The Prevalence and Risk Factors of Refractory Partial Seizure Thai Patients at Prasat Neurological Institute

SOMCHAI TOWANABUT, M.D.*,
LEK RUNGREANGYINGYOD, M.Sc.**,
CHUTHAMANEE SUTHISISANG, Ph.D.***

Abstract

The prevalence of refractory partial seizure Thai patients at Prasat Neurological Institute was retrospectively from patient charts from January 1995 - December 1996 and further prospectively analysied. All epileptic patients were screened by direct questions regarding the anti-epileptic drugs (AEDs) regimen, the frequency, nature of seizure attacks and risk factors of seizure. The criteria of clinical refractory partial seizure was defined as partial seizure which cannot be controlled by a combination of at least two AEDs for four weeks. The results were 3,018 cases of total epileptic patients out of 300,008 visits. These were classified as 2,802 cases of generalized seizures (92.8%), 184 cases of partial seizures (6.1%), and 32 cases of unclassified seizures (1.1%). In the partial seizures group, the number of clinical refractory partial seizures was found to be 48 cases (26.1% of partial seizure). We found that the major risk factor of refractory partial seizures was lack of therapeutic AEDs blood level monitoring (64.5% of cases) and the other risk factors were lack of compliance, loss of follow-up but continued medication, concomitant medication, and improper drug storage. AEDs dosage was adjusted until the blood levels were in the therapeutic range, and correction of other risk factors and patient counseling was given. The number of true refractory partial seizures was reduced to 10 cases (5.4% of partial seizure). This procedure revealed that AED blood level monitoring and correction of other risk factors were essential in controlling seizure frequency.

Thus, the prevalence of true refractory partial seizure in our study was 3.3 cases of refractory partial seizure per 1,000 cases of the seizure population. We recommend that AEDs blood level monitoring and exclusion of other risk factors should be added to the criteria for the definition of refractory partial seizures. This criteria should be applied when considering the use of new AEDs as an add-on therapy in refractory Thai patients.

* Department of Medicine, Prasat Neurological Institute, Bangkok 10400,
** Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400,
*** Department of Pharmacology, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand.

Epilepsy is the second most common neurological disorder after headache, affecting approximately 1-2 per cent of the population[1,2]. Most incidence studies of epilepsy have been made in industrial countries where the incidence rate for unprovoked seizure ranges from 20 - 70 in a population of 100,000. Information from developing countries suggests that the incidence of epilepsy may be > 100 in 100,000[3]. A majority of the patients (about 70%) with diagnoses of epilepsy can be in remission stage, but for the remainder the condition will become chronic and in some of these patients seizures are resistant to drug therapy. In particular, complex partial seizures are usually refractory to anti-epileptic drugs (AEDs) therapy, carry a worse prognosis, and require higher AED blood level than that of generalized seizures.

Prevalence of active epilepsy in each country varies from 3.0 to 14.8 cases per 1,000 population[4-15]. In Thailand, the prevalence of refractory partial seizure has not been previously reported. However, the prevalence of total epilepsy in the general population was 29.2 cases per 1,000 population[16]. This seems to be much higher than the world prevalence. Since Prasat Neurological Institute is one of the neurological centers with the largest number of neurological patients in this country, thus, it is justified to verify the prevalence of refractory partial seizures in this institute.

In general, the definition of refractory partial seizure is defined as partial seizures which cannot be controlled by a combination of at least two AEDs for four weeks[17-21]. We would define this as "clinical" refractory partial seizure. In our country's economic situation, add-on of new AEDs such as lamotrigine, gabapentin, topiramate, etc to these patients by using only "clinical" refractory partial seizure definition can be costly.

