SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF COMPLEX FEBRILE SEIZURE AND ITS ASSOCIATION WITH ABNORMAL ELECTROENCEPHALOGRAPHY

by

DR MOHD IFTITAH B HASHIM

Dissertation Submitted In Partial Fulfillment Of The Requirements For The Degree Of Master Of Medicine (EMERGENCY MEDICINE)



ACKNOWLEDGEMENT

In the name of Allah, the Most Gracious and the Most Merciful

All praises to Allah for the strength and His blessing in completing this dissertation.

First and foremost, my sincere gratitude goes to my supervisor Dr Tuan Hairulnizam bin Tuan Kamauzaman, Emergency Physician, Hospital Universiti Sains Malaysia (HUSM) for his supervision and constant support throughout this research starting from proposal until submission of the dissertation. Thank you for all the experience, the knowledge, and the unfailing encouragement that you have ever so ready to provide and share.

I am also truly indebted and thankful to Associate Professor Dr Sarimah Abdullah from Unit of Biostatistics and Research Methodology, HUSM for her help in data analysis. Thank you for answering all my statistical questions and doubts and giving me suggestion and advices on statistic part. I deeply appreciate the time that you willing to allocate despite of your busy schedule.

My sincere thanks to all the lecturers and colleagues in Emergency Department, HUSM for their enthusiasm, kindness and moral support throughout my master programme. Not forgetting to the staffs of the Unit of EEG and Record Office HUSM for their help and assistance in tracing EEG and medical records; my truly appreciation and thanks to them.

Last but not least, I would like to thank my loving and supportive family. Thank you for your support, love and guidance. With your constant encouragement and love, I had able to complete this dissertation on time. You'll always have my unconditional love, today and forever.

TABLE OF CONTENTS

PAGE

TITLE	i
ACKNOWLEDGEMENT	ii
TABLE OF CONTENT	iii
ABSTRAK (BAHASA MALAYSIA)	v
ABSTRACT (ENGLISH)	vii

CHAPTER 1: INTRODUCTION

1.1	Introduction		1	_

CHAPTER 2: OBJECTIVES OF THE STUDY

2.1	General Objective	5
2.2	Specific Objectives	5

CHAPTER 3: MANUSCRIPT

3.1	Title page	6
3.2	Abstract	7
3.3	Introduction	8
3.4	Methods	11
3.5	Results	12
3.6	Discussion	14
3.7	Conclusion	17
3.8	References	18
3.9	Table and Figures	21

3.10	Guidelines/ Instructions to Authors of selected Journal	24

CHAPTER 4: STUDY PROTOCOL

4.1	Study Protocol submitted for Ethical Approval	27
4.2	Ethical Approval Letter	49

CHAPTER 5: APPENDICES

5.1	Additional Tables/ Graphs	55
5.2	Raw Data on SPSS Softcopy	56

ABSTRAK

SOSIO-DEMOGRAFI DAN CIRI-CIRI KLINIKAL PESAKIT DEMAM SAWAN KOMPLEKS DAN HUBUNGKAITNYA DENGAN KEPUTUSAN ELEKTROENSEFALOGRAFI YANG TIDAK NORMAL

Pengenalan: Demam sawan merupakan sejenis sawan yang lazim berlaku kepada kanakkanak. Buat masa ini, ujian elektroensefalografi (EEG) tidak perlu dilakukan dikalangan pesakit demam sawan ringkas. Namun keperluan melakukan ujian EEG dikalangan pesakit demam sawan kompleks masih belum jelas. Disebabkan risiko yang tinggi untuk mendapat penyakit epilepsi selepas ini, maka kajian ini dibuat untuk menyiasat taburan sosio-demografi dan ciri-ciri klinikal dikalangan pesakit demam sawan kompleks serta hubungkaitnya dengan keputusan ujian EEG yang tidak normal.

Metodologi: Kesemua ujian EEG yang telah dilakukan dikalangan pesakit demam sawan di Hospital Universiti Sains Malaysia sebelum ini dikaji (Januari 2005 sehingga December 2015). Pesakit yang memenuhi kriteria demam sawan kompleks sahaja dipilih untuk kajian ini. Hubungkait antara sosio-demografi dan ciri-ciri klinikal dengan keputusan EEG yang tidak normal dianalisa.

Keputusan: Seramai 77 pesakit dipilih untuk kajian ini. Empat belas pesakit (18.2%) menunjukkan keputusan EEG yang tidak normal. Purata umur pesakit adalah 34.36±26.28 bulan, 46 orang adalah kanak-kanak lelaki (59.7%), 31 orang adalah kanak-kanak perempuan (40.3%) dan hampir kesemuanya berbangsa Melayu (96.1%). Kesemua

pesakit mempunyai fungsi neurologi yang normal selepas berlakunya sawan. Dengan menggunakan analisis multivariate, kekerapan sawan melebihi 2 kali dalam masa 24 jam mempunyai hubungkait yang signifikan terhadap keputusan EEG yang tidak normal jika dibandingkan kekerapan sawan hanya sekali. (AOR 4.01, 95% CI 1.02-15.59, p=0.046).

Kesimpulan: Kekerapan sawan melebihi 2 kali dalam masa 24 jam merupakan faktor yang penting dalam mengjangkakan keputusan EEG yang tidak normal dan sepatutnya dijadiakan indikasi untuk ujian EEG dikalangan pesakit demam sawan kompleks. Kumpulan pesakit ini memerlukan rawatan dan pemantauan susulan untuk kemungkinan sawan tersebut berulang ataupun mengidap penyakit epilepsi selepas ini.

