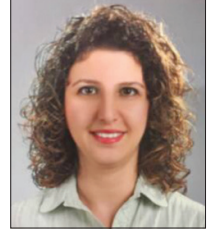


Epilepsy due to Intracranial Surgery: 15 Years of Experience

Intrakranial Cerrahi Geçiren Hastalarda Epilepsi: On beş yıllık deneyimimiz



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Summary

Objectives: Epidemiological studies have shown increased incidence of epilepsy in cases of brain trauma, central nervous system infection, cerebrovascular disease (CVD), and brain tumours. The etiology of epilepsy vary by age of the patient. In the etiology of partial and secondarily generalized partial seizures in adult patients, CVD is the most common cause of acute, symptomatic seizures. Frequency of seizures is estimated to be 15% to 20% after cranial operation.

Methods: Eighty-four patients who were admitted to epilepsy clinic between 2000 and 2015 with history of cranial surgery and symptomatic seizures were included in the present study.

Results: Etiology conditions were 41 (48.8%) cases of space-occupying lesions (SOL), 19 (22.6%) instances of trauma, 19 (22.6%) cases of CVD, and 5 (6.0%) with ventriculoperitoneal shunt. Preoperative seizures had been observed in 17 (20.2%) of patients. No seizure was seen in 11 (13.1%) patients. Electroencephalography findings revealed focal abnormalities in 39 (46.4%) patients, and were normal in 26 (31.0%) patients. Total of 43 (51.2%) patients were treated with monotherapy, and 32 (38.1%) patients were under polytherapy.

Conclusion: Most common etiological factor for patients with pre- or postoperative epilepsy who had undergone cranial surgery was SOL. Focal EEG results commonly indicate lesions. Onset of seizures may be delayed. Patients responded well to monotherapy treatment of seizures.

Keywords: Antiepileptic drugs; postsurgical epilepsy; symptomatic epilepsy.

Özet

Amaç: Epidemiyolojik çalışmalar beyin travmaları, santral sinir sistemi (SSS) enfeksiyonu, beyin damarsal hastalığı (BDH) ve beyin tümörlerinin epilepsi insidansını artırdığını göstermiştir. Epilepsi etiyolojisi yaşlara göre değişiklik göstermektedir. Yetişkin hastalarda sekonder jeneralize ve parsiyel nöbetlerin etiyolojisinde en sık serebrovasküler hastalık yer almaktadır. Ayrıca kranyal operasyon sonrası nöbetlerin sıklığı %15–20 olduğu tahmin edilmektedir.

Gereç ve Yöntem: Çalışmamıza 2000–2015 yılları arasında epilepsi polikliniğimize başvuran, semptomlu epilepsi nedeniyle cerrahi öyküsü olan 84 hasta dahil edildi. Diğer semptomlu nöbet geçiren hastalar ve epilepsi cerrahisi yapılan hastalar çalışmaya alınmadı.

Bulgular: Etiyolojide 41 kişide (%48.8) yer kaplayan lezyon (YKL) ilk sırada iken, 19 (%22.6) kişide travma, 19 (%22.6) kişide beyin damar hastalıkları (BDH), 5 (%6.0) kişide ventriküloperitoneal şant (VPS) görülmekteydi. On yedi (%20.2) hastada ameliyat öncesi dönemde nöbet gözlemlendi. On bir (%13.1) hastada nöbet görülmedi. Elektroensefalografi (EEG) bulguları 39 (%46.4) hastada fokal bulgular saptanırken, 26 (%31.0) hastada normal idi. Kırk üç (%51.2) hasta monoterapi, 32 (%38.1) hasta politerapi altındaydı.

Sonuç: Kranyal cerrahi geçiren ameliyat öncesi/sonrası epilepsili hastalarda en sık görülen etiyolojik nedenin yer kaplayan lezyonlar olduğu, nöbetlerin en çok geç dönemde geliştiği, EEG bulgularının en çok lezyon ile uyumlu fokal bulgular gösterdiği, nöbetlerin monoterapi ile kontrol altında olduğu, hastaların tedaviye iyi yanıt verdiği görülmüştür.

Anahtar sözcükler: Antiepileptik ilaç; ameliyat sonrası epilepsi; semptomlu epilepsi.