The general practice in Thailand, AEDs blood level monitoring is not usually concluded to a tool of convulsive control. However, we believe that AEDs blood level monitoring is one of the essential factors in epileptic therapy. In addition, other risk factors could contribute to refractoriness. The other purpose of our study is to find these risk factors. The information of these risk factors will help us adjust the "clinical" refractory partial seizure definition to be more appropriate to our clinical setting. We called this new criteria "true" refractory partial seizure. The data will serve as baseline descriptive information and illustrate the major contributing factor affecting AED resistance.

MATERIAL AND METHOD

Study design

The study was firstly conducted as a retrospective survey for epilepsy cases from the total number of out-patient records at Prasat Neurological Institute from January 1995 to December 1996. All partial seizures cases were collected and then screened for refractory cases by physical examination and interviewing for seizure frequency. The seizure type was classified according to the classification of the International League Against Epilepsy (ILAE)[22]. The patients whose seizures could not be controlled by at least two AEDs for four weeks were called "clinical" refractory partial seizures.

Determination for risk factors and true refractory partial seizures

Patients who were diagnosed as "clinical" refractory partial seizures were interviewed to find out the risk factors. Baseline AED blood levels were performed. In each case, counseling of concomitant medications, drug compliance, drug storage, lifestyles and avoidance of trigger factors was also performed by a clinical pharmacist. Then they were asked to visit the physician again after a two week period. If they still had seizure attacks during the 2-week period, the dosage of AEDs was adjusted to the maximum tolerable dose which could be confirmed by monitoring blood levels or another conventional AED was added until the seizures were controlled. If the seizure attacks still occurred after these adjustment the patients were classified as "true" refractory cases.

Data analysis

Prevalence of "true" refractory partial seizure is calculated based on the number of true refractory partial seizures per 1,000 epileptic cases during a specific period of time. Risk factors and the definition of "true" refractory partial seizure are described.

RESULTS

The total number of out-patients screened from January 1995 to December 1996 was 300,008 visits. Of these, there were 3,018 cases of seizures

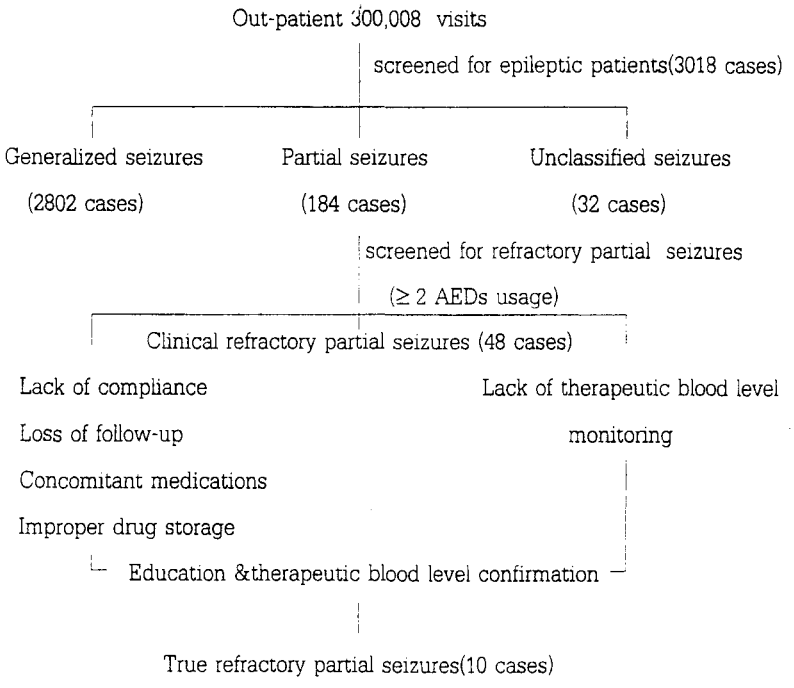

Fig. 1. Result of refractory partial epileptic patient screening.

which were classified as 2,802 cases of generalized seizures (92.8%), 184 cases of partial seizures (6.1%), 32 cases of unclassified seizures (1.1%) as shown in Fig. 1. Of 184 cases of partial seizures, 48 cases were classified as "clinical" refractory partial seizures (26.1%). This first screening for refractory partial seizure was based on the criteria that the seizure was inadequately controlled by the combination of more than two AEDs for four weeks without AED blood level data and other risk factors.