ABSTRACT

SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF COMPLEX FEBRILE SEIZURE AND ITS ASSOCIATION WITH ABNORMAL ELECTROENCEPHALOGRAPHY

Introduction: Febrile seizures were the commonest convulsive event during childhood. Currently there is no role of electroencephalography (EEG) study in simple febrile seizure. The precise role of EEG in evaluation of patients with complex febrile seizures (CFS) has not been established. In view of increased risk of future epilepsy in these patients, this study determines and to investigate the socio-demographic and clinical characteristics of CFS and its associations with an abnormal EEG outcome.

Methods: All available EEG records at Hospital Universiti Sains Malaysia (HUSM) were retrospectively reviewed to identify those EEGs performed for the indication of febrile seizure (January 2005 to December 2015). From this cohort, those patients fulfilling criteria of CFS were selected. The association between socio-demographic, clinical characteristic and abnormal EEG was analysed.

Results: A total of 77 patients were selected into the study. Of these, 14 patients (18.2%) had abnormal EEG. The mean age was 34.36 ± 26.28 months, 46 were boys (59.7%) and 31 were girls (40.3%) and most of them were Malay (96.1%). All patients had normal neurological assessment post seizure. With multivariate analysis, frequency of seizure more than 2 episodes within 24-hour was significantly associated to abnormal EEG as compared to one episode of seizure (AOR 4.01, 95% CI 1.02-15.59, p=0.046).

Conclusions: The seizure frequency of more than 2 episodes within 24-hour was an important predictor of abnormal EEG and should be an indication for EEG study among CFS patients. This group of patients warrant for further follow-up and monitoring for recurrence of seizure or epilepsy later.

1.1 INTRODUCTION

Febrile seizures are the most common type of convulsive event in childhood of less than 5 years old with an incidence of 2-5%.¹⁴ Generally it has an excellent prognosis but may also signify a serious underlying acute infectious disease such as sepsis or bacterial meningitis. A febrile seizure is defined as a seizure occurring between 3 month and 6 years of age, accompanied by fever, in which there was no evidence of intracranial pathology or metabolic derangement.⁴⁶

A simple febrile seizure is usually associated with a core temperature that increases rapidly to 39°C or greater.⁵ The seizure is usually generalized, tonic clonic and last a few seconds to 15 minute and is followed by brief post-ictal drowsiness. Complex febrile seizures (CFS) are depending on duration (more than 15 minutes), presence of focal features during onset or evolution, and more than one episode of seizure during febrile episode or recurrence within twenty four hour and/or with residual neurological deficit post-ictal.^{5,6}

Approximately 30-50% of children have recurrent seizures with later episodes fever and small minorities have numerous recurrent seizures.⁵ Although children with simple febrile seizures are at no greater risk of later epilepsy than the general population, some factors are associated with increased risk. These include CFS, positive family history of epilepsy, and initial febrile seizure before 9 month of age, delayed developmental milestones, or pre-existing neurologic disorder.⁵⁹ The incidence of epilepsy is approximately 9% when several risk factor present, compared with an incidence of 1% in children who have febrile convulsions and no risk factor.⁶

Epilepsy is a neurological condition characterized by recurrent unprovoked epileptic seizures. An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. An epileptic syndrome is a complex of sign and symptoms that define a unique epilepsy condition. Syndromes are classified on the basis of seizure type, clinical context electroencephalography (EEG) feature and neuroimaging.⁵⁶

Currently there is no role of EEG in simple febrile seizure. However the precise role of EEG in evaluation of patients with CFS has not been established. In view of the increased risk of epilepsy in this group (4.1%),² it is not uncommon for both paediatricians and specialists to recommend EEGs on these patients. The Paediatric Protocols for Malaysian Hospital Third Edition stated that EEG is not indicated even if multiple recurrences febrile seizure or CFS.⁵ The American Academy of Paediatrics Practice Parameter on Febrile Seizures states that EEG should not be part of routine investigation after simple febrile seizure in neurologically normal children due to its lack of ability in predicting recurrence risk or future epilepsy.⁶⁷

Charuta Joshi et al., 2005 conducted study to assess utility of clinical variable at presentation in predicting the likelihood of an abnormal EEG. All EEG requisitions were retrospectively reviewed to identify those EEGs performed for the indication of seizure with fever over an 11 year period (1990-2001) and meet the criteria for CFS.¹² The relationship between clinical variables like age, timing of EEG since onset of CFS, family history of seizures, neurological assessment and EEG abnormalities was analysed.¹² One hundred and seventy five children were included in the study.⁸ The mean age was 17.31 month and 39.43% had EEG abnormalities.¹² Factors predictive of abnormal EEGs in children with CFS were; age >3 years (70.6%) EEGs performed

within 7 days (59.1%) and an abnormal neurological exam (73.3%).¹² A history of febrile seizures was more likely to be associated with a normal EEG (88%).¹²

In retrospective review by Maytal et al., 2000 found that, 33 patients with CFS mean age 17.8 months and neurologically normal children had a normal EEG report within 1 week. These finding showed practiced of EEG in neurologically normal children with CFS was not substantiated. However an abnormal bedside neurological examination in children with CFS is a predictive variable of likelihood of an abnormal EEG finding.¹²

Yucel et al., 2004 reported abnormal EEG in 71 from 159 (44.6%) children who had been treated for CFS. This retrospective review done over 7 years and 51 children (32%) were diagnosed with epilepsy during follow up the children within 6 month to 7 years. Detection of epileptic discharges is unusual within the first postictal week and it also difficult in patient aged less than 3 years.¹⁵ Half of children with focal seizure showed abnormal epileptiform EEG as compared to 24.4% in generalized seizure.

