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Research Article

Comorbid Diseases in Patients With Epilepsy

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Summary

Objective: The purpose of the study was to evaluate the frequency of comorbid diseases in our patients with epilepsy and to determine the relationship between these comorbidities and demographic, clinical and radiological findings.
Methods: We analyzed 365 patients who were followed up in our epilepsy outpatient clinic between 2011 and 2014, retrospectively. Demographic and clinical findings of the patients, neurological, psychiatric and systemic comorbid diseases were recorded. The association of comorbid diseases with age, gender, type of epilepsy syndromes and radiological findings were evaluated.
Results: The most common comorbid diseases in our patients were psychiatric disorders (21.1%) and headache (11.2%) and they were followed by hypertension, thyroid diseases, anemia, gastrointestinal diseases, coronary artery disease, diabetes mellitus, hyperlipidemia, asthma, genito-urinary diseases, cerebrovascular disease and cancer. Anxiety disorders and depression were the most common psychiatric comorbidities. Migraine was more common than tension-type headache. Mean age of the patients having hypertension, hyperlipidemia, coronary artery disease, cerebrovascular diseases and diabetes mellitus were significantly older than the patients having other comorbid diseases. Women had greater tendency to have psychiatric diseases, thyroid diseases, headache and anemia than men. Patients with symptomatic and cryptogenic epilepsies had psychiatric diseases, hypertension and thyroid diseases more frequently than the patients having idiopathic epilepsy syndromes.
Conclusion: A wide variety of psychiatric, neurological and systemic disorders may accompany epilepsy. The diagnosis and treatment of comorbid diseases are necessary for the improvement of life qualities of epilepsy patients. Identifying and treating these comorbidities in patients epilepsy is as important as seizure treatment.

Key words: Epilepsy, seizures, comorbidity

Epilepsi Hastalarında Görülen Komorbid Hastalıklar

Özet

Amaç: Çalışmanın amacı, epilepsisi olan hastalarımızda komorbid hastalıkların sıklığını hesaplamak ve bu komorbid hastalıkların demografik, klinik ve radyolojik bulgular ile ilişkisini değerlendirmekti.
Metod: Epilepsi polikliniğimizde, 2011-2014 yılları arasında takip edilmiş olan hastalarımız, retrospektif olarak değerlendirildi. Hastaların demografik, klinik bulguları, nörolojik, psikiyatrik ve sistemik komorbid hastalıkları kaydedildi. Komorbid hastalıkların, yaş, cinsiyet, epilepsi sendromları ve radyolojik bulgularla ilişkisi araştırıldı.

Sonuçlar: Hastalarımızda görülen en sık komorbid hastalıklar, psikiyatrik hastalıklar (%21,1) ve başağrısı (%11.2) iken hipertansiyon, tiroid hastalıkları, anemi, gastrointestinal hastalıklar, koroner arter hastalığı, diabetes mellitus, hiperlipidemi, astım, genito-üriner hastalıklar, serebrovasküler hastalıklar ve kanser onları takip ediyordu. Anksiyete bozuklukları ve depresyon, en sık psikiyatrik komorbid hastalıklardı. Migren, gerilim tipi başağrısından daha sıktı. Hipertansiyon, hiperlipidemi, koroner arter hastalığı, serebrovasküler hastalıklar ve diabetes mellitusu olan hastaların ortalama yaşı, diğer komorbid hastalıkları olan hastalara göre, daha yüksekti. Kadınlarda psikiyatrik hastalıklar, tiroid hastalıkları, başağrısı ve anemi, erkeklere göre daha sıktı. Semptomatik ve kriptojenik epilepsisi olan hastalarda psikiyatrik hastalıklar, hipertansiyon ve tiroid hastalıkları, idiyopatik epilepsisi olan hastalara göre daha fazla idi.
Tartışma: Epilepsiye, psikiyatrik, nörolojik ve sistemik hastalıklardan oluşan geniş bir yelpazede pek çok hastalık eşlik edebilir. Komorbid hastalıkların tanı ve tedavisi, epilepsisi olan hastaların hayat kalitelerinin arttırılması için gereklidir. Epilepsi hastalarında, komorbiditelerin tanımlanması ve tedavi edilmesi, nöbetlerin tedavisi kadar önemlidir.

