

Refractory Seizures in a Young Army Cohort

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Abstract

This survey covered male Singapore citizens born in 1974 who were medically screened at the age of 18 years before enlistment for compulsory military service. Suspected epileptics were referred to government hospitals for further management. Out of 20 542 men, there were 121 epileptics, giving a cumulative incidence of 5 per 1000 by age 18 years. We had information on 106 (87%) of these individuals and were able to interview them and review their hospital records. Seventy-three of the 106 (69%) epileptics had generalised seizures while 14 (13%) had refractory seizures. There was no statistically significant racial bias amongst these epileptics.

Unprovoked afebrile seizures occurred early in these patients, half of whom had seizure onset before 7 years of age. Nine refractory epileptics had a history of febrile seizures, 4 of which were complex febrile seizures. Magnetic resonance imaging identified mesial temporal sclerosis in 2 patients and a hypothalamic lesion in 1 patient. Computed tomographic scans revealed focal cortical atrophy in 2 patients. Nine other patients had normal imaging studies. Nine out of 14 (64%) patients with refractory epilepsy had partial seizures; 4 (29%) had generalised seizures and 1 (7%) was unclassified. This is in contrast to the distribution of the entire cohort of epileptics studied. Two out of 9 patients with refractory partial seizures (gelastic epilepsy and mesial temporal sclerosis) had undergone surgery while 6 of the other 7 patients refused to consider surgery.

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Introduction

This survey of Singaporean males born in 1974 studied the characteristics of young men diagnosed to have epilepsy on enlistment, and in particular attempted to characterise those with refractory seizures. There being little local data¹ on the epidemiology of epilepsy in Singapore, this survey attempts to clarify the patterns of epilepsy using a cohort of individuals where accurate information on seizure patterns could be obtained.

Patients and Methods

Male citizens in Singapore are medically screened at the age of eighteen years before enlistment for compulsory military service. Suspected epileptics identified by this process are then referred to government hospitals for further management. We interviewed all such patients and their parents, and reviewed their hospital records. At the time of this survey, the 1974 enlistment cohort was either close to completing or had just com-

pleted full-time national service, making our interviews easier and more convenient.

Additionally, these patients were unlikely to conceal their illnesses, as they were exempted from strenuous activities when so diagnosed.

Definitions

Epilepsy was defined as a chronic condition characterised by recurrent seizures unprovoked by any immediate identifiable cause.²

Febrile seizures were defined as seizures occurring in infancy or childhood, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous non-febrile seizure are excluded.³

Complex febrile seizures were defined as febrile seizures lasting longer than 15 minutes, or having a focal onset, or occurring as multiple seizures within 24 hours.⁴

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Unprovoked afebrile seizures were defined as seizures which occurred in the absence of fever and which were not symptomatic of any recognised acute neurological illness.²

We used a practical definition of “refractory epileptic” as a patient who has been on supervised medical therapy for the past two years but is still having seizures, either frequent or severe enough, to disrupt his lifestyle.⁵

Results

Out of 20 542 men, there were 121 epileptics, out of whom we had information on 106 (87%). The cumulative incidence of epilepsy by age 18 was 5 per 1000 in this cohort. Ninety-four (88%) epileptics were Chinese, 7 (7%) Malays and 5 (5%) Indians. From our sample of 16 613 Chinese, 2407 Malays and 1046 Indians, the cumulative incidence of epilepsy in Chinese was 5.7 per 1000, Malays 2.9 per 1000 and Indians 4.8 per 1000 (Table I). The different rates of epilepsy in the three races were not statistically significant (chi-square test, $P = 0.2$). Seventy-three (69%) epileptics had generalised and 23 (22%) had partial seizures. Ten (9%) had seizures which were unclassified.

Eighty-three epileptics required anti-convulsants at some time in their lives. The remaining 23 epileptics had either refused medication or had sporadic seizures which did not require medication. Of the 83 epileptics who required anti-convulsants, 46 had their seizures controlled within one year. From the remaining 37 epileptics whose seizures were still uncontrolled within the year, 14 patients eventually developed refractory seizures.