The total number of partial seizures and clinical refractory partial seizures before AED dosage adjustment as classified by age-group are shown in Table 1. Most of the patients were in the age range of 10-49 years and were predominantly male.

After AED dose adjustment to the maximum tolerable dose which was confirmed by blood level measurement, patient counseling was provided to these 48 cases, 38 cases were seizure free and only 10 cases remained uncontrolled. These 10 cases were considered as "true" refractory partial seizure (5.4% of partial seizure). Some demographic data of each patient is shown in Table 2. The majority of cases had a long history of seizures with the average number of years after diagnosis of 17.5 years (range 7-46 years) and patients education level were from high school graduates or university level.

The types of partial seizure in each patients according to ILAE are summarized in Table 3. Complex partial seizures with automatism was the most common type found in our study, whereas, only one simple partial seizure case with motor sign was refractory to conventional AED therapy.

The therapeutic blood level of conventional AEDs in each patient is shown in Table 4. Serum level of AEDs after dosage adjustment were the maximum tolerable for each patient. The rational treatment with AEDs for these 10 cases of true refractory partial seizures were diverse in which carbamazepine was the mainstay AED in the majority of the cases.

The risk factors of active partial seizure are shown in Table 5. The most common risk factors were lack of therapeutic blood levels (64.5%), and the second most common cause was lack of compliance (14.6%), the other risk factors were loss of follow-up but medication was continued, concomitant medications, and improper drug storage.

Table 1. Total number of patients with partial seizure and clinical refractory partial seizure as classified by age groups.

Age groups (year)	No. of partial seizure case (%)	No. of clinical refractory partial seizure before dosage adjustment case (%)	
		Male	Female
0-9	12 (6.5)	0	0
10-19	42 (22.8)	0	1 (6.7)
20-29	46 (25.0)	5 (15.2)	2 (13.3)
30-39	34 (18.5)	9 (27.3)	3 (20.0)
40-49	23 (12.5)	8 (24.2)	6 (40.0)
50-59	14 (7.6)	7 (21.2)	2 (13.3)
60-69	5 (2.7)	3 (9.1)	1 (6.7)
70-79	6 (3.3)	1 (3.0)	0
80-89	2 (1.1)	0	0
Total case (%)	184 (100.0)	33 (100.0)	15 (100.0)

Table 2. Demographic data of patients with true refractory partial seizures.

Gender	Age (year)	No. of years after diagnosis	Education	Residence
Male	24	16	Graduated	Bangkok
Male	25	16	High school	Nakornphathom
Male	28	17	Primary school	Nonthaburi
Male	30	21	Graduated	Bangkok
Male	34	7	Graduated	Bangkok
Male	35	10	Graduated	Bangkok
Male	45	10	High school	Bangkok
Male	50	46	Graduated	Bangkok
Female	24	16	Primary school	Samutprakarn
Female	33	16	High school	Bangkok

Table 3. Classification of true partial seizures in refractory cases*

Partial seizure type according to ILAE classification	No. of refractory partial seizure patients	
	Male	Female
A. Simple partial seizures (consciousness not impaired)		
1. With motor signs	1	0
2. With somatosensory or special sensory symptoms	0	0
3. With autonomic symptoms	0	0
4. With psychic symptoms	0	0
B. Complex partial seizures (with impairment of consciousness)		
1. Beginning as simple and progressing to unconsciousness	0	0
2. With impairment of consciousness at onset		
a. With impairment of consciousness only	1	1
b. With automatisms	6	1
C. Partial seizures with secondary generalized	0	0
Total cases	8	2

* Based on ILAE (International League Against Epilepsy)

Table 4. The individual therapeutic blood levels of true refractory partial seizures.