Submitted (Geliş): 18.04.2016

Accepted (Kabul) : 10.10.2016

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Introduction

Epilepsy is clinical picture of recurrent seizures with an abnormal hypersynchronous discharge of a population of neurons in the cortical and subcortical brain regions. It affects about 1% of general population.^[1] In adult patients, cerebrovascular disease (CVD) is the most common etiology of secondary generalized and partial seizures, and it causes acute symptomatic seizures. CVD is primary etiological factor in approximately 11% of epilepsy patients.^[2,3] In cases of non-traumatic supratentorial craniotomy, the incidence of seizure is estimated to be 15% to 20%, with risk of seizure varying between 3% and 92% over 5-year period.^[4] Epilepsy is the second most common symptom in patients with cerebral arteriovenous malformation (AVM).^[5] In the literature, up to 40% of patients with symptomatic meningioma experienced seizures before tumour removal.^[6] It has been reported that head trauma can cause development of motor and cognitive disability, and seizures are the most common complication.^[7] In the present study, preoperative seizure presence, tumour location, and large tumour resection were considered risk factors for postoperative seizure development. For patients without seizures, there is no definite data in the literature supporting pre- or postoperative antiepileptic drug (AED) prophylaxis.^[6] The aim of the present study was to retrospectively investigate characteristics (demographics, operation etiology, number of operations, seizure type, seizure frequency, and status of AED use) of patients who underwent cranial surgery.

Materials and Methods

The files of patients who presented at epilepsy polyclinic of Eskisehir Osmangazi University Faculty of Medicine neurology department between 2000 and 2015 were reviewed. Patients who had seizures following cranial surgery, who were using AEDs, and those with surgical history of symptomatic epilepsy were included in the study. Patients with other symptomatic seizures and patients with epilepsy surgery were excluded. Total of 84 patients with postoperative epilepsy who had an adequate follow-up clinical data were included in the study. Demographic characteristics of the patients, reason for cranial surgery, age at time of operation, number of operations, date of onset of seizures, seizure type and frequency, electroencephalography (EEG) findings, and antiepileptic drug therapy information were recorded. Patients were divided into 4 groups according to etiological features: space-occupying lesions (SOL) (e.g., benign or ma-

lignant mass, abscess), trauma (e.g., fall from height, traffic accident), CVD (e.g., hemorrhagic stroke, cavernoma, AVM, aneurysm), and ventriculoperitoneal shunt (VPS) operation. Seizure type was classified as simple partial, complex partial, or generalized seizure, based on the International League Against Epilepsy 1981 criteria. Seizure timing was classified as early-onset seizure (EOS), developing during first 14 days, or late-onset seizure (LOS) for onset on 15th day or later. EEG findings were classified as normal, nonspecific (breach rhythm and low-amplitude rapid trace were included), diffuse slowing, diffuse epileptiform activity, focal slowing, or focal epileptiform activity. Patients were divided into 3 groups according to AED use: patients receiving polytherapy, patients receiving monotherapy, and patients not receiving any AED therapy. Also, patients were also separated into 4 groups according to seizure frequency: patients without seizure during the past year, patients with 1 seizure during the last 6 to 12 months, patients with 1 seizure during the last 3 to 6 months, and patients with 1 seizure during the last 3 months or less.

Statistics

Continuous quantitative data were expressed as n, mean, and standard deviation, and qualitative data were expressed as n, median, 25th, and 75th percentiles. Kruskal-Wallis one-way analysis of variance on ranks test was used for non-normally distributed independent variables. Chi-square tests were used for categorical variables.

Results

Thirty-eight (45.2%) female and 46 (54.8%) male patients were included in the study. The mean age of patients was 47.9±14.5 years (min: 21, max: 76 years). The mean age at time of operation was 37.1±17.8 years (min: 1, max: 76 years). Sixteen (19.0%) patients had been operated on at least twice, while 1 patient had undergone 4 operations. In terms of etiology, 41 (48.8%) patients had SOL, 19 (22.6%) had trauma, 19 (22.6%) had CVD and 5 (6.0%) had VPS. There were 17 (20.2%) patients who experienced seizures before operation. Also, eight (9.5%) patients underwent necessary emergent surgery just after seizure. Seventy-one (84.5%) patients experienced seizures after surgery, and 11 (13.1%) patients had no seizures. Fourteen (52.4%) patients had seizures in late postoperative period, and 8 (9.5%) had seizures in early postoperative period. In 17 (20.2%) patients, therapy was terminated and seizures re-emerged in 8 (47.1%) patients. Most common seizure type

