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Prognosis of febrile seizures in Singapore children

*Wei Ling LEE MBBS(Hon) FRCP(Edin), **Poh Sim LOW MBBS MMed, ***Kwok Chan LUN PhD, ****Uma RAJAN MBBS DPH

**Department of Neurology, Tan Tock Seng Hospital, Singapore. **Department of Paediatrics, National University of Singapore. ***Department of Community, Occupational and Family Medicine, National University of Singapore. ****School Health Services, Ministry of Health, Singapore.*

Abstract

This is a long term outcome study of 856 children with febrile seizure, who were born in two Singapore government hospitals between 1/1/80 and 31/12/82. The cumulative risk for afebrile seizures 5 years later was 1.5%. Clinical features which predicted an increased risk were: febrile seizures lasting more than 30 minutes, febrile seizures with focal features, developmental delay at the time of first febrile seizure and recurrent febrile seizures. This study confirms febrile seizure as a benign paediatric disease, with a small but definite increase in risk for subsequent unprovoked afebrile seizures and epilepsy.

Keywords: febrile seizures, prognosis, recurrence, afebrile seizures, epilepsy, developmental delay, Singapore.

INTRODUCTION

Febrile seizures (FS) occur world-wide with a prevalence of approximately 5% in preschool children. The risk of developing afebrile seizures (AFS) after FS and the prognostic factors have been defined in comprehensive population-based studies in USA.[1,2,3,4] No similar studies have been published from Asian countries. Singapore is a small multiracial country with 78% Chinese, 14% Malay, 7% Indians, 1% other races. Follow-up is available in nearly 100% of patients because there is little migration of the population. This gives us an ideal opportunity to study long-term outcome and to compare this between different races sharing a relatively homogeneous environment.

MATERIALS AND METHODS

Definition

A *febrile seizure* was defined as a seizure that occurs in childhood after age one month, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seiures or previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures. This is the definition recommended in the guidelines for epidemiologic studies on epilepsy issued by the International League Against Epilepsy.[5]

Most patients had their seizures before admission, and if the parents reported a history of fever, this was accepted as a FS. For seizures occurring in the hospital, an axillary temperature of 37.8 °C or more was accepted as fever.

An *unprovoked afebrile seizure* (AFS) is one which occurs in the absence of fever or infectious illness, and is not symptomatic of recognised acute neurological illness.

Subjects and method

The population base of the study were 30,754 children born in two government hospitals (Toa Payoh Hospital and Alexandra Hospital) between 1/1/80 and 31/12/82 who subsequently developed febrile seizure. The cumulative incidence of febrile seizure estimated from this study is the subject of a separate report.[6] This is a report of the long term follow up of these children. The Toa Payoh Hospital and Alexandra Hospital were chosen as population base of the study because the patients who were delivered in these two government hospitals tended to be from the lower socioeconomic classes and less likely to seek treatment in private hospitals when they subsequently became ill. Hence, case indentification by review of hospital records of government and university hospitals was likely to be more complete.

The data of the long term follow up is based on case tracing from hospital records as well as further contact with examination by physicians. Hospital discharge diagnoses of all government and university hospitals between 1/1/1980 and 31/12/1993 were searched for diagnoses of seizures, epilepsy and any disease which may be

Address correspondence to Dr. Wei Ling LEE, Department of Neurology, Tan Tock Seng Hospital, Moulmein Road, Singapore 308433

associated with seizures such as meningitis, encephalitis, encephalopathy, Reye's syndrome, cerebral palsy, mental retardation etc. The records of all patient born between 1/1/1980 and 31/12/1982 with any of the above diagnoses were traced, patients with seizures of any type were identified and their records abstracted.

The electroencephalography (EEG) laboratories at Tan Tock Seng Hospital, Singapore General Hospital and National University Hospital serve all the government and university hospitals in Singapore as well as many of the private practitioners. The name and birth certificate number of all patients who were born between 1/1/1980 and 31/12/1982 who had EEG studies in any of the three laboratories were obtained. Their medical records were traced, those with seizures identified and their records abstracted.