Anahtar Kelimeler: Epilepsi, nöbet, komorbidite

INTRODUCTION

Patients with epilepsy have a higher prevalence of psychiatric and medical comorbid disorders than the general population[32,37]. Some of the reported medical comorbid conditions include allergies, arthritis/rheumatism, cerebrovascular accidents, chronic pain, diabetes, disorders of the musculoskeletal system, gastrointestinal system, and respiratory system, fractures, infections, migraine, neoplasia and obesity[17,30]. Among psychiatric comorbidities, mood disorders, anxiety, attention-deficit, psychotic and personality disorders are frequently associated with epilepsy[2,3,10,11,15,16,23,33,35,37]. There exist a complex relationship between psychiatric disorders and epilepsy. Patients with epilepsy are at greater risk of developing psychiatric disorders, but also those with primary psychiatric disorders are at risk of developing epilepsy[15,16,17].

Comorbidities may contribute to functional impairment of people with epilepsy, complicate epilepsy treatment, add to the cost of care and increase mortality[3]. Diagnosis and treatment of comorbidities are necessary to improve care for people with epilepsy.

The Institute of Medicine's 2012 report on epilepsy emphasized that patients with epilepsy were at risk not only for seizures but also for many comorbid conditions[6]. Gilliam et al stressed that comorbidities accompanying epilepsy had a greater effect on quality of life in people with epilepsy than the seizures themselves[11]. Further understanding of the comorbidities, the underlying mechanisms or causality between epilepsy and certain comorbidities may improve diagnosis and management of comorbidities associated with epilepsy. In this study, we aimed to evaluate the frequency of comorbid diseases in our patients with epilepsy and to determine the relationship between these comorbidities and demographic, clinical and radiological findings.

MATERIAL AND METHODS

We analyzed 365 patients who were followed up in our epilepsy outpatient clinic between 2011 and 2014, retrospectively. Patients with a confirmed diagnosis of epilepsy were included in our study. Information about comorbid diseases was obtained during the interview or from the medical reports. Primary caregivers were asked about the comorbidities, if the patient was unable to participate to the interview. Besides

demographic and clinical findings of the patients, neurological, psychiatric and systemic comorbid diseases were recorded. Epilepsy syndromes were classified according to the ILAE classification as idiopathic, symptomatic and cryptogenic[5]. The association of comorbid diseases with age, gender, type of epilepsy syndromes and radiological findings were evaluated.

Statistical analysis was performed by NCSS (Number Cruncher Statistical System) 2007 program (NCSS, LLC Kaysville, Utah, USA). Besides descriptive statistical methods (mean, standard deviation, median, frequency and ratio), data was analyzed by Pearson's chi-square test ($\chi 2$), Yates Community Correction, Fisher's exact test and Fisher Freeman Halton test for qualitative variables. Data was evaluated within a 95% confidence interval and a p value <0.05 was considered statistically significant.

RESULTS

A total of 365 patients were included in our study. The clinical characteristics of patients and the frequencies of comorbidities are given in Table 1 and 2, respectively. The most common comorbid diseases in our study group were psychiatric disorders and headache. Anxiety disorders (8.8%) and depression (6.6%) were the most common psychiatric comorbidities, even 2 patients had suicidal attempts. Other psychiatric comorbidities consisted of psychosis, obsessive compulsive disease, agitation, behavioral problems, autism, panic and conversion disorders. Among headache comorbidity, migraine (7.9%) was more common than tension-type headache (3.3%).

Decreasing in order of frequency, these two were followed by hypertension, thyroid diseases, anemia, gastrointestinal diseases, coronary artery disease, diabetes mellitus, hyperlipidemia, asthma, genito-urinary diseases, cerebrovascular disease and cancer. Ischemic cerebrovascular accidents (CVA) were more common than hemorrhagic CVA. Lung cancer, acute lymphoblastic leukemia and tumor of the adrenal gland were reported in the patients with cancer.

