行政院國家科學委員會補助專題研究計畫成果報告

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※ （計畫名稱）台灣地區癲癇症臨床及流行病學研究
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計畫主持人：劉宏輝

共同主持人：

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執行單位：台大醫院神經部

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行政院國家科學委員會專題研究計畫成果報告

計畫名稱:台灣地區癲癇症臨床及流行病學研究

The Clinical and Epidemiological Studies of Epilepsy in Taiwan

計畫編號：NSC 89-2314-B-002-145

執行期限：88 年 8 月 1 日至 89 年 7 月 31 日

主持人：劉宏輝

執行機構及單位名稱:台大醫院神經部

中文摘要

本研究的目的在估計台灣本土點頭癲癇症之發生率、盛行率和死亡率；同時嘗試找出該症相關危險因子。從一家醫學中心找出所有被診斷為癲癇症的病患共 12694 個，再從此族群找出 1985 至 1997 年被確診為點頭癲癇症的 69 個病患作為一回溯性研究世代。利用點頭癲癇症回溯性研究世代和台灣全民健保資料及全國死亡檔估計發生率、盛行率和死亡率。利用醫院病例對照研究法探討相關危險因子。69 個點頭癲癇症病患中僅 25 位完成電訪問卷調查。從同一個醫學中心其他疾病類別隨機抽樣得 106 個有病的人組成「疾病對照組」。另外從同一時期在該醫學中心出生的小孩隨機抽樣得 139 個人組成「正常對照組」。利用迴歸分析估算危險對比值和 95%信賴區間。該醫學中心點頭癲癇症發生率估計為每一千活產數約 0.06 人；0 到 9 歲點頭癲癇症盛行率為每一千人約 0.05。點頭癲癇症的死亡率比疾病對照組約高兩倍。危險因子包括結節性硬化症、腦性麻痺和除中樞神經系統外其他先天性畸形；週產期危險因子包括新生兒窒息。產後因素如發病前發展遲緩和點頭癲癇症呈高度相關。本研究所獲得之結果不僅可以幫助我們瞭解台灣點頭癲癇症之流行病學，也更清楚的詮釋了點頭癲癇症之相關病因。

Abstract

A retrospective cohort with IS is obtained from one medical center to identify 69 IS cases (from 1985 to 1997). This cohort in conjunction with claim data from national health insurance was used to estimate prevalence, and incidence. A hospital-based case-control study was conducted to find out risk factors. Only 25 out of 69 IS are completed by telephone interview with questionnaire. A total of 106 subjects and 139 subjects in Disease Control and Normal Control, respectively were obtained as comparison groups. Unconditional logistic regression was used to calculate odds ratios and 95% CI. Incidence and prevalence (aged 0-9 years) are estimated as 0.06 per thousand live births and 0.05 per thousand. Significant prenatal factors include tuberous sclerosis, cerebral palsy, and other congenital anomalies. Neonatal asphyxia (perinatal factor) significantly accounts for the occurrence of IS. Developmental delay before onset of disease (postnatal factor) is highly associated with IS. Information obtained in this study not only make a clear understanding of disease burden of IS in this society but clarify more etiology of IS than before.

Introduction

Annual incidence rate of IS was reported to range from 0.16 to 0.42 per thousand lives. Prevalence rate of was IS reported ranging from 0.14 to 0.21 per thousand children aged from birth through 9 years. It is timely to conduct a population-based survey to estimate descriptive epidemiological profiles in Taiwan. However, doing so is costly and time-consuming. To tackle this problem, an efficient capture-recapture design plus data-linkage is therefore proposed to estimate the disease frequency of IS.

It is also worthwhile to identify risk factors associated with IS in order to prevent IS. Empirical evidence on risk factors associated with IS is rather meager and limited. To tackle both problems, one may need to use multiple comparison groups. It is worthwhile to conduce a case-control study using multiple comparison groups among Taiwanese.

Materials and Methods

A total of 69 IS cases with International Classification Code (ICD) related to epilepsy from 1985 through 1997 were ascertained from Computerized Information Center at National Taiwan University Hospital (NTUH), This forms the retrospective cohort of this study. Through the use of capture-recapture analysis, this cohort was linked with data on National Health Insurance (NHI) to estimate nationwide IS cases.

