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Mortality in adult patients with epilepsy in Taiwan

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ABSTRACT – To investigate mortality in adult patients with epilepsy in Taiwan, a total of 263 patients with epilepsy aged ≥ 17 years, referred to the outpatient epilepsy clinic between 1 Jan and 31 December 1991, were prospectively enrolled and followed up until 31 December 2000. A total of 32 deaths were reported. Overall case-fatality rate was 12.2%. The age-adjusted standard mortality ratio (SMR) was calculated to compare the risk of death in patients with epilepsy to the general population. Patients with epilepsy had a 3.5-fold higher risk of death as compared with the general population (SMR: 3.47, 95% CI: 2.46-4.91). The Cox proportional hazards regression model was used to assess relevant clinical contributions to death. Patients with an age-at-onset ≥ 40 years had a 4-fold higher risk of death as compared with those with an earlier onset. The multivariate analysis revealed that age-at-onset between 40 and 59 years, tumor etiology, and being male increased the risk of death in epilepsy. One-third of the deaths in patients with age-at-onset between 40-59 years died of liver cirrhosis and hepatoma. Hepatitis B virus infection is endemic in Taiwan, and this is closely associated with liver cirrhosis and hepatoma. Whether anticonvulsants contributed to the hepatotoxicity that led to fatal liver disease in this group needs further investigation.

Key words: epilepsy, mortality, Taiwan, SUDEP

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A population-based, door-to-door neurological survey in Taiwan revealed a prevalence of 0.23% for active epilepsy for age ≥ 40 years (Su *et al.* 1998). Epilepsy can cause a series of unexpected injuries, and can result in an increased risk of death. Mortality in patients with epilepsy has been reported to be 2-3 times higher than in the general population in Western countries (Cockerell *et al.* 1994, Hauser *et al.* 1980, Lhatoo *et al.* 2001, Gaitatzis and Sander 2004). Common causes of death in epilepsy include tumor, trauma, vascular disease, infectious disease, and other etiologies (Nilsson *et al.* 1997, Gaitatzis and Sander 2004). Mortality in epilepsy in Orientals has rarely been reported (Kurokawa *et al.* 1982, Wakamoto *et al.* 2000, Thomas *et al.* 2001) and factors contributory to mortality and the cause of death in patients with epilepsy have not been widely discussed in oriental countries.

A population-based survey in Taiwan revealed the three most common causes of active epilepsy were head injury (28%), cryptogenic (28%) and stroke (20%) (Su *et al.* 1998). Various infections of the CNS, and poor obstetric care during birth make significant contribution to the etiology of epilepsy and infection. Maternal and pe-

rinatal causes account for the majority of deaths in developing countries. Since the clinical course of epilepsy from onset, recurrence, and finally to death is rather diverse, the association between clinical features and epilepsy should be investigated from country to country. We therefore performed a prospective, hospital-based, cohort study to assess the relationships between the clinical features (including age-at-onset of epilepsy, frequency of episodes, types of epilepsy, imaging findings, and etiology of epilepsy), and mortality in patients with epilepsy in Taiwan.

Methods

Study design and subjects

Epilepsy is defined as recurrent seizures without an acute cause (ILAE 1981). We prospectively recruited patients with epilepsy who were at least 17-years-old and newly referred to the outpatient epilepsy clinics at the National Taiwan University Hospital (NTUH) between 1st January 1991 and 31 December 1991. The NTUH is the largest university teaching hospital and one of the major tertiary referral centers in Taiwan. All the patients underwent thorough clinical assessment to ensure that they had active epilepsy, this definition being restricted to patients with epilepsy who had experienced recurrent seizures within the past 5 years or who had been taking anticonvulsants within the last 5 years (Hauser *et al*. 1991). Patients with seizures provoked by acute symptomatic causes were excluded. A total of 263 patients with active epilepsy formed the dataset for analysis. For the etiological causes of remote symptomatic epilepsy, we followed the definition and classification described by Hauser *et al.* (1991).
Each patient received a closed form questionnaire, which included demographic characteristics, age-at-onset of epilepsy, duration of seizures and frequency of episodes, *etc*. The clinical seizure pattern, EEG results, neuroimaging findings (CT and/or MRI), anticonvulsants regimen and etiology of epilepsy were carefully recorded. All of the patients underwent at least one EEG examination (awake and/or asleep), and 217 patients had undergone brain imaging studies. The seizure type was classified on the basis of the International League Against Epilepsy (ILAE) classification (ILAE 1981). All the above information was collected on entry into the study.
This cohort was followed until 31 December 2000. We recorded 32 deaths out 263 patients. The cause of death was assessed in the light of documentary evidence, including medical charts, autopsy findings, and pathological reports. Sudden unexpected death (SUD) was defined as, non-traumatic death in a patient with epilepsy who had been previously healthy or had suffered from a disease which would not normally be expected to result in immediate or sudden death, and those deaths not directly related to seizure or status epilepticus (SE) (Annegers 1998).

