in the present study but there was unknown etiology in Wirrell's study.

In this research study, perinatal complication could lead to epilepsy. This was consistent with research in the data etiology of epilepsy, that the most cause of intractable epilepsy was structural brain abnormality (congenital brain anomaly, traumatic brain injury, birth asphyxia).

Prior status epilepticus in our research was 12/22 (54%) OR 12.00, 95% CI 3.67 to 39.32, p = 0.02 compare to Wirrell[1] previous studies OR 2.55, 95% CI 1.09 to 5.91, p = 0.031, both of studies had significant statistical values.

Abnormal CT/MRI brain especially structural brain abnormality was the cause of epilepsy. Finding of our investigation supported Wirrell's finding[1]. Thirty three percent of Wirrell's and the present study had both abnormal CT/MRI imaging. Among abnormal CT/MRI imaging, structural brain abnormality, namely cortical dysplasia (40%), and holoprosencephaly (4.5%) were major finding.

Generalized epilepsy in the present study was the only risk factor from multivariable logistic regression analysis. However, in previous studies of both Wirrell[1] and Javad[6], focal seizure was a risk factor for intractable epilepsy. The patient's actual seizure pattern might start from focal seizure and then turn to generalize seizure. The semiology of seizure was from only parents or care takers reports.

Wirrell and co-workers[1] , study in 1 and 36 months epileptic patients concluded that risk factors associated with intractable epilepsy during age less than 12 years at diagnosis, developmental delay at time of diagnosis, abnormal neuroimaging, and focal slowing on initial EEG [1]. Finding of this investigation supported Wirrell's included abnormal CT/MRI imaging and delayed developmental at aged of diagnostic.

Javad studied epileptic patients at age of 15 years or less in Iran. They reported that neurological defects, myoclonic seizure, male gender, neonatal seizure, and age under one year of diagnosis, were risk factors of having intractable epilepsy[6] . Current findings at BAH showed that major factors were neurological defect and abnormal CT scan. At BAH, spastic cerebral palsy was the only neurological defect found same as reported by Javad's.

The limitation in current study was retrospective design and single center. It came from chart review by ICD 10 coding G 400 - 409 in the past 10 years.Some data had been missing. These patients's data were eliminated from research. Incomplete information or with restrictions on entering data on the computer in BAH came from the previously hospital system that manual chart written was scanned into a computer.

Some information was missing, even the CT/MRI brain and EEG were disappeared from

the system. The largest number of ruled out cases was 145, accounting for 62 percent. This resulting in small number of cases in the analysis. Some risk factors were not significant as the previous studies.

Conclusion

A comprehensive risk factors of intractable epilepsy, namely developmental delay at diagnosis, perinatal complication of birth asphyxia, prior status epilepticus, generalize epilepsy, and structural brain abnormality seen as abnormal CT/MRI bran scan were found in children with seizure between one month and three years of life from BAH database using 12 years retrospective data.

These factors should carefully be monitored by health practitioners in young patients with seizure as a screening tools for intractable epilepsy surveillance. Children with greater numbers of predictors factors should be monitors carefully.

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Conflict of interest

The authors declare no conflict of interest

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ปัจจัยเสี่ยงที่ทำให้เกิดภาวะชักที่คุมไม่ได้ในผู้ป่วยเด็กอายุน้อยกว่า 3 ปี ในโรงพยาบาลภูมิพลอดุลยเดช กรมแพทย์ทหารอากาศ

สุทธิดา ศุภพงศ์, ศิริลักษณ์ อัศวบำรุงกุล, ฐิติพร ฟางสะอาด

ความเป็นมา: โรคลมชัก เป็นความผิดปกติทางระบบประสาทที่รุนแรงโรคหนึ่ง ถ้ามีอาการของโรคลมชักตั้งแต่อายุยังน้อย จะส่งผลต่อพฤติกรรมทางอารมณ์ ทักษะการเข้าสังคม และความสามารถในการเรียนรู้ของเด็ก

วัตถุประสงค์: เพื่อศึกษาปัจจัยเสี่ยงที่ทำให้เกิดภาวะชักที่คุมไม่ได้ในผู้ป่วยเด็กอายุน้อยกว่า 3 ปี