To avoid recall bias, two types of control were chosen as comparison groups, including "Disease Control", a group of etiologically-defined diseases and "Normal Control" derived from all neonates in the contemporary period as the IS group at the same medical center. Approximately two controls per case in Disease control and Normal control were randomly sampled in light of the above criteria.

Mothers of every subject in IS group and control groups were contacted by the trained physicians. All attendants were interviewed with a closed-structure questionnaire. Information of the questionnaire consists of demographic characteristics, family history of epilepsy or seizure, central nervous system anomaly and psychiatric disease, prenatal complications, gestational history, and Infants' disease history, In addition, developmental condition of IS on status of seizures and mental retardation were also collected.

The content validity of questionnaire was checked on the basis of expert opinions including one expert in epidemiology and two experts in specialty of neurology. Of 69 IS, only twenty-five cases were successfully completed by telephone interview with mothers of cases or patients. A total of 106 subjects and a total of 139 subjects in Disease Control group and Normal Control group, respectively, were willing to answer the questionnaire during the interview.

Univariate and multivariate analysis using unconditional logistic regression was performed to identify significant factors accounting for IS. Statistical significant level was set up at level of 0.05.

Results

Among 25 cases available for analysis, 21 are symptomatic cases and 4 cases are cryptogenic. Using the method of capture-recapture yields 142 estimated prevalent cases of IS from 1985 to 1997 in Taiwan. Prevalence of IS aged 0-9 years could be estimated as 0.046 per thousand by dividing this figure with numbers of population aged 0-9 years who registered in our NHI system. According to vital statistics issued by Ministry of Interior in 1997, there are 3226109 children aged 0-9 years. Suppose 95% children have accessibility to national health insurance system, the denominator was estimated as 3064803. The prevalence of IS for those aged 0-9 years is therefore estimated as 0.046 per thousand children.

Only 2 cases out of 69 IS were delivered in NTU hospital and the rest are referred from other

hospital. There were a total of 33263 live births in NTU hospital in the contemporary period as IS cases. Annual incidence rate of IS is estimated as 0.060 per thousand live births.

Table 1 shows results of univariates analysis for demographic features and risk factors. As regards prenatal factor on family history, IS is more likely to have family history of psychiatric disease than two other groups. Congenital cerebral anomaly is more frequent in the IS group and Disease Control group than in the Normal Control group. The corresponding odds ratio for cerebral anomaly other than hydrocephalus and microcephaly is 4.60 (95% CI=0.96-21.97). The IS group is approximately four times (OR=3.73, 95% CI=1.26-11.10) and three times (OR=2.84, 95% CI=1.14-7.08) more likely to have TS and CP, respectively, than the Disease Control group.

For perinatal factors, the IS and Disease Control group are more susceptible to neonatal asphyxia than the Normal Control group. Compared with Normal Control, there is a fourteen-fold (OR=13.7, 95% CI=2.36-79.71) risk for neonatal asphyxia in the IS group.

Concerning postnatal factor, febrile convulsion after delivery tends to be more frequent in the IS group than two other control groups. IS group is much more likely to have developmental delay than the Disease Control group (OR=2.11, 95% CI=0.87-5.14) and the Normal Control group (OR=100.50, 95% CI=20.10-502.40). The occurrence of CNS infection in the IS groups is not significantly higher than the other two groups. No information on head injury is obtained for the IS group.

Table 2 shows results of multivariate analysis for the adjusted OR using IS versus Normal Control by incorporating significant factors in the univariate analysis plus age and sex. After adjustment for variables in each other, significant factors still persist including developmental delay (adjusted OR=30.12, 95% CI=5.58-162.49), asphyxia (adjusted OR=29.57, 95% CI=3.04-287.41), other cerebral congenital anomalies (adjusted OR=4.51, 95% CI=1.02-19.94). Results of multivariate analysis for the adjusted OR using IS versus Disease Control group are as follows (Table 3). Adjusted odd ratios for significant factors are 15.61 (95% CI=1.37-178.26), 9.05 (95% CI=2.24-36.59), 4.86 (95% CI=1.58-14.99) for postterm, tuberous sclerosis and cerebral palsy, respectively.

Among 25 interviewed cases, 46% are still under the attack of seizure, 77% have developmental delay and around 60% have suffered from CP or limbs handicap. Fifteen cases out of seventeen cases (68%) with developmental delay are considerably severe.