Statistical methods

The log-linear model was used to identify significant clinical attributes associated with age-at-onset, gender, frequency of episodes, etiology, seizure type, and imaging findings. To compare the risk of death in patients with epilepsy with that in the general population, the age-adjusted, standard mortality ratio (SMR) for the overall group and the covariate-specific group was calculated following the Breslow and Day method (1987), given age-specific mortality rates from 2000 of the Taiwan mortality registry and person-years stratified by ten-year band age groups. We also used the Cox regression model to calculate adjusted hazard ratios and their 95% confidence intervals for the effect of relevant variables on risk of death including gender, age-at-onset, etiology, imagining, type of seizure, and medication.

Results

Patient description

Table 1 shows the descriptive results for the 263 patients with epilepsy with respect to sex, age-at-onset, epilepsy status, frequency of episodes, medication, imaging findings, and etiological pattern. There was a preponderance of males. Of the 263 patients, 21% had generalized seizures and 79% partial seizures. The frequency of episodes was > 1/day in 8% of patients, 1/day-> 1/week in 22%, 1/week-> 1/month in 24%, and ≤ 1/month in 46%. Sixty percent of patients were receiving monotherapy. The causes were cryptogenic in 60% and remote symptomatic in 40%; in the latter group, the causes were trauma (24%), vascular lesion (23%), congenital malformation (15%), neoplasm (13%), infection (11%), metabolism (9%), and others (2%). The main etiology for those patients with an age-at-onset younger than 20 years was cryptogenic, whereas vascular and neoplastic lesions were the main causes in patients with an age-at-onset ≥ 60 years.

Mortality

Twelve percent (n = 32) of the patients with epilepsy died during the course of the study. The case-fatality rate by age-at-onset was 5.6% for onset between 0-19 years, 9.5% for 20-39 years, 32.1% for 40-59 years, and 46.7% for ≥ 60 years.
Table 2 shows the detailed information on these deaths by groups with age-at-onset of between 1-19 years, 20-39 years, 40-59 years, and ≥ 60 years, respectively. Sixteen patients, with age-at-onset before 40 years, died, the etiology of the epilepsy was similar, and the cause of death was SE or SUD (18.8%), suicide, traumatic head injuries, brain tumor or infection (12.5%), and pulmonary collapse or lymphoma (6.3%). Another 16 patients with age-at-onset after 40 years, died, the cause of death being liver

Table 1. Description of 263 patients with epilepsy in the NTUH.

	Number	%
1. Sex		
Female	119	45.2%
Male	144	54.8%
2. Age-at-onset (yrs)		
0-19	125	47.5%
20-39	95	36.1%
40-59	28	10.6%
60+	15	5.7%
3. Seizure type		
Generalized seizure	53	20.5%
Partial seizure	210	79.5%
4. Frequency		
> 1/day	21	8.0%
1/day - > 1/week	58	22.1%
1/week - > 1/month	63	24.0%
≤ 1/month	121	46.0%
5. Medication		
Monotherapy	157	59.7%
Polytherapy	106	40.3%
6. Imaging findings		
Normal	132	60.8%
Abnormal	85	39.2%
Not done	46	--
7. Abnormal imaging findings		
Atrophy	19	22.1%
Vascular lesions	31	36.0%
Tumor	15	17.4%
CNS infection	4	4.7%
Other	16	19.8%
8. Etiology		
a) remote symptomatic	**105**	**39.9%**
Perinatal	3	2.9%
Neoplasm	14	13.3%
Vascular lesions	24	22.9%
Trauma	25	23.8%
Infection	12	11.4%
Metabolism	9	8.6%
Congenital malformation	16	15.2%
Other	2	1.9%
b) cryptogenic	**158**	**60.1%**

disease, cerebrovascular disease, or malignancy (18.8%), infection, heart disease (12.5%), andasthma, head injury or motor neuron disease (6.3%).