Other comorbid conditions, which were less common, consisted of hormonal imbalance, parasomnia, deafness, polyneuropathy, glaucome, congenital hip dislocation, normal pressure hydrocephalus, deformities in feet, Behçet's disease, acute lymphoblastic leukemia, allergic rhinitis, congestive hearth failure, atrial septal defect, interatrial septal aneurysm, valvular hearth disease (thrill), chronic hepatitis, idiopathic thrombocytopenic purpura, allergy, peripheral arterial diseases, poliomyelitis, acne, cardiac arrhythmia, vertigo, tuberculosis, bruxism, pulmonary insufficiency and lumbar herniated disc.

Table 1. Clinical characteristics of the patients

N=365		Min-Max	Mean±SD
Age (year)		10-83	30.88±13.91
Age at seizure onset (year)		0-80	17.59±12.83
		n	**%**
Sex	**Female**	182	49.9
	Male	183	50.1
Epilepsy Syndrome	**Idiopathic**	141	38.6
	Symptomatic	143	39.2
	Cryptogenic	81	22.2
Mental status	**Normal**	315	86.3
	Mild retardation	43	11.8
	Severe retardation	7	1.9

Table 2. Frequencies of common comorbid diseases of our study population

N=365	n	%
Psychiatric disorders	77	21.1
Headache	41	11.2
Migraine	29	7.9
Tension-type headache	12	3.3
Hypertension	17	4.7
Thyroid diseases	17	4.7
Anemia	15	4.1
Gastrointestinal diseases	11	3.0
Coronary artery disease	9	2.5
Diabetes Mellitus	8	2.2
Hyperlipidemia	7	1.9
Asthma	6	1.6
Genito-urinary diseases	5	1.4
Cerebrovascular diseases	4	1.1
Cancer	3	0.8
Others	64	17.5

As many comorbid diseases were influenced by age and sex, we analyzed the relationship between comorbid diseases and age, sex (Table 3 and Table 4). We found significant differences in the frequency of hypertension, hyperlipidemia, coronary artery disease, cerebrovascular diseases and diabetes mellitus with regard to age (p=0.001, p=0.001, p=0.001, p=0.007 and p=0.024, respectively). Mean age of the patients having these comorbid diseases were significantly older than the patients having other comorbid diseases. Also, significant relationship was detected in the frequency of psychiatric diseases, thyroid diseases, headache and anemia with respect to sex (p=0.027, p=0.046, p=0.012 and p=0.008). Women had greater tendency to have psychiatric diseases, thyroid diseases, headache and anemia than men.

There was a significant difference in the frequency of psychiatric diseases, hypertension, thyroid diseases and ‘others' with regard to epilepsy syndromes (p=0.019, p=0.037, p=0.041 and p=0.050) (Table 5). Patients who were diagnosed to have symptomatic and cryptogenic epilepsies had psychiatric diseases, hypertension and thyroid diseases more frequently than the patients having idiopathic epilepsy syndromes.

Pathological findings in neuroimaging modalities were found in 158 patients (43.3%). The most frequently detected pathological findings were encephalomalacia (29.7%), periventricular ischemic-gliotic lesions (19.0%), global or regional (fronto-temporal) atrophies (12.7%) and mesial temporal sclerosis (10.1%). They were followed by arachnoid cyst (6.3%), periventricular leucomalacia (5.7%), cortical dysplasia (5.1%), diffuse white matter lesions (3.8%), infarction (3.2%), hemiatrophy (3.2%), tumors (1.9%) and aneurysms (0.6%). A significant difference was found in hypertension and cerebrovascular diseases with respect to radiological findings (p=0.010 and p=0.034) (Table 6). Patients having pathological findings in neuroimaging modalities had greater tendency to report hypertension and cerebrovascular diseases in their medical history than the patients having normal radiological findings.

Neurological examination was unremarkable in 77.5% of the patients. Smoking in 63 (17.3%) and alcohol consumption in 14 (3.8%) patients were reported.

Electroencephalography (EEG) revealed pathological patterns in 207 (56.7%) patients.

Table 3. Comparision of comorbid diseases with regard to age.