Millichap et al., 1960 reported EEG abnormalities in 36% of patients whose seizures lasted more than 20 minutes, in comparison to just 10% abnormalities in those children whose seizures were less than 20 minutes (p<0.05).¹⁸ All the EEGs were studied at least seven days after the febrile seizure.

A review of published literature suggests that between 2 and 86% of EEGs are abnormal after febrile seizures.¹³ This wide variation can be attributed to differences in criteria used in subject selection by different authors, varying definitions of EEG abnormalities, and relationship of age, maturity, and timing since ictus to EEG findings.^{13,14} The purpose of this study was to determine and to investigate the socio-demographic and clinical characteristics of CFS and its associations with abnormal EEG result. This finding can be used to screen CFS patients for whom an EEG should be considered.

2.1 General Objective

1) To evaluate the socio-demographic and clinical characteristics of CFS cases and its association with abnormal EEG

2.2 Specific Objectives

1) To determine the socio-demographic and clinical characteristics in cases of CFS at HUSM

2) To determine the association between socio-demographic and clinical characteristics with an abnormal EEG result in cases with CFS at HUSM

3.1 TITLE: SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF COMPLEX FEBRILE SEIZURE AND ITS ASSOCIATION WITH ABNORMAL ELECTROENCEPHALOGRAPHY

Author:

Mohd Iftitah B Hashim, MD Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan. Tuan Hairulnizam B Tuan Kamauzaman, MMED

Department of Emergency Medicine,

School of Medical Sciences, Universiti Sains Malaysia,

16150 Kota Bharu, Kelantan.

Corresponding Author:

Dr Mohd Iftitah B Hashim

Department of Emergency Medicine, School of Medical Sciences,

Universiti Sains Malaysia, Kota Bharu, 16150 Kota Bharu, Kelantan, MALAYSIA

Email: m.iftitah83@gmail.com; Tel: +609-7676721; Fax: +609-7673219

Disclosure of funding:

None of authors receive any financial support for this study.

3.2 ABSTRACT

Introduction: Febrile seizures were the commonest convulsive event during childhood. Currently there is no role of electroencephalography (EEG) study in simple febrile seizure. The precise role of EEG in evaluation of patients with complex febrile seizures (CFS) has not been established. In view of increased risk of future epilepsy in these patients, this study determines and to investigate the socio-demographic and clinical characteristics of CFS and its associations with an abnormal EEG outcome. **Methods:** All available EEG records at Hospital Universiti Sains Malaysia (HUSM) were retrospectively reviewed to identify those EEGs performed for the indication of febrile seizure (January 2005 to December 2015). From this cohort, those patients fulfilling criteria of CFS were selected. The association between socio-demographic, clinical characteristic and abnormal EEG was analysed. Results: A total of 77 patients were selected into the study. Of these, 14 patients (18.2%) had abnormal EEG. The mean age was 34.36±26.28 months, 46 were boys (59.7%) and 31 were girls (40.3%) and most of them were Malay (96.1%). All patients had normal neurological assessment post seizure. With multivariate analysis, frequency of seizure more than 2 episodes within 24-hour was significantly associated to abnormal EEG as compared to one episode of seizure (AOR 4.01, 95% CI 1.02-15.59, p=0.046). Conclusions: The seizure frequency of more than 2 episodes within 24-hour was an important predictor of abnormal EEG and should be an indication for EEG study among CFS patients. This group of patients warrant for further follow-up and monitoring for recurrence of seizure or epilepsy later.

Keywords: Complex febrile seizure, electroencephalography, epilepsy, febrile seizure

7

3.3 INTRODUCTION

Febrile seizures are the most common type of convulsive event in childhood of less than 5 years old with an incidence of 2-5%.¹⁴ Generally it has an excellent prognosis but may also signify a serious underlying acute infectious disease such as sepsis or bacterial meningitis. A febrile seizure is defined as a seizure occurring between 3 month and 6 years of age, accompanied by fever, in which there was no evidence of intracranial pathology or metabolic derangement.⁴⁶

A simple febrile seizure is usually associated with a core temperature that increases rapidly to 39°C or greater.⁵ The seizure is usually generalized, tonic clonic and last a few seconds to 15 minute and is followed by brief post-ictal drowsiness. Complex febrile seizures (CFS) are depending on duration (more than 15 minutes), presence of focal features during onset or evolution, and more than one episode of seizure during febrile episode or recurrence within twenty four hour and/or with residual neurological deficit post-ictal.^{5,6}

Approximately 30-50% of children have recurrent seizures with later episodes fever and small minorities have numerous recurrent seizures.⁵ Although children with simple febrile seizures are at no greater risk of later epilepsy than the general population, some factors are associated with increased risk. These include CFS, positive family history of epilepsy, and initial febrile seizure before 9 month of age, delayed developmental milestones, or pre-existing neurologic disorder.⁵⁹ The incidence of epilepsy is approximately 9% when several risk factor present, compared with an incidence of 1% in children who have febrile convulsions and no risk factor.⁶