Discussion

To the best of our knowledge, this is the first report to use a retrospective cohort design in combination with a hospital-based case-control study to estimate disease frequency, and risk factors associated with IS in Taiwan. Our results showed prevalence rate and annual incidence rate among children aged under 10 years were estimated as 0.046 per thousand and 0.06 per thousand live births, respectively. This is only one-third of figures estimated from western countries. This may be partly due to underascertainment of IS or partly due to the classification of IS into other types of epilepsy in Taiwan. These estimates are very helpful for understanding the natural history and burden of IS in this country.

The risk factors for IS were investigated via prenatal, perinatal, and postnatal periods in this study. The prenatal risk factors for IS found in this study include TS, CP and other cerebral congenital anomalies. The positive association among TS, CP and IS were consistent with the previous findings. A perinatal factor, neonatal asphyxia, was found to be an account for the occurrence of IS. Postnatal factors such as developmental delay before onset of disease is

highly associated with IS occurrence of IS. This is also in agreement with biological plausibility.

From methodological viewpoint, our study design gets several advantages over other previous studies. Firstly, a retrospective cohort plus NHI information using capture-recapture method provides an efficient way to estimate incidence and prevalence of IS. This dispenses with using a large nationwide survey for estimating these basic epidemiological figures. However, it could be argued that estimation of parameters using the capture-recapture method requires some premises. For instance, it is assumed that the probability of being listed in NHI is independent of that identified in NTUH. It means that those who were not re-captured by 1997 NHI system for IS between 1985 and 1997 in NTU would have been as equal chance of getting access to NHI system and of being misclassified as other types of epilepsy as those who were re-captured in 1997 system had they been enlisted in NHI system. In addition, we also assume that the characteristics of IS in other hospital in the same period as NTUH and not listed in NHI system would be similar to that of 52 IS in NTUH and not identified in NHI system. However, these two assumptions are not unreasonable since NHI system has already covered 95% population and subjects with IS seeking for medical services may be rather similar.

Second, a hospital-based case-control study in the present study provide an opportunity to identify risk factors that cannot be found using data on case series due to lacking of comparison. Furthermore, another advantage is the use of two control groups. The merit of using two controls is to assess recall bias that has been commonly observed in retrospective studies since those who had disease is more vigorous to recall relevant events than those who had not. If one can get consistent results from two series of controls, the result will be more convincing.

There are two other major caveats in this study. Firstly, as only 25% IS cases participated in this study, it could be criticized that risk factors associated with IS for non-respondents may be different from respondents and therefore 25 IS in this study may not be representative of the whole cohort. However, this may not be a serious issue according to the following evidences. The reasonable finding on peak age at onset as mentioned in the above suggests that it is unlikely that 25 IS cases are a biased sample. In addition, as the proportion of cryptogenic type in the whole cohort is identical to the present sample this suggests that the present sample may be representative of the whole retrospective cohort.

In conclusion, the present study used a retrospective cohort study design in combination with claim data on health insurance and population-based mortality data to estimate the disease frequency and prognosis of IS. These estimates are very helpful for understanding the natural history and burden of IS in this country. Elucidation of risk factors associated with IS was also performed by a hospital-based case-control study. Information on age onset plus the following risk factors can provide an empirical evidence on consultation with mothers who are at increased risk of IS. Our results not only make a clear understanding of disease burden of IS in this society but clarify more etiology of IS than before.

References

Hauser WA. The prevalence and incidence of convulsion disorders in children. Epilepsia 1994;35 suppl 2:S1-6.

Luthvigsson P, Olafsson E, Sigurthardottir S, Hauser WA. Epidemiologic features of infantile spasms in Iceland. Epilepsia 1994;35:802-5.

Trevathan E, Murphy CC, Allsopp MY. The descriptive epidemiology of infantile spasms among Atlanta children. Epilepsia. 1999;40:748-51.

Cowan LD, Hudson LS. The epidemiology and natural history of infantile spasms. J Child Neurol 1991;6:355-64.

infantile spasms. J Child Neurol 1991;6:355-64.

Rantala H, Shields WD, Christenson PD, et al. Risk factors of Infantile spasms compared with other seizures in children under 2 years of age. Epilepsia. 1996;37:362-6.