Eight hundred and sixty patients met the criteria and were included in the study. The clinical features of the FS (single or multiple in 24 hours, duration, and presence of any focal features), developmental milestones, family history of seizures, findings on physical examination, and results of laboratory investigations were obtained from the medical records. The families were contacted between 1988 and 1994 and were asked to come to the School Health Clinic for medical evaluation. Families who refused to come to the School Health Clinic were interviewed by telephone, and the academic results of these patients were obtained from their schools.

At follow-up, a detailed seizure history, family history of seizures in first degree relatives, and developmental history was obtained in all patients. For those patients who came to the School Health Clinic a complete physical and neurological examination as well as an IQ test (the Colored Progressive Matrices) were performed. Where possible, the medical records of the relatives reported to have seizures were traced and reviewed.

Of the 860 children who were identified, 18 did not come for the medical evaluation. However, follow-up information on 14 children was available either from hospital records or through telephone calls to the family. Only 4 had no follow-up information available.

Statistical Analysis

Because length of follow-up influences the probability of observing further seizures, the variable length of follow-up for each patient was taken into account in the statistical methods of analysis used for calculating risk of AFS. Univariate analyses were performed using the Kaplan-Meier procedure with test of significance done using the log-rank method. Multivariate analysis using Cox proportional hazards model was carried out to examine the extent to which potential prognostic factors were associated with the subsequent development of AFS. The model was used to derive rate ratios - that is, the ratio of the rate of AFS in patients with a given factor to that in patients without that factor.

RESULTS

Of the 860 patients identified, 4 were excluded from the study because no follow-up information was available. The other 856 patients had an average follow-up duration of 6.8 years. There were 502 males and 354 females. The average age at the first FS was 21.4 months, with a range of 31 days to 11.6 years.

Twenty patients subsequently developed AFS, of whom 16 had recurrent AFS or epilepsy. The average duration between the first FS and the first AFS was 4.1 years. The cumulative risk for AFS at 5 years follow-up was 1.54%.

Univariate analysis showed that age and sex were not significant risk factors. There was a racial difference in risk for AFS. The cumulative risks at 5 years for Chinese, Indian and Malay patients were 1.27%, 4.23%, 0.92% respectively. Only the difference between Chinese and Indians was significant ($P<.02$).

Family history of seizures in first degree relatives (either FS or AFS)was not a significant risk factor. The presence of developmental delay at the time of first FS was a highly significant factor for risk of subsequent AFS. The cumulative risk at 5 years was 0.8% for patients who were developmentally normal, and 7.61% for patients who were developmentally delayed ($P<.0001$).

Of the features of the FS, multiple seizures within 24 hours did not significantly increase the risk for subsequent AFS. The risk associated with duration of FS was analysed by comparing three groups of patients, those with FS lasting 15 minutes or less, those with FS lasting more than 15 to 30 minutes, and those with FS lasting more than 30 minutes. The cumulative risk at 5 years were 1.1%, 0%, and 17.2% respectively. Only those with FS lasting more than 30 minutes had a significant increase in risk ($P<.0001$). FS with focal features had a greatly increased risk compared to FS with no focal features. The cumulative risk at 5 years for AFS was 22.8% vs 0.97% ($P<.0001$).

Recurrent FS was a significant risk factor. The cumulative risks at 5 years for patients with one FS, two FS and more than two FS were 0.51%, 3.83%, 3.91% respectively. The differences were significant between patients with one and two FS (P=.0005), and between patients with one and more than two FS (P=.001). There was no significant difference in risk between those with two FS vs those with three or more FS.

On multivariate analysis, FS with focal features, FS with seizures lasting more than 30 minutes, presence of developmental delay and recurrent FS were significant risk factors (Table 1). Sex, age at time of first FS, age at time of last FS, more than one seizure in 24 hours and family history of seizures of any type were not significant risk factors. Indian patients had an increased risk but this did not reach statistical significance (P<.07)

Six children had cerebral palsy, 5 of the 6 were also mentally retarded. All 6 had developmental delay when they presented with their first FS. 12 children had moderate to severe mental retardation without cerebral palsy. 9 of the 12 had developmental delay and 3 were recorded as being developmentally normal when they presented with their first FS. One single patient had FS lasting 6 hours with twitching of right limbs followed by post-ictal right hemiparesis and aphasia which persisted for a few months and then resolved completely.