	Disease (-) **Age;** *Mean±SD*	**Disease (+)** **Age;** *Mean±SD*	***P***
Psychiatric disorders	30.51±13.87	32.26±14.03	***0.328***
Hypertension	29.73±12.88	54.41±13.56	***0.001*****
Asthma; *(median)*	30.76±13.73 (26)	37.83±22.89 (25)	***[a]0.457***
Diabetes Mellitus	30.63±13.75	41.88±17.42	***0.024****
Thyroid diseases	30.59±13.83	36.88±14.47	***0.068***
Cancer	30.79±13.86	41.67±19.01	***0.178***
Hyperlipidemia	30.46±13.62	52.43±11.86	***0.001*****
Headache	30.77±14.29	31.76±10.51	***0.669***
Anemia	31.00±13.99	28.00±11.90	***0.414***
Coronary artery disease	30.42±13.60	49.22±14.09	***0.001*****
Gastrointestinal diseases	30.82±13.87	32.73±15.79	***0.655***
Genito-urinary diseases ; *(median)*	30.86±13.86 (26)	32.20±18.67 (22)	***[a]0.935***
Cerebrovascular diseases	30.47±13.39	67.75±11.53	***0.007*****
Others	30.82±13.59	31.14±15.38	***0.869***

Independent Samples Test *[a]Mann-Whitney Test* **p<0.05* ***p<0.01*

Table 4. Comparision of comorbid diseases with regard to sex.

	Female N(%)	**Male N(%)**	***P***
Psychiatric disorders	47 (25.8)	30 (16.4)	***[a]0.027****
Hypertension	7 (3.8)	10 (5.5)	*[a]0.463*
Asthma	2 (1.1)	4 (2.2)	*[b]0.685*
Diabetes Mellitus	4 (2.2)	4 (2.2)	*[b]1.000*
Thyroid diseases	13 (7.1)	4 (2.2)	***[c]0.046****
Cancer	2 (1.1)	1 (0.5)	*[b]0.623*
Hyperlipidemia	4 (2.2)	3 (1.6)	*[b]0.724*
Headache	28 (15.4)	13 (7.1)	***[a]0.012****
Anemia	13 (7.1)	2 (1.1)	***[c]0.008***
Coronary artery disease	2 (1.1)	7 (3.8)	*[b]0.174*
Gastrointestinal diseases	8 (4.4)	3 (1.6)	*[c]0.217*
Genito-urinary diseases	0 (0)	5 (2.7)	*[b]0.061*
Cerebrovascular diseases	0 (0)	4 (2.2)	*[b]0.123*
Others	25 (13.7)	39 (21.3)	*[a]0.057*

*[a]Pearson Chi Square test [b]Fisher's Exact Test [c]Yates Continuity Correction *p<0.05 **p<0.01*

Tablo 5. Comparision of comorbid diseases with regard to epilepsy syndromes.

	Idiopathic **N(%)**	**Symptomatic** **N(%)**	**Cryptogenic** **N(%)**	^{d}p
Psychiatric disorders	19 (13.5)	37 (25.9)	21 (25.9)	^{a}***0.019****
Hypertension	2 (1.4)	11 (7.7)	4 (4.9)	***0.037****
Asthma	2 (1.4)	3 (2.1)	1 (1.2)	*1.000*
Diabetes Mellitus	1 (0.7)	6 (4.2)	1 (1.2)	*0.147*
Thyroid diseases	9 (6.4)	2 (1.4)	6 (7.4)	***0.041****
Cancer	1 (0.7)	0 (0)	2 (2.5)	*0.067*
Hyperlipidemia	2 (1.4)	2 (1.4)	3 (3.7)	*0.540*
Headache	20 (14.2)	15 (10.5)	6 (7.4)	^{a}*0.298*
Anemia	6 (4.3)	4 (2.8)	5 (6.2)	*0.409*
Coronary artery disease	4 (2.8)	5 (3.5)	0 (0)	*0.261*
Gastrointestinal diseases	5 (3.5)	5 (3.5)	1 (1.2)	*0.680*
Genito-urinary diseases	2 (1.4)	3 (2.1)	0 (0)	*0.641*
Cerebrovascular diseases	0 (0)	4 (2.8)	0 (0)	*0.080*
Others	17 (12.1)	27 (18.9)	20 (24.7)	***0.050****

^{a}*Pearson Chi Square test* ^{d}*Fisher Freeman Halton Test* *$p<0.05$ **$p<0.01$

Tablo 6. Comparision of comorbid diseases with regard to radiological findings.