Up to 31 December 2000, 263 subjects had been followed up for an average of 8.2 years to yield a total of 2,154 person-years. By combining age-specific mortality and the corresponding person-years, an age-adjusted SMR of 3.47 (2.46-4.91) was estimated *(table 3)*. This suggests that patients with active epilepsy have a 3.5-fold higher risk of death than the general population. *Table 3* also shows other covariate-specific SMRs.

Table 4 shows the hazard ratio (HR) estimated by univariate and analysis for the variables of age-at-onset, frequency of episodes, imaging findings, etiology, and medication. Compared to patients with an age-at-onset of < 40 years, patients with an age-at-onset between 40 and 59

Table 2. Etiology and cause of death in 32 epilepsy patients, presented by age-at-onset of epilepsy.

Age-at-onset	Age-at-death	Gender	Seizure type	Etiology	Cause of death
1-19 yrs					
1	37	M	SPS+CPS+2°G	Cryptogenic	SUD
15	36	M	CPS+2°G	Perinatal insult	SUD
6	56	F	SPS+2°G	Cryptogenic	Status epilepticus
12	30	F	CPS+2°G	Cryptogenic	Status epilepticus
6	20	F	CPS+2°G	Cerebral infarct	Encephalitis
8	46	M	CPS+2°G	Cryptogenic	Traumatic head injury
14	32	F	SPS+CPS+2°G	Cryptogenic	Sepsis
20-39 yrs					
22	28	M	GTC	Meningitis	Suicide
23	28	M	CPS+2°G	Trauma	Suicide
24	30	M	GTC	Cryptogenic	Status epilepticus
25	36	F	CPS+2°G	Cryptogenic	SUD
29	33	M	GTC	Astrocytoma	Glioblastoma multiforme
36	38	F	SPS	Astrocytoma	Brain tumor
32	39	M	CPS	Astrocytoma	Lymphoma
35	50	F	CPS	Cryptogenic	Pulmonary collapse
39	45	M	CPS+2°G	Cryptogenic	Traumatic head injury
40-59 yrs					
41	42	M	GTC	Trauma	Liver cirrhosis
44	54	M	SPS+CPS+2°G	Cryptogenic	Liver cirrhosis
47	47	F	SPS	Liver neoplasm with brain metastasis	Liver neoplasm with brain metastasis
53	64	F	GTC	Oligodendrioma	Gastric tumor
42	59	M	CPS	Cryptogenic	Hypertensive heart disease
52	55	M	CPS+2°G	Vascular	Rheumatic heart disease
42	50	M	SPS	Cryptogenic	Pneumonia
55	66	M	SPS	Intracerebral hemorrhage	Sepsis
58	64	M	GTC	Cryptogenic	Traumatic head injury
60+ yrs					
71	78	M	GTC	Multiple infract	Cerebral vascular disease
80	88	M	GTC	Intracerebral hemorrhage	Cerebral vascular disease
82	85	M	SPS	Multiple infract	Cerebral vascular disease
60	61	M	SPS+2°G	Renal cell carcinoma	Renal cell carcinoma
67	76	M	SPS+2°G	Cerebral infarct	Malignancy of pancreas
60	74	M	SPS+2°G	Meningoma	Asthma
73	76	M	GTC	Trauma	Motor neuron disease

SPS: simple partial seizure, CPS: complex partial seizure, 2°G: secondary generalization, GTC: generalized tonic clonic seizure, SUD: sudden unexpected death.

years had a 3.76-fold (1.19-11.92) higher risk of death. The risk of death in males was double that in females (HR = 2.19, 1.01-4.73). Compared to patients with cryptogenic etiology, those with an etiology of neoplastic lesion had a 5.61-fold (2.20-14.30) higher risk of death.