was generalized tonic-clonic seizure (GTC) (58.3%). Ten (11.9%) patients had no seizures. Forty-seven (56.0%) patients were seizure-free for the past year, and 19 (22.6%) patients had seizure every 3 to 4 months. EEG findings demonstrated focal slowing in 30 (35.7%) patients and were normal in 42 (50.0%) patients. Nine (10.7%) patients did not use AED, 43 (51.2%) patients were under monotherapy, and 32 (38.1%) patients were under polytherapy. Most frequently used AED was levetiracetam (LEV), in 56 (66.7%) patients. Carbamazepine (CBZ), oxcarbazepine (OXC), phenytoin, valproic acid (VPA), lamotrigine (LTG), topiramate (TPM), zonisamide (ZNS), pregabalin (PGB), clobazam (CLB), and phenobarbital were the other AEDs used.

Patients were grouped by etiology (Table 1). There were 41 patients operated on due to SOL. The mean patient age at first operation was 40.82 years (± 17.54 years; min: 3, max: 76). Six patients were operated on twice, and 1 patient was operated on 4 times. Thirteen (31.7%) patients had seizures before the operation. The number of patients with CVD history was 19. The mean age at first operation of these patients was 42.21 ± 11.76 years (min: 26, max: 64 years). Four patients were operated on twice. Four patients presented with seizures. The number of patients operated on due to trauma was 19. The mean age of patients at first operation was 29.78 ± 19.69 years (min: 1, max: 74 years). In this group, 2 patients were operated on twice. VPS was reason for surgery in 5 patients. The mean age at first operation was

Table 1. Patient characteristics according to operation etiology

	Space-occupying lesion	Cerebrovascular disease	Trauma	Shunt
Number of patients	41 (20 M, 21 F)	19 (9 M, 10 F)	19 (14 M, 5 F)	5 (3 M, 2 F)
Mean age (years)	49.46 \pm 14.91 (23–76)	50.05 \pm 10.03 (34–72)	48.16 \pm 15.45 (27–76)	26.00 \pm 4.18 (21–32)
Mean age at first operation (years)	40.82 \pm 17.54 (3–76)	42.21 \pm 11.76 (26–64)	29.78 \pm 19.69 (1–74)	16.40 \pm 10.33 (1–25)
Preoperative seizure, n (%)				
Yes	13 (31.7)	4 (21.1)	0 (0)	0 (0)
No	28 (68.3)	15 (78.9)	19 (100)	5 (100)
Postoperative seizure, n (%)				
Yes	35 (85.4)	16 (84.3)	16 (84.2)	4 (80.0)
No	6 (14.6)	2 (10.5)	2 (10.5)	1 (20.0)
Seizure frequency, n (%)				
No seizure (last year)	26 (63.4)	12 (63.2)	7 (36.8)	2 (40.0)
1 seizure (6–12 months)	0 (0)	2 (10.5)	1 (5.3)	0 (0)
1 seizure (3–6 months)	4 (9.8)	3 (15.8)	6 (31.6)	2 (40.0)
1 seizure (0–3 months)	11 (26.8)	2 (10.5)	5 (26.3)	1 (20.0)
Seizure type, n (%)				
Simple partial	12 (29.3)	5 (26.3)	5 (26.3)	1 (20.0)
Complex partial	10 (24.4)	3 (15.8)	5 (26.3)	1 (20.0)
Generalized tonic clonic	23 (56.1)	11 (57.9)	12 (63.2)	3 (60.0)
Electroencephalography, n (%)				
Normal	12 (29.3)	6 (31.6)	5 (26.3)	3 (60.0)
Nonspecific	12 (29.3)	4 (21.1)	0 (0)	0 (0)
Focal slowing	10 (24.4)	8 (42.1)	11 (57.9)	1 (20.0)
Focal epileptiform	5 (12.2)	1 (5.3)	3 (15.8)	0 (0)
Generalized slowing	1 (2.4)	0 (0)	0 (0)	0 (0)
Generalized epileptiform	1 (2.4)	0 (0)	0 (0)	1 (20.0)
Antiepileptic therapy, n (%)				
No	6 (14.6)	1 (5.3)	1 (5.3)	1 (20.0)
Monotherapy	18 (43.9)	14 (73.7)	9 (47.4)	2 (40.0)
Polytherapy	17 (41.5)	4 (21.1)	9 (47.4)	2 (40.0)