Murphy DJ, Hope PL, Johnson A. neonatal risk factors for cerebral palsy in very preterm babies: case-control study. Brit Med J. 1997;314:404-8.

Ozawa H, Hashimoto T, Endo T, et al. West syndrome with periventricular leukomalacia : A morphometric MRI study. Pediatr Neurol 1998;19:358-63.

Cusmai R, Ricci S, Pinard JM, et al. West syndrome due to perinatal insults. Epilepsia 1993;34:738-42.

Dulac O, Feingold J, Plouin P, et al. Genetic predisposition to West syndrome. Epilepsia 1993; 34:732-7.

Table 2 Multivariate analysis of cases versus normal controls after model fitting and adjusting for age and sex

Variable	OR	95% CI
Developmental delay	30.12*	5.58, 162.49
Asphyxia	29.57*	3.04, 287.41
Other congenital cerbral anomaly**	4.51*	1.02, 19.94
Preterm	7.45	0.63, 88.79
Hydrocephalus	2.42	0.07, 86.48
Febrile convulsion	1.03	0.17, 6.03
Age	1.06	0.97, 1.17
Sex	1.06	0.47, 2.40

* Statistically significant, P<0.05

**Cerebral anomaly other than microcephaly and hydrocephalus

Table 3 Multivariate analysis of cases versus disease controls after model fitting and adjusting for age and sex

Variables that are ncluded in the mode	Odds Ratio	95 % CI
Postterm	15.61 *	1.37, 178.26
Tuberous sclerosis	9.05 *	2.24, 36.59
Cerebral palsy	4.86 *	1.58, 14.99
Febrile convulsion	1.95	0.51, 7.54

*Statistically significant, p<0.05.

Table 1 Univariates analysis for the association between infantile spasms and possible risk factors in Taiwan

Variable	IS N (%)	Disease Controls, N (%)	Normal Controls, N (%)	IS/Disease Control, OR (95% CI)	IS / Normal Control, OR (95% CI)
Age of onset				--	--
(m/o)	0	35(46.7)	0		
0~3	18(78.3)	14(18.6)	0		
>3~8	4(17.4)	5(6.7)	0		
>8~12	1(4.3)	12(16.0)	0		
>12	0	9(12.0)	0		
Premature		31	0		
Gestational age (weeks)					
Preterm	4(16.0)	35(34.0)	1(0.7)	0.37(0.1,1.1)	25.52(2.2,239
Term	18(72.0)	67(65.0)	117(86.7)	1.00	0.95
Postterm	3(12.0)	1(1.0)	17(12.6)	13.9(1.38, 140.07)	(0.26, 3.51)
Family history of psychiatric diseases					
Yes	3(12.0)	6(5.7)	6(4.3)	2.25(0.52, 9.79)	3.02(0.77, 12.98)
No	22(88)	99(94.3)	133(95.7)	1.00	1.00
Hydrocephalus					
Yes	2(8.0)	6(5.7)	1(0.7)	1.45 (0.28,7.65)	12.00 (1.05,137.77)
No	23(92.0)	100(94.3)	138(99.3)	1.0	1.00
Congenital cerebral anomaly*					
Yes	3(12.0)	21(19.8)	4(2.9)	0.55 (0.15,2.02)	4.60 (0.96,21.97)
No	22(88.0)	85(80.2)	135(97.1)	1.00	1.00
Neonatal asphyxia					
Yes	4(16.7)	33(31.1)	2(1.4)	0.44(0.10, 1.40)	13.70(2.36, 79.9)
No	20(83.3)	73(68.9)	137(98.6)	1.00	1.00
Febrile convulsions					
Yes	6(24.0)	10(9.4)	10(7.2)	3.03	4.04
No	19(76.0)	96(90.6)	128(92.8)	1.00	1.00
CNS infection **					
Yes	1(4.0)	3(2.9)	5(3.6)	1.42(0.14, 14.22)	1.10(0.12, 9.85)
No	24(96.0)	102(97.1)	132(96.4)	1.00	1.00
Developmental delay					
Yes	15(60.0)	44(41.5)	2(1.5)	2.11(0.87,5.1	100.50(20.10, 502)
No	10(40.0)	62(58.5)	134(98.5)	1.00	1.00

*Congential brain anomaly other than microencephaly and Hydrocephalus

**Central nervous system infection before onset of disease.