วิธีการ: การศึกษานี้เป็นการศึกษาระบาดวิทยาเชิงวิเคราะห์แบบย้อนหลัง โดยรวบรวมข้อมูลจากเวชระเบียน ผู้เข้าร่วมงานวิจัยเป็นผู้ป่วยที่ได้รับการวินิจฉัยเป็นโรคลมชัก โดยมีอายุช่วง 1 - 36 เดือน ที่รับการรักษาในโรงพยาบาลภูมิพลอดุลยเดช ประเทศไทย ระหว่างวันที่ 1 มกราคม 2551 ถึง 30 มิถุนายน 2562 โดยแยกผู้ป่วยเป็น 2 กลุ่มคือ กลุ่มที่ไม่สามารถคุมชักได้และกลุ่มที่คุมชักได้

ผลลัพธ์: จำนวนผู้ป่วยโรคลมชักทั้งหมด 233 ราย 145 ราย ถูกตัดออกจากการศึกษา (19 ราย เป็นชักจากไข้สูง 126 ราย ไม่ใช่โรคลมชัก) มีผู้ป่วยทั้งหมด 88 ราย ที่ได้รับการเข้าร่วมในงานวิจัย ผู้ป่วยที่ไม่สามารถคุมชักได้และกลุ่มที่สามารถคุมชักได้ประกอบด้วย 22 และ 66 คนตามลำดับ จากงานวิจัยนี้ พบผู้ป่วยเพศชาย 51.14% (45/88) และผู้ป่วยเพศหญิง 48.86% (43/88) โรคลมชักที่ไม่สามารถคุมชักได้ พบว่ามีภาวะพัฒนาการล่าช้าตั้งแต่ที่ได้รับการวินิจฉัยโรคลมชัก 100% (22/22), มีภาวะแทรกซ้อนตอนแรกคลอด 72% (16/22), การเจ็บครรภ์คลอดก่อนกำหนด 18% (4/22), เคยมีประวัติชักจากไข้ 36% (8/22), เคยมีประวัติอาการชักแบบต่อเนื่อง 54% (12/22), รูปแบบการชักเป็นแบบชักทั้งตัว 63% (14/22), ผลของ CT / MRI ระบบประสาท ผิดปกติ 81% (18/22), มีภาวะคลื่นไฟฟ้าสมองผิดปกติ 40% (4/22), มีประวัติโรคลมชักในครอบครัว 4 % (1 /22) ปัจจัยเสี่ยงที่ทำให้เกิดภาวะชักที่คุมไม่ได้ที่มีนัยสำคัญทางสถิติ มีด้วยกัน 5 ปัจจัยเสี่ยง ได้แก่ มีภาวะพัฒนาการล่าช้าตั้งแต่ที่ได้รับการวินิจฉัยโรคลมชัก มีภาวะแทรกซ้อนตอนแรกคลอด เคยมีประวัติอาการชักแบบต่อเนื่อง รูปแบบการชักเป็นแบบชักทั้งตัว ผลของ CT / MRI ระบบประสาทผิดปกติ เมื่อนำปัจจัยเสี่ยงทั้ง 5 เข้าในแบบการวิเคราะห์การถดถอยโลจิสติก พบเพียงปัจจัยเสี่ยงเดียวที่มีนัยสำคัญทางสถิติ คือรูปแบบการชักเป็นแบบชักทั้งตัว

สรุป: พบผู้ป่วยโรคลมชักที่ไม่สามารถควบคุมชักได้ ในช่วงอายุ 1 เดือน ถึง 3 ปี ทั้งหมด 25% โดยปัจจัยเสี่ยงที่ก่อให้เกิดโรคลมชักที่ไม่สามารถคุมชักได้ ได้แก่ มีพัฒนาการล่าช้าตั้งแต่ที่ได้รับการวินิจฉัยโรคลมชัก มีภาวะขาดออกซิเจนในช่วงแรกคลอด เคยมีประวัติอาการชักต่อเนื่อง รูปแบบการชักเป็นแบบชักทั้งตัว ความผิดปกติของโครงสร้างระบบประสาท ที่เจอในผลของ CT / MRI ระบบประสาทที่ผิดปกติ

คำสำคัญ: ภาวะที่ไม่สามารถคุมชักได้, โรคลมชัก, เด็กเล็ก

**กองกุมารเวชกรรม โรงพยาบาลภูมิพลอดุลยเดช กรมแพทย์ทหารอากาศ*