Table 2. Association between operation etiology and age

	Median	25%	75%	<i>p</i>	Multiple comparisons
Age (years)					
Trauma	44.00	35.00	63.00	=0.008	VPS-trauma, VPS-SOL, VPS-CVD
SOL	50.00	37.00	62.00		
CVD	48.00	44.00	60.00		
VPS	25.00	22.50	30.00		
First operation age					
Trauma	26.00	19.00	40.00	=0.002	VPS-SOL, VPS-CVD
SOL	40.00	29.50	55.00		
CVD	37.00	32.00	53.00		
VPS	20.00	6.00	25.00		
Second operation age					
Trauma	42.50	15.00		=0.357	NS
SOL	22.00	17.00	45.00		
CVD	42.00	31.50	65.25		
VPS	25.00	13.00			

CVD: Cerebrovascular disease; NS: Not significant; SOL: Space-occupying lesion; VPS: Ventriculoperitoneal shunt. Kruskal-Wallis test.

16.40±10.33 years (min: 1, max: 25 years). Three patients were operated on twice. There was significant relationship between etiology and age, as well as etiology and age at first operation (Table 2). The mean age of patients with VPS was lower than those with trauma, SOL, or CVD. The mean age at first operation was also found to be lower in patients with VPS than those with SOL or CVD. It was determined that seizure was present during preoperative period in patients with SOL and CVD. It was also seen that first seizures were frequently seen in the patients with trauma, SOL, or CVD during late postoperative period (78.9%, 39.0%, and 52.6%, respectively; $p < 0.001$, $p = 0.002$, $p = 0.008$).

Generalized epileptiform activity and generalized organizational impairment in EEGs were significantly lower in SOL group ($p = 0.001$). Ratio of normal, nonspecific, and focal EEG findings was similar. There was no significant difference in EEG findings between patients operated on due to trauma, CVD, or shunt. Focal EEG findings were consistent with lesion lateralization. It was determined that most common seizure type was GTC, and most commonly used AED was LEV.

Discussion

Epilepsy affects 0.5% to 1% of the whole population and the incidence of lifetime epilepsy varies between 2% and 5%.^[8,9] Seizures may occur in more than 2% of the population as result of metabolic disorders during neonatal pe-

riod, central nervous system (CNS) infection during childhood, trauma during young adulthood, or vascular disease in old ages. Epidemiological studies have shown that brain trauma, CNS infection, CVD, and brain tumours increase the incidence of epilepsy.^[10] The etiology of epilepsy varies with age. In the present study, the mean age of the patients who underwent cranial surgery for VPS was found to be significantly lower than that of trauma, SOL, and CVD patients. When the mean age at first operation was examined, the mean age of the patients with VPS was found to be statistically lower than the mean age of the patients with SOL or CVD. As in the literature, we concluded that CVD and SOL frequently occur at older age. There is no definite data available supporting preoperative or postoperative AED prophylaxis for patients without seizures.^[6] In this study, 10 patients (11.9%) had no seizures. The total of 80% of these patients were using antiepileptic drug therapy. Of those, 50% had SOL, 20% had CVD, 29% had trauma, and 10% had VPS. Two patients who did not receive antiepileptic drug therapy had SOL and VPS, respectively. EEG examination of these patients was evaluated as nonspecific and normal. First choice drugs for symptomatic epilepsies have been reported to be CBZ, LTG, OXC, Valproate, TPM, and LEV.^[11] The age of patients age, comorbidities, necessity of chemotherapy, and multi-drug interactions should be considered when drug selection is made. Most frequently used AED in present study was LEV, with 66.7% of patients using the drug.