Case No.	Seizure type	Baseline serum level of AEDs (μg/mL) before dosage adjustment					Serum level of AEDs (μg/mL) after dosage adjustment				
		CBZ	PHT	PHB	VPA	CNP	CBZ	PHT	PHB	VPA	CNP
1	SPS	0.50	8.41	18.66	-	-	6.08	12.81	24.96	-	-
2	CPS	5.88	-	-	25.48	-	9.36	-	-	61.46	-
3	CPS	6.93	16.58	12.22	-	-	6.93	16.58	22.26	-	-
4	CPS	8.35	-	10.60	-	0.009	8.35	-	20.88	-	0.009
5	CPS	10.99	-	-	-	0.013	10.99	-	-	-	0.013
6	CPS	8.12	9.76	22.62	-	-	6.88	14.34	21.34	-	-
7	CPS	-	7.11	-	30.18	0.006	-	14.32	-	30.18	0.006
8	CPS	7.61	-	-	-	0.007	7.61	-	-	-	0.007
9	CPS	2.57	27.17	-	15.57	0.006	6.22	15.57	-	70.80	0.006
10	CPS	10.50	-	-	67.80	-	10.50	-	-	67.80	-

Abbreviation : SPS = simple partial seizures, CPS = complex partial seizure, CBZ = carbamazepine, PHT = phenytoin, PHB = phenobarbital, VPA = sodium valproate, CNP = clonazepam

Therapeutic blood level : CBZ = 4-12 μg/mL
PHT = 10-20 μg/mL
PHB = 20-40 μg/mL
VPA = 50-100 μg/mL
CNP = 0.005-0.070 μg/mL

Table 5. The classification of seizure active according to risk factors.

Risk factors	No. of partial seizure active patients	
Lack of therapeutic blood levels confirmation	31	(64.5%)
Lack of compliance	7	(14.6%)
Loss of follow-up but medication was continued	5	(10.4%)
Concomitant medications	3	(6.3%)
Improper drug storage	2	(4.2%)
Total	48	(100.0%)

DISCUSSION

Prevalence is the parameter which shows the epidemiology of diseases and is valuable for the purpose of health planning. The prevalence of refractory partial seizure has not been surveyed in Thailand. The prevalence of refractory partial epileptic Thai patients at Prasat Neurological Institute was estimated as 3.3 per 1,000 cases of the epilepsy population. The majority of the cases were adults in range of working period group. Complete control of their seizure attacks will regain their work effectiveness.

It was found that these uncontrollable seizure attacks were associated with risk factors such as lack of AEDs blood level determination, lack of compliance of concomitant medications, improper drugs storage, and loss of follow-up. The monitoring of antiepileptic drug concentrations in the serum is necessary for the optimal drug therapy of seizures, because the therapeutic and toxic effects of these drugs are better related to serum concentration than to administered dosage. Monitoring appeared to have an impact on improving the effectiveness and safety of antiepileptic drug therapy. Serum drug concentration monitoring is particularly useful to ensure compliance and in helping to manage combinations of antiepileptic

drugs that invariably interact. The addition or deletion of other antiepileptic drugs may need dosage adjustments. Therefore, routine monitoring of antiepileptic drug serum concentrations would be extremely useful, especially in the pediatric population, and in patients who require combined antiepileptic medications[23]. Plasma concentrations of all conventional AEDs reached the steady state in two weeks[24]. Thus, therapeutic blood level should be performed once or twice a month. In patients receiving more than one AED, the effective plasma concentration may be influenced by medications. Almost all conventional antiepileptic drugs are enzyme inducers such as carbamazepine, phenytoin, and phenobarbital, except sodium valproate which is an enzyme inhibitor. For example, phenobarbital induces phenytoin biotransformation but also competes with it as a substrate for the induced enzyme. The dual effects leads to varying results that may negate each other or produce a rise or fall in drug levels. Effects in individual patients depend on the state of induction by previous drug intake, and the dose of both phenytoin and phenobarbital[26]. Concerning carbamazepine, this drug is an autoinducer which leads to increased clearance, shortening of serum half-life and progressive decrease in serum levels. Increments in daily dosage are necessary to maintain plasma concentration. Autoinduction is usually completed in 20 to 30 days at any particular dose. In the postinduced state, a new steady state and half-life occurs[25]. For this reason, therapeutic blood level is significant in epileptic management. Thus, clinicians should titrate AEDs with therapeutic blood level information together with the clinical signs and symptoms of the patients.