TABLE I: CUMULATIVE INCIDENCE OF EPILEPSY BY RACE IN A COHORT OF SINGAPOREAN MALES BORN IN 1974

Chinese	5.7 per 1000
Malays	2.9 per 1000
Indians	4.8 per 1000

These 14 patients (13 Chinese and 1 Malay) with refractory epilepsy represented 13% of the 106 epileptics in our cohort. They had their onset of unprovoked afebrile seizures early in life (Table II). By their parents' reports, 9 refractory epileptics had a history of febrile seizures, and 4 had complex febrile seizures. Two out of 14 patients with refractory seizures had a history of meningitis and one had birth hypoxia. None of these 14 epileptics had a family history of seizures. Nine refractory epileptics had partial seizures, 4 had generalised seizures and 1 was unclassified (Table III). Imaging was performed on all 14 patients with 9 patients having computed tomographic (CT) studies only, 3 patients with magnetic resonance imaging (MRI) only, while 2 patients had both CT and MRI. Nine patients had normal studies while structural abnormalities were found in 5 patients: 2 had mesial temporal sclerosis, 1 showed hemiatrophy of the brain, and another parietal/occipital lobe atrophy while the remaining patient had a hypothalamic lesion (Table IV). Electroencephalographic abnormalities were found in 10 patients; 5 had epileptiform activity (4 focal and 1 generalised) whilst the other five merely showed slowing (3 generalised and 2 focal). Two out of the 9 patients with refractory partial seizures had already undergone surgery for epilepsy. Of the remaining 7 patients, only 1 patient agreed to consider epilepsy surgery.

TABLE II: AGE OF ONSET OF UNPROVOKED AFEBRILE SEIZURES IN FOURTEEN PATIENTS WITH REFRACTORY SEIZURES

Age of onset of unprovoked afebrile seizures	Number of patients
Birth to <1 year	3 (21%)
1 to <7 years	4 (29%)
7 to <13 years	3 (21%)
13 to 17 years	4 (29%)

TABLE III: RADIOLOGICAL AND ELECTROENCEPHALOGRAPHIC FINDINGS IN 14 PATIENTS WITH REFRACTORY EPILEPSY

Patient	Seizure Type	CT Findings	MRI Findings	EEG Findings
A	Partial	Not done	Right mesial temporal sclerosis	Right temporal epileptiform activity
B	Partial	Suprasellar mass	Hypothalamic lesion	Generalised intermittent slow
C	Partial	Normal	Pending	Left temporo-occipital epileptiform activity
D	Partial	Normal	Not done	Left temporal slow
E	Partial	Normal	Not done	Normal
F	Partial	Right parieto-occipital lesion	Not done	Generalised intermittent slow
G	Partial	Normal	Not done	Left frontal epileptiform activity
H	Partial	Right hemiatrophy	Not done	Right hemispheric slow
I	Partial	Not done	Right mesial temporal sclerosis	Right temporal epileptiform activity
J	Generalised	Not done	Normal	Generalised intermittent slow
K	Generalised	Normal	Not done	Normal
L	Generalised	Normal	Not done	Generalised epileptiform activity
M	Generalised	Normal	Not done	Normal
N	Unclassified	Normal	Normal	Normal

CT: computed tomographic; MRI: magnetic resonance imaging; EEG: electroencephalography

TABLEIV: PRESUMED AETIOLOGY OF SEIZURES IN FOURTEEN PATIENTS WITH REFRACTORY SEIZURES

Presumed Aetiology	Number of patients
Complex febrile seizures	4*
Meningitis	2
Birth asphyxia	1
Structural lesions	5
Mesial temporal sclerosis (2)*	
Hypothalamic lesion (1)	
Right parieto-occipital lobe lesion (1)	
Right hemiatrophy of the brain (1)	
Unknown	3

* One patient who had a history of complex febrile seizures also had mesial temporal sclerosis, and was listed in both categories.

Discussion

The cumulative incidence of epilepsy by age 18 years in our army cohort was 5 per 1000, a figure comparable to an earlier epidemiological survey by Puvanendran.¹ In his study, he compared the data collected from hospitals, school health clinics and army recruits, and concluded that the most accurate epidemiological data was obtained from army recruits, whose life-time prevalence of epilepsy was 3.8 per 1000. However, collection of data in this manner meant that only males were sampled. As was noted in the Rochester⁶ survey, males had a 15% higher incidence of epilepsy compared to females. This was one limitation in methodology which we shared with Puvanendran. In addition, our survey was limited only to the cohort born in 1974. Also, although we found no significant racial bias in our survey, our sample of non-Chinese epileptics was relatively small (7 Malays and 5 Indians). A larger sample is necessary to assess this lack of racial bias, especially so when the prevalence of epilepsy in Pakistan⁷ was noted to be 9.75 per 1000 but only 4.36 in China⁸ and 3.70 in India.⁹ The majority of epileptics in the entire cohort had generalised seizures (69%), while partial seizures occurred in 22%, a figure comparable to the Rochester experience. In contrast, partial seizures were commoner (64%) in refractory epileptics, while affecting only 15% of non-refractory epileptics (Table V).

Our finding that 13% (14 epileptics) had refractory seizures is a figure comparable to that of other

studies.^{6,10,11} Most of our refractory epileptics had their first unprovoked febrile seizure early in life. Seven of the 14 patients (50%) had their onset by 7 years of age, of which 3 patients presented in the neonatal period. This is similar to the experience in Rochester¹⁰ and Denmark¹¹ where the rates of epilepsy were very high during the first year of life.