Epilepsy is a neurological condition characterized by recurrent unprovoked epileptic seizures. An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. An epileptic syndrome is a complex of sign and symptoms that define a unique epilepsy condition. Syndromes are classified on the basis of seizure type, clinical context electroencephalography (EEG) feature and neuroimaging.⁵⁶

Currently there is no role of EEG in simple febrile seizure. However the precise role of EEG in evaluation of patients with CFS has not been established. In view of the increased risk of epilepsy in this group (4.1%),² it is not uncommon for both paediatricians and specialists to recommend EEGs on these patients. The Paediatric Protocols for Malaysian Hospital Third Edition stated that EEG is not indicated even if multiple recurrences febrile seizure or CFS.⁵ The American Academy of Paediatrics Practice Parameter on Febrile Seizures states that EEG should not be part of routine investigation after simple febrile seizure in neurologically normal children due to its lack of ability in predicting recurrence risk or future epilepsy.⁶⁷

Charuta Joshi et al., 2005 conducted study to assess utility of clinical variable at presentation in predicting the likelihood of an abnormal EEG. All EEG requisitions were retrospectively reviewed to identify those EEGs performed for the indication of seizure with fever over an 11 year period (1990-2001) and meet the criteria for CFS.¹² The relationship between clinical variables like age, timing of EEG since onset of CFS, family history of seizures, neurological assessment and EEG abnormalities was analysed.¹² One hundred and seventy five children were included in the study.⁸ The mean age was 17.31 month and 39.43% had EEG abnormalities.¹² Factors predictive of abnormal EEGs in children with CFS were; age >3 years (70.6%) EEGs performed

within 7 days (59.1%) and an abnormal neurological exam (73.3%).¹² A history of febrile seizures was more likely to be associated with a normal EEG (88%).¹²

In retrospective review by Maytal et al., 2000 found that, 33 patients with CFS mean age 17.8 months and neurologically normal children had a normal EEG report within 1 week. These finding showed practiced of EEG in neurologically normal children with CFS was not substantiated. However an abnormal bedside neurological examination in children with CFS is a predictive variable of likelihood of an abnormal EEG finding.¹²

Yucel et al., 2004 reported abnormal EEG in 71 from 159 (44.6%) children who had been treated for CFS. This retrospective review done over 7 years and 51 children (32%) were diagnosed with epilepsy during follow up the children within 6 month to 7 years. Detection of epileptic discharges is unusual within the first postictal week and it also difficult in patient aged less than 3 years.¹⁵ Half of children with focal seizure showed abnormal epileptiform EEG as compared to 24.4% in generalized seizure.

Millichap et al., 1960 reported EEG abnormalities in 36% of patients whose seizures lasted more than 20 minutes, in comparison to just 10% abnormalities in those children whose seizures were less than 20 minutes (p<0.05).¹⁸ All the EEGs were studied at least seven days after the febrile seizure.

A review of published literature suggests that between 2 and 86% of EEGs are abnormal after febrile seizures.¹³ This wide variation can be attributed to differences in criteria used in subject selection by different authors, varying definitions of EEG abnormalities, and relationship of age, maturity, and timing since ictus to EEG findings.^{13,14} The purpose of this study was to determine and to investigate the socio-demographic and clinical characteristics of CFS and its associations with abnormal EEG result. This finding can be used to screen CFS patients for whom an EEG should be considered.

3.4 METHODOLOGY

All available EEG records at Hospital Universiti Sains Malaysia (HUSM) were retrospectively reviewed to identify those EEGs performed for the indication of febrile seizure (January 2005 to December 2015). In this study febrile seizure is defined as seizures occurring between three months and six years of age, accompanied by fever, in which there was no evidence of intracranial pathology or metabolic derangement.^{5,6} When more than one EEG had been performed, only the initial record was evaluated. From this cohort those patients fulfilling criteria of CFS (focal, duration of greater than 15 minutes or more than one seizure episodes in a 24-hour period)^{5,6} were selected in the current study.

CFS are depending on duration (more than 15 minutes), presence of focal features during onset or evolution, and more than one seizure during febrile episode or recurrence within twenty four hours and/or with residual neurological deficit postictal.^{5,6} Hospital medical records of the patients were reviewed to confirm the inclusion criteria and the diagnosis of CFS. Patients with an episode of afebrile seizure and evidence of developmental delay or neurological impairment prior to the CFS episode were excluded from this study.

Details such as socio-demographic data, timing of first EEG done, age at the time of seizure, neurological assessment, duration of seizure, frequency of seizure within 24-

hour, seizure type, family history of epilepsy or febrile seizures and EEG result were recorded . EEG patterns were categorized as normal or abnormal on the basis of presence of interictal epileptiform activity (sharp waves, spikes, and/or spike wave complexes) and or abnormality in the background rhythms (slow waves, focal and/or generalized).¹² The EEG records included awake and sleep states and had been analysed by paediatric neurologist in HUSM.