Noncompliance with AEDs is a major factor in the recurrence of seizures in patients with epilepsy[26]. One of the noncompliance problems found in our study was compliance with medication ingestion (either missed dose or irregular ingestion). Another one concerned the patient's lifestyle such as exposure to heat and loud noise. Thus, patients and their families should be counseled about the importance of medication ingestion, medical appointments, and lifestyle. Our study revealed that patient counseling is essential, since it helped alleviate the refractory problem in all patients. We strongly emphasize that patient counseling to epileptic patients either by the treating physician or a clinical pharmacist should be performed in every epilepsy clinic. In establishing the counseling program, the topics that should be covered are listed in Table 6.

Table 6. Topics for counseling of epileptic patients.

Medical
Medication ingestion / storage / concomitant medications
Prescription filling
Medical appointments
Lifestyle
Sleep patterns
Alcohol use
Psychological stress
Exposure to music, strobe lights
Drug abuse
Menstruation
Psychological support

In our study, two patients took theophylline and albendazole as concomitant medications. These two drugs are reported to seizure threshold[27], however the mechanisms are still unknown. The proposed mechanism of theophylline may be due to its CNS stimulant activity. Thus, physicians should avoid administering drugs that can lower the seizure threshold to epileptic patients.

Some patients stored all medications in the same container and poured them out when administrated, so these drugs were exposed directly to moisture. Studies from FDA indicate that carbamazepine tablets could lose up to one- third of their effectiveness if stored in humid conditions[28]. This appears to be due to formation of a dihydrate form which leads to hardening of the tablet resulting in poor dissolution and absorption[29]. As the dihydrate has also been detected after storage under ambient conditions, some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets[28]. For patients, FDA is re-emphasizing its traditional advice to store drug products in a cool, dry, tightly closed container in a dry location away from bathrooms, showers, and humidifiers to reduce exposure to moisture[28].

From this study, elimination of some risk factors such as lack of compliance, concomitant medications, drug storage, and loss of follow-up by giving patient counseling could help control the seizure attacks in all cases. We also found that after

adjusting the AED blood level, there were only 10 cases who remained refractory. Thus, before deciding whether the patients are refractory cases, these factors should be ruled out.

The result of this study also gives us an idea that the definition of true refractory partial seizures should be strictly defined as partial seizure which cannot be adequately controlled by at least two maximal tolerable doses of AEDs, lack of concomitantly medicine, with patient counseling as described before. If patients are still seizure active for four weeks then an add-on antiepileptic drug is necessary. At the present time, there are many new antiepileptic agents available such as lamotrigine, gabapentin, topiramate, and tiagabine. These drugs are usually indicated as an add-on therapy in refractory partial seizures. They showed good efficacy in both open and controlled trials[24]. However, these drugs are rather expensive compared to the price of conventional AEDs. Thus, add-on therapy with new AEDs in epileptic patients without checking the baseline conventional AEDs level and other risk factors probably would not be cost-effective.