Neuroimaging	Normal N(%)	Pathological N(%)	*P*
Psychiatric disorders	39 (18.8)	38 (24.1)	[a]*0.227*
Hypertension	4 (1.9)	13 (8.2)	***[c]0.010****
Asthma	2 (1)	4 (2.5)	[b]*0.409*
Diabetes Mellitus	3 (1.4)	5 (3.2)	[b]*0.300*
Thyroid diseases	12 (5.8)	5 (3.2)	[a]*0.318*
Cancer	3 (1.4)	0 (0)	[b]*0.261*
Hyperlipidemia	2 (1)	5 (3.2)	[b]*0.247*
Headache	25 (12.1)	16 (10.1)	[a]*0.618*
Anemia	9 (4.3)	6 (3.8)	[c]*1.000*
Coronary artery disease	5 (2.4)	4 (2.5)	[b]*1.000*
Gastrointestinal diseases	5 (2.4)	6 (3.8)	[b]*0.542*
Genito-urinary diseases	1 (0.5)	4 (2.5)	[b]*0.171*
Cerebrovascular diseases	0 (0)	4 (2.5)	***[b]0.034****
Others	36 (17.4)	28 (17.7)	[a]*0.934*

[a]*Pearson Chi Square test* [b]*Fisher's Exact Test* [c]*Yates Continuity Correction* *$p<0.05$

DISCUSSION

Comorbid diseases are common in people with epilepsy[8,18,25,31,32,37]. These comorbid diseases may have important influences on diagnosis, treatment, medical costs and quality of life of patients with epilepsy[2,28,36]. Early recognition and treatment of comorbid diseases may have positive impact on the clinical management of patients[10,15].

Our study demonstrated that psychiatric disorders (21.1%) and headache (11.2%) were the most common comorbidities in patients with epilepsy. Among psychiatric disorders, anxiety disorders were more common than depression. Migraine was more frequently reported than tension-type headache regarding the comorbidity of headache.

Some previous reports emphasized the high prevelance of psychiatric diagnosis in

patients with epilepsy[2,10,12,15,16,30,33,37]. Psychiatric disorders were reported as the most frequent comorbidity in the patients with epilepsy in a previous study[37]. Fiest et al stated that depression was highly prevelant in patients with epilepsy[7]. Another study stated that mood disorders were the most frequent conditions associated with epilepsy and they were followed by anxiety, attention-deficit, psychotic and personality disorders[10]. Although psychiatric disorders were the most frequent comorbidity, anxiety disorders were more common than depression in our series. This might be related several factors such as cultural features, socioeconomic status or education levels.

It was suggested that epilepsy and psychiatric comorbidities had a very complex and bidirectional relationship[15,16,17]. Patients with epilepsy were at higher risk of developing psychiatric disorders and also patients who had primary psychiatric disorders were at higher risk of developing epilepsy. The study concluded that future studies might determine whether early management of a psychiatric comorbidity might lead to a better course of epilepsy[16]. Nonetheless, Kanner concluded that the treatment of psychiatric comorbidities should have aimed to reach complete remission of psychiatric symptoms, just as seizure-free state was the goal of the treatment of epilepsy[15].

New and validated screening instruments and guidelines may help for the early detection and treatment of comorbid disorders as stated in a study[17]. These efforts may enhance our understanding of epilepsy, including the association of epilepsy and comorbidities, shared risk factors and bidirectional relationship. Clinicians should orient their questioning on the comorbidities of epilepsy during the follow-up of patients. Both the investigation and the treatment of the comorbid conditions should be considered as well as the treatment of epilepsy.

Our analysis of comorbidities with respect to sex revealed that women had greater tendency to have psychiatric diseases, thyroid diseases, headache and anemia than men. This finding was in agreement with previous reports in which psychiatric disorders were found to be more common in women than in men[19,27,33]. Kimiskidis et al. concluded that high risk of psychopathology in women might be related with increased occurrence of adverse psychosocial problems relative to men and physiological stressors such as menstruation and pregnancy[19]. Wilner et al. suggested that anxiety and depression were more common in women whereas psychosis was more common in men and also stressed that further research on gender disparity of psychiatric comorbidities in patients with epilepsy was needed[37].