The Human Research Ethics Committee Universiti Sains Malaysia approved this study (USM/JEPeM/15030103). The Director of HUSM gave permission to review the EEG and medical records. All data were managed and analysed by IBM SPSS version 21.0. The continuous variable will be described as mean and standard deviation. Categorical variables will be described in frequency and percentage. For Univariate Analysis, Simple Logistic Regression method was used to determine the association factors of abnormal EEG in CFS. Factors with p<0.250 were incorporated into Multiple Logistic Regression analysis. A p \leq 0.050 was considered as statistically significant for all statistical analyses in this study and will be applied to determine the association between socio-demographic and clinical characteristics of CFS with an abnormal EEG result.

3.5 RESULTS

Seventy seven patients had been coded with a diagnosis of CFS to be included in our analysis. The socio-demographic and clinical characteristics of the patients were shown in Table 1. The mean age was 34.36 ± 26.28 months and the majority of them (n=46, 59.7%) were younger or equal 36 months. Forty six patients (59.7%) were boys. Most of them were Malay (n=74, 96.1%) and only 3 patients (3.9%) were Chinese.

Pertaining to clinical characteristics, almost all patients presented with generalized seizure (n= 76, 98.7%) and only 1 patient (1.3%) had focal seizure. The mean duration of seizure were 11.74 ± 11.35 minutes, with the majority of them (n=61, 79.2%) had seizure less than 20 minutes duration. All of the patients had normal neurological assessment post seizure. Thirty two patients (41.6%) had only one episode of seizure within a 24-hour period, 23 patients (29.9%) had two episodes of seizure and 22 patients (28.5%) had more than two episodes of seizure. Among patients with family history of seizure (n=40, 52%), 34 patients (44.2%) for family history of febrile seizure and 6 patients (7.8%) for family history of epilepsy.

Timing of EEG records were divided into either done within 7 days from onset of seizure (n=40, 51.9%) or after 7 days (n=37, 48.1%). The mean time for EEG study in CFS patients were 32.64 ± 51.05 days. Out of the 77 patients, 14 patients (18.2%) were classified as having abnormal EEG records. The distribution of socio-demographic and clinical characteristics according to the EEG results is shown in Table 2.

Using univariate analysis, socio-demographic and clinical characteristics of CFS patients that were significantly associated with abnormal EEG findings were frequency of seizure within 24-hour and presence of family history of seizure (Table 3). Frequency of seizure more than two episodes within 24-hour had 4.00 times the odds of having abnormal EEG than one episode of seizure (95% CI 1.03-15.6, p=0.046). Presence of family history of epilepsy has 4.12 times the odds of having abnormal EEG than no family history seizure (95% CI 0.56-30.16, p=0.163). Presence of family history of seizure has 2.53 times the odds of having abnormal EEG than no family history of seizure (95% CI 0.69-9.37, p=0.162).

On multivariate analysis, the seizure frequency of more than two episodes within 24hour remained the only clinical characteristic that was significantly associated with abnormal EEG in CFS patients (AOR 4.01, 95% CI 1.02-15.59, p=0.046).

3.6 DISCUSSION

There was a wide range of abnormal EEG rate after febrile seizures reported in previous literatures ranging from 2 to 86%.¹⁵ This variation can be explained by difference in inclusion criteria by different authors, varying definitions and subdivision of EEG abnormalities, and relationship of age, maturity, and time to EEG recording post seizure.⁸ CFS is associated with increased risk of future epilepsy and EEG is frequently studied in some centers.¹²

Our study is the first to specifically examine the association of socio-demographic and clinical characteristics CFS patients among Malaysian population on the EEG outcome. After reviewing patient data of all EEG record in HUSM from January 2005 till December 2015, 77 patients fulfilled the criteria for CFS and were included in this study. The limited number of sample was due to uncommon practice of EEG to be studied in CFS in our setting. EEG study is not specified currently in Malaysian Paediatric Protocol Third edition.⁵

To simplify the definition of EEG outcome, we categorized it into normal or abnormal base on final impression made by paediatric neurologist. Our results showed that 14 patients (18.2%) had abnormal EEG and this was low as compared to previous literature by Joshi et al., 2005 (39.43%) and Yucel et al., 2004 (44.65%).^{12,15} This could be due to variation definition of abnormal EEG by other authors.^{16,17} Yucel et al., 2004 categorized

normal or abnormal EEG based on abnormality in the background rhythms (slow waves, focal and / or generalized), and / or the presence of interictal epileptiform activity (sharp wave, spikes, and / or spike waves complexes) or both.¹¹ Other authors did not confine their definition of paroxysmal activity to spike, or spike waves, and also included phantom spike wave and high voltage slow wave bursts.^{13,14,18}

Age of the child at the time of the first CFS presentation had no influence towards EEG findings. In contrast to previous literature, there was no significant difference between age group of above 36 months and below 36 months towards EEG abnormality.^{12,19} However the mean age of abnormal EEG group was slightly higher (36.36±27.68 months) than of normal EEG group (33.92±26.16 months). This finding was comparable to previous study which found that there was a linear trend for the detection of higher rates of abnormal EEG records with increasing of age.^{10,20-22}

This study showed a predominance of boy compared to girl and Malay compared to other races. This is an agreement with epidemiology study of febrile seizure in Malaysia done by Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia in 1994.²³ Male gender is found to be one of the risk factor for recurrence of febrile seizures^{6,24} but our study shown that gender and race were not significant predictors of abnormal EEG. No previous study was found specifically discussed association of these variables with EEG abnormality.