Results of multivariate analysis that included factors found to be significant in the univariate analysis are shown in *table 4*. Age-at-onset was still significant after adjustment for other factors. Compared to age-at-onset of less than 40 years, the adjusted relative mortality rate for age-at-onset of 40-59 was 3.56 (1.01-12.51) and ≥ 60 was 3.99 (0.67-23.72). The adjusted hazard ratio for males *versus* females was 2.28 (1.00-5.19). After adjustment for age-at-onset, age-at-entry, and sex, the etiology had an independent effect on the prognosis, the relative mortality rates compared to a cryptogenic etiology being 4.67 (1.76-12.37)

Table 3. Age-adjusted standard mortality ratio (SMR) of active epilepsy by gender and etiology.

Group	Observed deaths	Expected deaths	SMR (95%CI)
1. Gender			
Male	23	4.5	5.07 (3.37-7.63)
Female	9	4.7	1.92 (1.00-3.70)
2. Etiology			
a) remote symptomatic	19	4.5	4.25 (2.71-6.67)
Perinatal	1	0.0	26.37 (3.71-187.19)
Neoplasm	7	0.6	12.67 (6.04-26.57)
Vascular lesions	7	2.7	2.61 (1.25-5.48)
Trauma	3	1.0	3.06 (0.99-9.49)
Infection	1	0.2	4.62 (0.65-32.81)
b) cryptogenic	13	4.3	3.05 (1.77-5.25)
Overall	32	9.2	3.47 (2.46-4.91)

for neoplastic lesions, 1.37 (0.46-4.13) for a vascular etiology, 0.81 (0.22-2.95) for trauma, and 1.18 (0.15-9.27) for infection.

Discussion

The present study sheds light on the relationships between age-at-onset and mortality in adult patients with epilepsy. Patients with an age-at-onset ≥ 40 years had a 4-fold higher risk of death than those with an earlier onset. Such an increased mortality may be attributed to the high proportion of brain tumors and vascular lesions in epileptic patients, combined with later age-at-onset *(table 2)*. A high hazard ratio was noted among patients with neoplasm as the underlying cause of the epilepsy (4.67 [1.76-12.37]).

Moreover, the result of overall mortality in epileptic patients compared with general population was similar to the previous findings. Patients with epilepsy have a 3.47 times higher risk of death than the general population adjusted for age. Compared with previously reported SMR with follow-up cohort studies in Western countries, this figure is slightly higher than those for community-based studies in Sweden (2.4 [2.0-2.8]) (Alstrom 1950), UK (2.1 [1.8-2.4]) (Lhatoo *et al.* 2001) and Rochester (2.3 [1.9-2.6]) (Hauser *et al.* 1980), but similar to those reported for hospital-based series in Stockholm (3.6 [3.5-3.7]) (Nilsson *et al.* 1997), The Netherlands (3.2 [2.9-3.5]) (Shackleton *et al.* 1999) and the UK (5.1 [3.3-7.6]) (Nashef *et al.* 1995).

The case-fatality rate in the present study was 12.2%. Our result was higher than previous reports in Asia. In the follow-up of 385 Japanese patients with epilepsy, 5.7% had died during the first 10 years after the onset of epilepsy and another 2.9% between 11 and 24 years (Kurokawa *et al.* 1982). A population-based study in Japan with 18.9 mean years of follow-up, revealed that 7 (4.5%) out of 155 patients with epilepsy died (Wakamoto *et al.* 2000). Thomas *et al.* (2001) reported that 18 (7.3%) out of 246 patients died, without examination of the cause of death, during a follow-up period of 12 years, in a tertiary referral center in Kerala, India. Our multivariate analysis results showed that age-at-onset of epilepsy between 40 and 59 years, tumor and being male were important risk factors responsible for mortality in epilepsy.

From *table 2*, it is very interesting to note that, regarding causes of death among patients with onset between 40 and 59 years, one-third died from hepatic diseases. Accumulating evidence has shown that liver cirrhosis and hepatoma are closely related to hepatitis B virus (HBV) infection (Sung 1981, Beasley *et al.* 1981, Yang *et al.* 2002), and Taiwan is a highly endemic area for HBV infection. A survey of Taiwan in 1980 revealed that over 90% of the general population under 40 years old had been infected by HBV, and 15-20% of these are reported to be chronic HBV carriers (Sung 1981). Patients with epilepsy were at greater risk of suffering from liver disease, and this increased risk is probably related to administration of anticonvulsants (Annegers 1998, Galeone *et al.* 1985, Olsen *et al.* 1995). The high prevalence of HBV infection combined with antiepileptic treatment should be considered as important factors related to fatal liver disease in patients with epilepsy in Taiwan. However, this hypothesis needs further investigation.