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ความชุกและปัจจัยเสี่ยงของ refractory partial seizures ในผู้ป่วยไทยที่สถาบันประสาทวิทยา

สมชาย โตวณะบุตร, พ.บ., ว.ว. (ประสาทวิทยา),*
*เล็ก รุ่งเรืองยิ่งยศ, ภ.ม. (เภสัชกรรมคลินิก)**, จุฑามณี สุทธิสีสังข์, ป.ร.ด. (เภสัชวิทยา)****

ความชุกของ refractory partial seizures ในผู้ป่วยไทยที่สถาบันประสาทวิทยาถูกประเมินโดยการศึกษาย้อนหลังจากเวชระเบียนระหว่างเดือน มกราคม พ.ศ. 2538 ถึง เดือน ธันวาคม พ.ศ. 2539 และติดตามผู้ป่วยทุกคนต่อไป. ผู้ป่วยลมชักทุกคนจะถูกสัมภาษณ์โดยตรงถึงขนาดยากันชักที่ใช้, ความถี่และลักษณะการชัก, รวมทั้งปัจจัยเสี่ยงที่ทำให้ชัก. โดยมีเกณฑ์ในการตัดสินผู้ป่วยว่าเป็น clinical refractory partial seizure คือผู้ป่วย partial seizure ที่ไม่สามารถถูกควบคุมด้วยการใช้ยากันชักอย่างน้อย 2 ชนิดขึ้นไปในเวลา 4 สัปดาห์. ผลการศึกษาจากเวชระเบียนผู้ป่วย 300,008 รายพบว่ามีผู้ป่วยที่เป็นโรคลมชัก 3,018 คน, ในจำนวนนี้แบ่งออกเป็น generalized seizures 2,802 คน (92.8%), partial seizures 184 คน (6.1%) และ unclassified seizures (1.1%). ในกลุ่มผู้ป่วยที่เป็น partial seizures มีผู้ป่วยที่จัดเป็น clinical refractory partial seizures จำนวน 48 คน (26.1% ของ partial seizure). พบว่าปัจจัยเสี่ยงที่สำคัญของการเกิด refractory partial seizures คือขาดการติดตามระดับยากันชักในเลือด (64.5%ของผู้ป่วยในกลุ่มนี้). ส่วนปัจจัยเสี่ยงอื่นๆ เช่น การรับประทานยาไม่สม่ำเสมอ (noncompliance), ไม่มาพบแพทย์แต่ซื้อยารับประทานเอง, ใช้ยาอื่น ๆ ร่วมด้วย, และเก็บยาไม่ถูกต้อง. ภายหลังจากการปรับระดับยาให้ได้ระดับที่ให้ผลในการรักษาและการแก้ไขปัจจัยเสี่ยงทั้งหมด รวมทั้งการให้คำปรึกษาแก่ผู้ป่วย. จำนวนผู้ป่วยที่ยังคงชักอยู่ซึ่งจะเรียกว่า "true" refractory ลดลงเหลือเพียง 10 คน (5.4% ของ partial seizures). กระบวนการเหล่านี้แสดงให้เห็นว่า การวัดระดับยากันชักและการแนะนำแก้ไขปัจจัยเสี่ยงต่างๆ ที่ทำให้เกิดอาการชัก มีความจำเป็นอย่างมากในการควบคุมอาการชัก.

ดังนั้นความชุกของ "true refractory partial seizures ในการศึกษานี้คือ 3.3 ต่อประชากรที่เป็นโรคลมชัก 1,000 คน. ผู้วิจัยขอแนะนำให้มีการเพิ่ม การวัดระดับยากันชักและการกำจัดปัจจัยเสี่ยงของการชักเข้าไปในนิยามของ refractory partial seizures ซึ่งควรใช้ข้อกำหนดนี้ในการพิจารณาใช้ยากันชักชนิดใหม่ ๆ เพิ่มเข้าไปในผู้ป่วยที่เป็น refractory partial seizures เพื่อความเหมาะสมกับภาวะเศรษฐกิจของไทย.

* สถาบันประสาทวิทยา, กรมการแพทย์, กระทรวงสาธารณสุข, กรุงเทพ ฯ 10400
** ภาควิชาเภสัชกรรม, คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล,
*** ภาควิชาเภสัชวิทยา, คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400