Multiple seizure within 24-hour of CFS had high risk for the development of epilepsy.¹⁵ 30.2% of 159 patients had multiple seizure and later 29.2% develop epilepsy within 7 years.¹¹ Annegers et al., 1987 stated that it was the most common features of unprovoked seizures after CFS.²⁵ In our study, we found that seizure occurring more

15

than two episodes within 24-hour from the onset of CFS had 4.01 times the odds of having abnormal EEG as compared to one episode of seizure only (AOR 4.01, 95% CI 1.02-15.59, p=0.046). This was the only variable that had significant association with abnormal EEG after multivariate analysis. Scarring of brain tissue after multiple seizures might be the cause of abnormal EEG in CFS cases and will develop epilepsy later.²⁶

Family history of epilepsy had 4.12 times odd to had abnormal EEG (OR 4.12 95% CI 0.56-30.16, p=0.163) as compared to no family history of seizure. However this data was not significant after multivariate analysis. It is possible that small numbers of patient with family history of epilepsy (n=6) in our study diluted the effect on multivariate analysis. Even though this finding was in agreement with Joshi et al., 2005, other literature found that a family history of epilepsy and complex febrile seizure has been associated two to five fold increases risk of epilepsy.^{4,27} In febrile convulsion with several risk factors for epilepsy, the incidence of epilepsy is approximately 9% when compared with an incidence of 1% in children who have febrile convulsions and no risk factor.⁵ Risk factors for occurrence of subsequent epilepsy are neurodevelopmental abnormalities, focal CFS, family history of epilepsy, fever less than one hour before febrile seizure, CFS, recurrent febrile seizures and simple febrile seizure.⁶²⁴ Thus family history of epilepsy remained clinical relevance and merits a further evaluation either by doing EEG or close follow up in the clinic.

With regards to the timing of EEG post seizure either done within 7 days or later, our study justified that it is not an important variable in determining the presence of abnormal EEG (OR 0.91 95% CI 0.28-2.90, p = 0.872). It is rare the abnormal EEG to be reported within 7 days of febrile convulsion however slowing wave is found to be

more in early post seizure.^{13,21} No EEG abnormalities seen in 33 neurologically normal patients who did EEG within 7 days postictal⁹ and only 22.5% of abnormal EEGs were reported within 6 days of onset complex febrile seizure.¹⁵ However early timing EEG within 7 days was shown to be significant variables by Joshi et al., 2005 These contradicting findings may be attributed by variation definition of abnormal EEG itself,¹⁵⁻¹⁷ effect of viral infections,²⁸ or transient changes that being observed in EEGs between 3 to 8 days after febrile seizure.²⁹

Other important clinical characteristic that was strongly associated with abnormal EEG in previous literature was abnormal neurological assessment post seizure.¹² However from our study all patients had normal neurological assessment hence further analysis were not carried out. Seizure type and duration of seizure remained not significant to predict abnormal EEG and this was similar with previous study.¹²

This study followed the usual methodological of retrospective case study. But taking into account of small sample size and detailed EEGs findings were not evaluated, we believed that this study was not sufficiently robust as compared to previous study. ^{12,13,15} Furthermore it's still limited to correlate the abnormal EEG and the risks of epilepsy later. Prospective series with larger sample size and follow-up are required to ascertain whether abnormal EEG is associated with later development of epilepsy.³⁰

3.7 CONCLUSIONS

Among CFS cases, frequency of seizure more than two episodes within 24-hour was significantly influence the likelihood of abnormal EEG.

3.8 REFERENCES

- Hauser WA, Kurland LT. The Epidemiology of Epilepsy in Rochester, Minnesota, 1935 Through 1967. Epilepsia 1975;16(1):1-66.
- Nelson KB, Ellenberg JH. Predictors of Epilepsy in Children Who Have Experienced Febrile Seizures. New England Journal of Medicine 1976;295(19):1029-33.
- Verity CM, Butler NR, Golding J. Febrile Convulsions in a National Cohort Followed Up From Birth. I—Prevalence and Recurrence in the First Five Years of Life. British Medical Journal (Clinical research ed) 1985;290(6478):1307.
- Whelan H, Harmelink M, Chou E, Sallowm D, Khan N, Patil R, et al. Complex Febrile Seizures—A systematic review. Disease-a-Month 2017;63(1):5-23.
- Ismail HIHM, Ng HP, Thomas T. Paediatric Protocols for Malaysian Hospitals Third Edition: Ministry of Health; 2012.
- Kliegman RM, Behrman RE, Jenson HB, Stanton BM. Nelson Textbook of Pediatrics: Elsevier Health Sciences; 2007.
- Graves RC, Oehler K, Tingle LE. Febrile Seizures: Risks, Evaluation, and Prognosis. Am Fam Physician 2012;85(2):149-53.
- Millar JS. Evaluation and Treatment of the Child with Febrile Seizure. Am Fam Physician 2006;73(10):1761-4.
- Sadleir LG, Scheffer IE. Febrile Seizures. BMJ: British Medical Journal 2007:307-11.
- Kuturec M, Emoto S, Sofijanov N, Dukovski M, Duma F, Ellenberg J, et al. Febrile Seizures: Is The EEG a Useful Predictor of Recurrences? Clinical Pediatrics 1997;36(1):31-6.