Mean age of the patients who had hypertension, hyperlipidemia, coronary artery disease, cerebrovascular diseases and diabetes mellitus were significantly older than the patients having other comorbid diseases in our study. This finding was similar to the findings of another study in which patients were grouped in three according to age: (1) 0 to 18 years, (2) 19 to 64 years and (3) 65 years and older[37]. The authors emphasized that hypertension and hyperlipidemia were more prevelant than psychiatric disorders for the two older age groups of 19 to 64 years and 65 years and older.

Our results showed that patients who had symptomatic and cryptogenic epilepsies reported psychiatric diseases, hypertension and thyroid diseases more frequently than the patients having idiopathic epilepsy syndromes. As some of the underlying causes of symptomatic epilepsies might be listed as trauma, perinatal incidents, mesial temporal sclerosis, tumors, stroke, central nervous system infections, congenital and

vascular malformations, psychiatric comorbidities might be observed as a consequence of most of these situations. Tunde-Ayinmode et al. claimed that psychiatric disorders were more frequently reported in patients with partial seizures than those with generalized seizures[33]. Studies evaluating electro-clinical features of patients in more detail might clarify the association of comorbid conditions with regard to seizure types and epilepsy syndromes.

Headache was the second most common comorbidity in patients with epilepsy. We found that migrane was more frequently reported than tension-type headache as suggested in a previous study[9]. Many studies have been performed on the association between migraine and epilepsy[4,9,21,24,26]. The frequency of epilepsy in patients with migraine was higher than in general population, just as the higher frequency of migraine in patients with epilepsy than healthy individuals[1,13,14,20,22,29,34]. It was suggested that both of these common, chronic and paroxysmal disorders shared many clinical features and underlying pathological mechanisms. Studies concluded that they might coexist by chance; they might be causally related with one leading to other; or there existed a shared pathophysiological or genetic basis[1,26].

Our study was subject to limitations. First limitation was that we did not compare the comorbidities of our patients with that of healthy population as our main purpose was to demonstrate the profile of comorbid conditions in patients with epilepsy in our out-patient clinic. Second limitation of the study was the small sample size. The findings of this study may be strengthened with further studies which are conducted as multicenter clinical trials or include larger number of patients.

Brooks-Kayal et al. defined the types of comorbidities as essential, secondary, iatrogenic, situational or complex/interacting comorbidities and presented animal models to study comorbidities as well as guidelines for preclinical studies[3]. Most of the previous studies on the relationship between epilepsy and comorbidities were on psychiatric disorders or headache. But studies on epilepsy and comorbidities in general are scant. Although we emphasized the comorbidities of psychiatric disorders and headache as the most frequently reported comorbidities in our study, our detailed data also revealed that a wide variety of diseases might be detected in patients with epilepsy. In our series, some of the comorbid diseases were relatively simple as allergic rhinitis, acne, bruxism whereas some of them were serious, disabling or life threatening diseases like acute lymphoblastic leukemia, valvular hearth disease, pulmonary insufficiency, tuberculosis or Behçet's disease. We suggest that it might not be easy to explore the relationship between epilepsy and some comorbid conditions. Further studies with larger patient population may enlighten whether these diseases are found coincidentally or have higher prevelance in patients with epilepsy than in general population.

CONCLUSION

Psychiatric, neurological and other systemic disorders may be together with epilepsy. Psychiatric disorders and headache were the most frequent comorbidities in our patients. Psychiatric disorders were more common in women, in those who were older and those with symptomatic and cryptogenic epilepsies. Complex relationship between epilepsy and migraine should always be considered in terms of diagnosis, follow up and treatment of these patients.

Physicians who treat patients with epilepsy should be aware of the major impact of comorbidities on these patients. Comorbidities may have a greater effect on quality of life than the seizures themselves. The diagnosis and treatment of comorbid diseases are necessary for the improvement

of life qualities of epilepsy patients. Identifying and treating these comorbidities in patients epilepsy is as important as seizure treatment.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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