The possible causes of epilepsy included meningitis (2 patients), birth asphyxia (1 patient) and structural abnormalities (5 patients). Complex febrile seizures were reported in 4 out of 14 patients with refractory seizures and appeared to be closely related. This is not unexpected as both Abou-Khalil et al¹² and Murakami et al¹³ had reported of a similar association, with 36% and 63% of their respective refractory epileptics having a history of complex febrile seizures. Of the 4 patients with complex febrile seizures, 3 developed unprovoked afebrile seizures shortly after, and the fourth patient after a period of five years. One patient who had a history of complex febrile seizures also had mesial temporal sclerosis (Table IV).

Based on history, EEG and CT/MRI findings, 9 of these refractory patients had partial seizures, 4 had generalised seizures and 1 was unclassified. This is consistent with the notion that partial seizures are more difficult to treat. Two such patients (1 with temporal lobe epilepsy and another with gelastic epilepsy) were operated upon. The patient with gelastic epilepsy was operated on in 1992 but his seizures remained fairly frequent; this was not unexpected as hypothalamic lesions causing gelastic epilepsy are usually not improved by surgery.¹⁴ The other patient with mesial temporal sclerosis was operated upon in March 1996 and is doing well. The other refractory partial epileptics were tried on various combinations of anti-convulsants, which included phenytoin, carbamazepine, phenobarbitone and sodium valproate. The mean duration of drug therapy was 13.6 years (Table VI). Although every patient claimed compliance to his medication, not everyone had drug levels assessed. However, most patients tolerated their medication well and only 1 epileptic complained of hirsutism (phenytoin) and another of drowsiness (sodium valproate).

Of the 9 patients with refractory partial epilepsy, 1 patient had daily seizures, 2 patients had seizures occurring at least once a week (weekly) and 5 patients had seizures occurring at least once a month (monthly); the one patient operated for mesial temporal sclerosis had been seizure-free postoperatively for 4 months when last reviewed in July 1996. Of the 5 patients with refractory generalised or unclassified seizures, 1 had weekly seizures and 4 had monthly seizures (Table VII).

The role of epilepsy surgery in the treatment of refractory partial epilepsy is well established, especially so for

TABLEV: COMPARING SEIZURE PATTERN BETWEEN ALL EPILEPTICS (106), REFRACTORY (14) AND NON-REFRACTORY EPILEPTICS (92)

	All epileptics (106)	Refractory epileptics (14)	Non-refractory epileptics (92)
Generalized seizures	73 (69%)	4 (29%)	69 (75%)
Partial seizures	23 (22%)	9 (64%)	14 (15%)
Unclassified	10 (9%)	1 (7%)	9 (10%)

TABLE VI: TREATMENT OF NINE PATIENTS WITH REFRACTORY PARTIAL SEIZURES

Patient	Types of medication tried	Total duration of medication in years	Decision for surgery	Seizure frequency
A	PHT, CBZ	12	Anterior temporal lobectomy	Seizure-free
B	CBZ	8	Exploratory surgery for gelastic epilepsy	At least 1/month
C	PHT, PB, CBZ, VPA	8	Agree to consider	At least 1/week
D	PHT,CBZ	7	Declined	At least 1/month
E	PHT, PB	22	Declined	At least 1/month
F	PHT, PB, VPA, CBZ	19	Declined	At least 1/month
G	Chinese medication, PB	22	Declined	Daily
H	PB	6	Declined	At least 1/month
I	LT, PHT, CBZ	18	Declined	At least 1/week

PHT: Phenytoin; PB: Phenobarbitone; CBZ: Carbamazepine; VPA: Valproate; LT: Lamotrigine

TABLE VII: FREQUENCY OF SEIZURES IN 14 PATIENTS WITH REFRACTORY SEIZURES

Frequency of seizures	No. of patients with partial seizures	No. of patients with generalised or unclassified seizures
Daily	1	0
At least once a week	2	1
At least once a month	5	4
Seizure-free	1 (after surgery)	0

mesial temporal sclerosis.^{15,16} As only 2 out of 9 patients with refractory partial seizures were operated upon, the authors personally interviewed and explained the merits of epilepsy surgery to the remaining 7 patients, hoping to convince them to consider surgery. In spite of this, only 1 patient agreed to surgery; the remaining 6 patients refused to even consider surgery (Table V). In the authors' experience with many refractory epileptics seen in the Tan Tock Seng Hospital Neurology Clinic, Singapore patients are generally very reluctant to have brain surgery for epilepsy. Our study of the present cohort of young epileptic men confirms this clinical impression.

Conclusions

In our present cohort of young men, the cumulative incidence of epilepsy was 5 per 1000 by age 18 years, with no significant racial bias. Thirteen per cent of epileptics in our cohort had refractory seizures, a figure similar to that reported in other series. Sixty-four per cent of patients with refractory epilepsy had partial seizures which may improve with surgery, yet very few of these would consider epilepsy surgery.

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