- 11. Seizure FSF. Practice Parameter The Neurodiagnostic Evaluation of the Child with a First Simple Febrile Seizure. Pediatrics 1996;97(5):769.
- Joshi C, Wawrykow T, Patrick J, Prasad A. Do Clinical Variables Predict an Abnormal EEG in Patients With Complex Febrile Seizures? Seizure 2005;14(6):429-34.
- Maytal J, Steel R, Eviatar L. The Value of Early Postictal EEG in Children with Complex Febrile Seizure. 2000.
- Yamatogi Y, Ohtahara S. EEG in Febrile Convulsions. Am J EEG Technol 1990;30:267-80.
- Yücel O, Aka S, Yazicioglu L, Ceran O. Role of Early EEG and Neuroimaging in Determination of Prognosis in Children With Complex Febrile Seizure. Pediatrics International 2004;46(4):463-7.
- Frantzen E, Lennox-Buchthal M, Nygaard A. Longitudinal EEG and Clinical Study of Children with Febrile Convulsions. Electroencephalography and Clinical Neurophysiology 1968;24(3):197-212.
- Doose H, Ritter K, Völzke E. EEG Longitudinal Studies in Febrile Convulsions. Neuropediatrics 1983;14(02):81-7.
- Millichap JG, Madsen JA, Aledort LM. Studies in Febrile Seizures V. Clinical and Electroencephalographic Study in Unselected Patients. Neurology 1960;10(7):643.
- Aicardi J, Chevrie J. The Significance of Electroencephalographic Paroxysms in Children Less Than 3 years of Age. Epilepsia 1973;14(1):47-55.
- Tsuboi T. Correlation Between EEG Abnormality and Age in Childhood. Neuropädiatrie 1978;9(03):229-38.
- Sofijanov N, Emoto S, Kuturec M, Dukovski M, Duma F, Ellenberg J, et al. Febrile Seizures: Clinical Characteristics and Initial EEG. Epilepsia 1992;33(1):52-7.

- Eeg-Olofsson O. The Development of The Electroencephalogram in Normal Children and Adolescents from The Age of 1 Through 21 Years. 1970.
- Deng C, Zulkifli H, Azizi B. Febrile Seizures in Malaysian Children: Epidemiology and Clinical Features. Med J Malaysia 1994;49(4):341-7.
- Mikati MA, Rahi AC. From Molecular Biology to Clinical Practice. Neurosciences 2005;10(1):14-22.
- Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors Prognostic of Unprovoked Seizures After Febrile Convulsions.New England Journal of Medicine 1987;316(9):493-8.
- Jankowiak J, Malow B. Seizures in Children with Fever: Generally Good Outcome. Neurology 2003;60(2):E1-E2.
- Berg AT. Febrile Seizures and Epilepsy: The Contributions of Epidemiology.
 Paediatric and Perinatal Epidemiology 1992;6(2):145-52.
- Wallace SJ, Zealley H. Neurological, Electroencephalographic, and Virological Findings in Febrile Children. Archives of Disease in Childhood. 1970;45(243):611-23.
- Store G. When Does an EEG Contribute to The Management of Febrile Seizures? Archives of Disease in Childhood. 1991; 66(4):554-7.
- Shah PB, James S, Elayaraja S. EEG for children with complex febrile seizures. The Cochrane Library 2015.

3.9 TABLES AND FIGURES

Variable	n (%)	Mean ±SD
Socio Demographic		
Age (month)		34.36±26.28
≤36 month	46 (59.7)	
>36 month	31 (40.3)	
Gender		
Boy	46 (59.7)	
Girl	31 (40.3)	
Race		
Malay	74 (96.1)	
Chinese	3 (3.9)	
Clinical Characteristics		
Timing of EEG (days)		32.64±51.05
\leq 7 days	40 (51.9)	
> 7 days	37 (48.1)	
Duration of Seizure (minutes)		11.74±11.35
< 20 minutes	61 (79.2)	
\geq 20 minutes	16 (20.8)	
Neurological Assessment		
Normal	77(100)	
Abnormal	0 (0)	
Family History of Seizure		
No	37 (48.0)	
Febrile Seizure	34 (44.2)	
Epilepsy	6 (7.8)	
Seizure Type		
Generalized Seizure	76 (98.7)	
Focal Seizure	1 (1.3)	
Frequency of Seizure in 24-Hour		
One	32 (41.6)	
Two	23 (29.9)	
More than two	22 (28.5)	

 Table 1. Socio-demographic and clinical characteristics of CFS patients (n=77)

Table 2. Distribution of socio-demographic and clinical characteristics of CFS patients

 according to EEG outcome

Variables	Abnormal EEG, n=14		Normal EEG, n=63	
	n(%)	Mean ± SD	n(%)	Mean ± SD
Demographic				
Age (month)		36.36±27.68		33.92±26.16
\leq 36 month	8 (17.4)		38 (82.6)	
> 36 month	6 (19.4)		25 (80.6)	
Gender				
Boy	9 (19.6)		37 (80.4)	
Girl	5 (16.1)		26 (83.9)	
Race				
Malay	13 (17.6)		61 (82.4)	
Chinese	1 (33.3)		2 (66.7)	
Clinical Characteristics				
Timing of EEG (days)		37.71±61.98		31.51±48.79
\leq 7 days	7 (17.5)		33 (82.5)	
> 7 days	7 (18.9)		30 (81.1)	
Duration of Seizure		9.79±12.90		12.17±11.04
(minutes)				
< 20 minutes	12 (19.7)		49 (80.3)	
\geq 20 minutes	2 (12.5)		14 (87.5)	
Neurological Assessment				
Normal	14 (18.2)		63 (81.8)	
Abnormal	0 (0)		0 (0)	
Family History of Seizure				
No	4 (10.8)		33 (89.2)	
Febrile Seizure	8 (23.5)		26 (76.5)	
Epilepsy	2 (33.3)		4 (66.7)	
Seizure Type				
Generalized Seizure	14 (18.4)		62 (81.6)	
Focal Seizure	0 (0)		1 (100)	
Frequency of Seizure in				
24-Hour				
One	4 (12.5)		28 (87.5)	
Two	2 (8.7)		21 (91.3)	
More than two	8 (36.4)		14 (63.6)	