Increased risk of death was found in epileptic patients with an age-at-onset ≥ 60 years. The increased mortality may be attributed to tumor *(table 4)*. The contribution of tumor to the increased mortality risk in epilepsy in our study is in agreement with that in other population-based studies (Cockerell *et al.* 1994, Hauser *et al.* 1980, Lhatoo *et al.* 2001).

Whether gender is related to mortality in epilepsy is still controversial (Lhatoo *et al.* 2001, Gaitatzis and Sander 2004). Our results show that the male patients had a 2.3-fold increased risk of death when compared to the female patients. It may be argued that a greater likelihood of developing tumors and vascular lesions leads to a

Table 4. Analysis of the association between clinical variables and death in patients with epilepsy.

		Univariate analysis	Multivariate analysis
Variable	**No. of deaths/total**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Age of onset			
0-39	16/220	1.00	1.00
40-59	9/28	3.76 * (1.19-11.92)	3.56* (1.01-12.51)
≥60	7/15	5.09 (0.96-26.92)	3.99 (0.67-23.72)
Frequency			
1/day – > 1/week	6/79	1.00	
1/week – > 1/month	11/63	1.58 (0.58-4.31)	_
≤ 1/month	15/121	1.03 (0.40-2.70)	
Imaging finding			
Normal	12/132	1.00	
Abnormal	15/85	1.18 (0.52-2.69)	_
Not done	5/46	0.97 (0.33-2.80)	
Type of seizure			
CP+2°G	8/88	1.00	
SP	9/45	1.16 (0.41-3.25)	_
SP+2°G	5/20	1.68 (0.51-5.52)	
CP	4/41	0.59 (0.17-2.05)	
GTC	3/38	0.63 (0.16-2.45)	
Etiology			
Cryptogenic	13/158	1.00	1.00
Perinatal	1/3	5.90 (0.75-46.09) $^{+}$	7.07 (0.89-55.97)$^{+}$
Tumor	7/14	5.61** (2.20-14.30)	4.67** (1.76-12.37)
Vascular lesions	7/24	1.69 (0.58-4.95)	1.37 (0.46-4.13)
Trauma	3/25	0.95 (0.27-3.38)	0.81 (0.22-2.95)
Infection	1/12	0.91 (0.12-6.93)	1.18 (0.15-9.27)
Medication			
Polytherapy	8/106	1.00	
Monotherapy	24/157	1.37 (0.61-3.08)	
Age at entry		1.04** (1.02-1.06)	1.00 (0.96-1.04)
Gender			
Female	9/119	1.00	1.00
Male	23/144	2.19 * (1.01-4.73)	2.28* (1.00-5.19)

$^{+}$ $0.1 \leq p < 0.05$ * $0.05 \leq p < 0.01$ ** $p \leq 0.01$

higher risk of death in males. However, such a relationship remains statistically significant even after adjustment for etiology in multiple regression analysis *(table 4)*. An exact relationship needs to be corroborated in the future.

The association between age-at-onset and mortality in epilepsy could be confounded by age, irrespective of epilepsy (Hauser *et al.* 1980, Nilsson *et al.* 1997). Age-at-entry was therefore controlled in the regression analysis model. After adjustment for age-at-entry, a significant relationship between age-at-onset of epilepsy, and mortality was still seen. This suggests that, in addition to an aging effect, age-at-onset of epilepsy may play an important role in mortality in epileptic patients.

A major limitation of the present study was the patient source, as enrolled patients with epilepsy were selected from a hospital population, rather than the general population. Although a hospital-based design may miss mild cases who did not attend hospital, it is unlikely to miss patients with active epilepsy, an inclusion criterion for our study. Moreover, this study was performed in a tertiary referral center, extrapolation of these findings to patients with epilepsy in general should therefore be cautious.

In conclusion, mortality in people with epilepsy is higher than that in the general population. Patients with age-at-onset greater than 40 years had a higher risk of death than those with earlier onset. Higher risk of death among patients with late onset may be determined by etiology, particularly tumor. □

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