DISCUSSION

The largest and most comprehensive study on FS is the National Institute of Neurological and Communicative Disorders and Stroke Collaborative Perinatal Project (NCPP). This was a multicentre study in which 1,706 patients with FS were followed up to 7 years. Most of the patients were seen only as outpatients for their FS. AFS developed by the age of seven years in 3.0%. The risk factors were suspect or abnormal neurologic or developmental status before any seizure, FS longer than 15 minutes, multiple seizures within 24 hours, FS with focal features, and family history of AFS in a first degree relative. Sex and race were not significant risk factors. Age less than one year at the time of first FS, and recurrent FS increased the risk for AFS on univariate but not on multivariate analyses.[1,2]

The other large population-based study is that by Annegers et al. They studied a cohort of 709 children who had an initial FS while residing in Rochester, Minnesota. They also found preexisting neurological deficits and/or mental retardation, FS longer than 30 minutes, multiple seizures within 24 hours, and FS with focal features to be significant risk factors. Family history of FS or AFS was not a significant risk factor on univariate or multivariate analysis. Recurrent FS was a signficant factor on univariate but not multivariate analysis. After excluding 22 children with mental retardation and/or cerebral palsy, the cumulative risk of AFS was 4.5% by age 10 years.[3,4]

Both the NCPP and the Rochester studies were population-based in contrast to our subjects all of whom were hospitalised. In the NCPP study, 7.6% had FS longer than 15 minutes, 16.2% had more than one seizure in 24 hours, 4.0% had focal seizures.[1] In our study, 11.9% had FS longer than 15 minutes, 22.4% had more than one seizure in 24 hours, 2.7% had focal features. Hence it appears that our patients had more "severe" FS than those in the NCPP study. Similar figures for comparision was not available from the Rochester study. However, that study

TABLE 1: Risk factors for subsequent AFS after FS

Risk factor	Proportional hazards model		
	Rate ratio	95% Confidence interval	P value
FS with focal features	8.5	2.9 – 24.6	.0001
Developmental delay	4.8	1.9 – 11.8	.0008
FS longer than 30 minutes	4.8	1.5 – 15.9	.01
One recurrence of FS	5.0	1.5 – 16.9	.01
Two of more recurrence of FS	4.0	1.3 – 12.5	.02

specifically excluded children with preceding neurological deficit or mental retardation in their final analysis,[4] and this would result in a remaining group of patients with lower risk for AFS than ours. In the NCPP study, AFS developed in 3.0% of the children by age 7 years.[1] In the Rochester study 4.5% developed AFS by age 10 years.[4] In our study, the average age at last follow-up was 8.6 years, 2.3% had developed AFS by the time of last follow-up. In spite of having higher rates for adverse prognostic factors for AFS, our patients have a lower risk of AFS following FS.

The risk factors for development of AFS after FS identified in our study are very similar to the two studies in USA.[1,2,3,4] FS with focal features, prolonged FS, presence of developmental delay when the patient presents with the first FS are all significant risk factors in both univariate and multivariate analyses in our study. Family history of seizures was not found to be a significant risk factor in either univariate or multivariate analysis. This differs from the finding of the NCPP[2] but is similar to the Rochester study.[4] Multiple seizures within 24 hours was not a significant risk factor on either univariate or multivariate analyses, in contrast to the findings in both the NCPP and the Rochester study.[1,3]

We found recurrence of FS to be a significant risk factor for subsequent AFS on both univariate and multivariate analysis. This differs from both the NCPP[2] as well as the Rochester study.[4] This has important clinical implications. If recurrence of FS increases the risk for subsequent AFS, then preventive treatment of FS is indicated. However, in our study, the risks for subsequent AFS after two vs. three or more FS were similar. It would not be practical to treat all patients presenting with a first FS, yet by the time a patient presents with the second FS, the increased risk has already been incurred. Hence, the arguement for preventive treatment of FS is not strong.

No case of persistent neurological deficit or death has resulted from FS in our study. Although we cannot exclude FS as a cause of mental retardation in the rare patient, it is a distinctly uncommon occurrence.

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