Brain tumour was found to be responsible for 3.6% of all epileptic cases and 12% of symptomatic epilepsies. Although tumour-associated epilepsy is seen in all ages, it is the most common in the age group 25–64 years.^[10] Also, some 40% of patients with symptomatic meningioma present with seizures.^[6] In our study, SOL was the most common reason among patients who underwent intracranial surgery, followed by CVD and trauma. First symptom is seizures in approximately 30% of patients with brain tumor.^[10] Epileptic seizure has been reported to be the first clinical sign in 30% to 50% of patients with brain tumour.^[12] In our study, first clinical sign was seizure in 31.7% of the patients who were diagnosed as having seizures due to SOL, which was consistent with the literature. In addition, 13 of 17 patients who had seizures before operation were found to have SOL. This was statistically significant, and it emphasized the importance of SOL when investigating seizure etiology in adults. One study indicated that complete seizure control was achieved in 67% of patients with low-grade gliomas during 12-month postoperative follow-up period. In the same study, rate of no improvement or worsening was 9%.^[13] In accordance with the literature, it was seen that 63.4% of the patients were seizure-free for the last year in our study. However, unlike the literature, 26.8% of our patients had frequent seizures. It has been shown that epileptic seizures may occur in 25% of patients with meningioma during postoperative period.^[14] In our study group, seizures occurred in 82.1% of SOL patients during postoperative period. Number of patients with SOL was thought to be higher in our study than in the literature due to inclusion of all brain tumours. Studies in patients who had intracranial mass lesions demonstrated that EEG findings were consistent with intracranial mass in approximately 40% of patients and that EEG abnormalities lateralized to side of mass.^[15] This rate was 36.6% in our study, which is similar to that reported in the literature. Regardless of tumour type, risk of recurrent seizures is higher in patients with brain tumours whose first sign is epileptic seizure, despite anti-epileptic drug treatment.^[16] In the present study, rate of use of polytherapy was found to be higher in patients who had seizures before operation than in patients who had postoperative seizures. However, this result was not statistically significant. In previous studies it has been reported that CVD appears to constitute 11% of adult epilepsy patients.^[2,3] The most commonly reported brain vascular malformations were AVM, cavernoma, venous angioma, and capillary telangiectasia in order of decreasing frequency, and it has

been demonstrated that clinical symptoms are epileptic seizures, hemorrhage, and rarely, mass effect symptoms.^[17–19] In our study, CVD was detected in 22.6% of all epilepsy etiologies. We found that the incidence of epilepsy was higher in patients with CVD. This was because the patients operated due to vascular malformations were included in the CVD group. It was reported in a study that late-onset seizures were found to be more common than early-onset seizures in the cases of ischemic and hemorrhagic stroke.^[20] In our study, it was observed that rate of late-onset seizure was 52.6% in CVD patient group, which was significantly higher than the other groups ($p=0.008$). It emphasizes importance of long-term follow-up of the patient. In previous studies, partial seizures, especially simple partial seizures, have been reported to be the most common seizure type, with frequency of 17% to 66%.^[14,21,22] Conversely, the most commonly seen seizure type was GTC (57.9%) in our study. This result suggested that CVD has worse prognosis than diseases that do not require surgical intervention.

Focal slowing is commonly determined on EEG (20). In our study, the most common EEG finding was focal disorganization (42.1%), but it was not statistically significant. Most of our patients were using monotherapy (73.7%; $p=0.001$), which was consistent with the literature.^[20]

Head trauma is one of the major risk factors for development of epilepsy. In the literature, one of the symptomatic epilepsies is thought to be post-traumatic epilepsy.^[23] In our study, the proportion of patients followed due to trauma was found to be 22.6%, which is consistent with the literature. When seizure initiation was evaluated in trauma group, it was seen that rate of LOS was 78.9%, which was statistically significant ($p<0.001$) and also consistent with the literature.^[24] When the patients were assessed according to the frequency of seizures, 36.8% of the patients were seizure-free for the past year, but no significant difference was detected. This ratio was similar to the literature.^[25] When the patients were evaluated regarding seizure type, GTC seizures were found at rate of 63.2%, but it was not statistically significant. In the literature, the frequency of GTC seizures is significantly higher than other seizure types.^[25] It was thought that our result was due to limited sample size. Consistent with the literature, focal EEG abnormalities compatible with lesion lateralization were seen in 73.7% of patients ($p=0.039$).^[25] Rate of monotherapy was reported as 47.4%.

It is known that the presence of VPS increases risk of developing epilepsy.^[26] Seizure developed in 80% of 5 patients with shunt after operation. We concluded that this ratio was high because of our limited sample size.

In summary, our study demonstrated that most common etiological cause of seizures is SOL in patients with epilepsy that developed before or after surgery, and that seizures frequently occur during late postoperative period. Focal EEG abnormalities compatible with lesion are commonly seen, seizures can be controlled by monotherapy, and patients respond well to treatment.

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