(95% CI) 1.00 1.14(0.35-3.68) 1.00 0.74(0.22-2.46)	(df) 0.048(1)	0.827
1.14(0.35-3.68) 1.00		0.827
1.14(0.35-3.68) 1.00		0.827
1.00		0.827
	0.240(1)	
	0.240(1)	
0.74(0.22-2.46)	0.240(1)	
	0.240(1)	0.625
1.00		
0.43(0.04-5.06)	0.456(1)	0.499
1.00		
0.91(0.28-2.90)	0.026(1)	0.872
1.00		
1.71(0.34-8.58)	0.430(1)	0.512
1.00		
2.53(0.69-9.37)	1.956(1)	0.162
.12(0.56-30.16)	1.949(1)	0.163
1.00		
	0.197(1)	0.657
4.00(1.03-15.6)	3.990(1)	0.046
	0.43(0.04-5.06) 1.00 0.91(0.28-2.90) 1.00 1.71(0.34-8.58) 1.00 2.53(0.69-9.37) 1.12(0.56-30.16) 1.00 0.67(0.11-3.99)	$\begin{array}{cccc} 0.43(0.04\text{-}5.06) & 0.456(1) \\ 1.00 \\ 0.91(0.28\text{-}2.90) & 0.026(1) \\ 1.00 \\ 1.71(0.34\text{-}8.58) & 0.430(1) \\ 1.00 \\ 2.53(0.69\text{-}9.37) & 1.956(1) \\ 1.12(0.56\text{-}30.16) & 1.949(1) \\ 1.00 \\ 0.67(0.11\text{-}3.99) & 0.197(1) \end{array}$

Table 3. Univariate analysis of variables in CFS patients and abnormal EEG outcome.

^a Simple Logistic Regression

3.10 GUIDELINES/ INSTRUCTIONS TO AUTHORS OF SELECTED

JOURNAL

The selected journal is Hong Kong Journal of Emergency Medicine

Hong Kong Journal of Emergency Medicine 香港急症醫學期刊



Web Search Q

Instruction to Authors

The Hong Kong Journal of Emergency Medicine is a peerreviewed bi-monthly biomedical publication of the Hong Kong College of Emergency Medicine and The Hong Kong Society for Emergency Medicine and Surgery. The Journal publishes original research articles, review articles, case reports, and educational information related to all aspects of clinical practice and emergency medicine research in the hospital and prehospital settings. The Journal is indexed in EMBASE/Excerpta Medica, Science Citation Index Expanded (SCIE) and Scopus.

Copyright

All manuscripts submitted to the Hong Kong Journal of Emergency Medicine must be original works that have not been previously published. Following acceptance, the Hong Kong Journal of Emergency Medicine reserves copyright of all published materials and such materials may not be reproduced in any form without the written permission of the Journal.

Liability and ethics

All statements in articles are the responsibility of the authors. The Editorial Board, the Hong Kong College of Emergency Medicine and The Hong Kong Society for Emergency Medicine and Surgery accept no responsibility or liability for materials contained herein. Authors are expected to comply with the provisions of the Declaration of Helsinki. Patient confidentiality and anonymity should always be preserved.

Style and review process

All manuscripts should be written in English. Spelling should follow the Concise Oxford Dictionary. Manuscripts should follow the style of the Vancouver agreement detailed in the International Committee of Medical Journal Editors' "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication".

All manuscripts will be subjected to editorial review. Those that do not comply with the instructions to authors, or those that are of insufficient interest, will be returned. Retained manuscripts will be sent for peer review. Reviewers and authors will be blinded to each other. The final decision of acceptance rests with the Editorial Board. Rejected manuscripts will be destroyed unless requested by the author, in advance, to be returned.

The Editorial Board reserves the right to edit all articles for the purpose of style, format and clarity. Authors may be required to revise their manuscripts for reasons of style and content. Manuscripts with excessive typographical errors may be returned to authors for retyping. Compliance by authors to requested revisions does not automatically bind the Journal to publish the articles. Submitted manuscripts for one category may be published under another category, subject to the decision of the Editorial Board. Illustrations will generally be published in black and white. Special request from authors for reproducing colour figures will be entertained only if they pay the whole cost in advance.

Manuscript submission

Manuscripts can only be submitted electronically through the email.

Manuscripts should be sent to: Editor-in-Chief, Hong Kong Journal of Emergency Medicine Hong Kong College of Emergency Medicine Room 809, HK Academy of Medicine Jockey Club Building 99 Wong Chuk Hang Road, Aberdeen Hong Kong, China Tel: (852) 28718877 Fax: (852) 2554 2913 Email: higem@hkam.org.hk

Number all pages in the following sequence, beginning with the title page as 1, as: -1. Title page; 2. Abstract:

3. Text;