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CONTENTS OF THE JOURNAL

COMORBID CONDITIONS IN PATIENTS WITH SYMPTOMATIC EPILEPSY

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Abstract. Objective: *To study the distribution of comorbid conditions among epilepsy patients of different age groups and to evaluate their statistical significance.Methods: The study included 103 patients diagnosed with epilepsy. Participants were divided into two age groups: 18–44 years (n=69) and 45–59 years (n=34). Comorbid conditions were analyzed in three categories: cardiovascular diseases, endocrine disorders, and gastrointestinal disturbances. The t-test was used for statistical analysis.*

Results: *The frequency of cardiovascular diseases was 13.0% in the younger group and 47.1% in the older group (p<0.001). Endocrine disorders were observed in 21.7% and 52.9% of patients, respectively (p<0.01), while gastrointestinal disturbances were found in 36.2% and 64.7% of cases (p<0.01).*

Conclusion: *Older patients with epilepsy show a significantly higher frequency of all types of comorbid conditions, underscoring the need for a comprehensive and multidisciplinary approach to treatment.*

Keywords: *epilepsy, comorbidity, age groups, cardiovascular diseases, endocrine disorders, gastrointestinal disturbances*

Introduction. Epilepsy is one of the most common neurological disorders, affecting more than 50 million people worldwide [1]. In modern medicine, epilepsy is considered not only an isolated neurological condition but also a complex multisystem disorder that frequently coexists with various somatic and psychiatric diseases [2].

Comorbidity significantly reduces the quality of life in epilepsy patients and negatively affects treatment outcomes [3]. According to published data, the frequency of comorbid conditions among individuals with epilepsy is reported to be 2–3 times higher than in the general population [4]. This phenomenon is associated with the disease itself, the adverse effects of antiepileptic drugs, and genetic predisposition [5].

Age plays a critical role in the distribution of comorbidities. The prevalence of these conditions tends to increase with age, which can be explained by physiological aging, metabolic alterations, and the cumulative effects of long-term antiepileptic therapy [6]. The most frequently encountered comorbidities in epilepsy patients are cardiovascular, endocrine, and gastrointestinal disorders [7].

Cardiovascular diseases in epilepsy patients often present as ischemic heart disease, arterial hypertension, or arrhythmias [8]. Certain antiepileptic drugs, particularly carbamazepine and phenytoin, are known to have cardiotoxic effects that may provoke rhythm disturbances [9]. Among endocrine disorders, diabetes mellitus, osteoporosis, and reproductive dysfunctions are predominant [10]. Sodium valproate has been associated with the development of metabolic syndrome and polycystic ovary syndrome [11], while phenytoin and carbamazepine may disrupt vitamin D metabolism, leading to osteoporosis [12].

Gastrointestinal complications such as hepatotoxicity, peptic ulcer disease, and functional dyspepsia are also relatively common [13]. Many antiepileptic medications induce hepatic enzymes, which can lead to hepatocellular injury [14].

Nevertheless, the distribution of comorbid conditions and their statistical significance across different age groups remain insufficiently studied, highlighting the need for further investigation in this area.

Research Objective. The objective of this study was to examine the distribution of comorbid conditions among patients with epilepsy in different age groups and to assess their statistical significance.

Materials and Methods. This prospective cross-sectional study was conducted at the Department of Neurology, Tashkent Medical Academy, during 2022–2023. The research protocol was approved by the institutional bioethics committee, and written informed consent was obtained from all participants. A total of 103 patients diagnosed with epilepsy were enrolled. Diagnosis was established based on the International League Against Epilepsy (ILAE) classification criteria (2017).

Inclusion criteria included: age above 18 years, confirmed diagnosis of epilepsy for at least six months, and completion of all clinical and paraclinical assessments. Exclusion criteria comprised the presence of psycho-organic syndrome, severe somatic decompensation, pregnancy or lactation, and refusal to participate.

Patients were divided into two age groups: 18–44 years (n=69) and 45–59 years (n=34). The age group boundaries were determined according to the World Health Organization (WHO) age classification and epileptological age-related characteristics. All subjects underwent standardized medical history collection, neurological examination, electroencephalography (EEG), magnetic resonance imaging (MRI) or computed tomography (CT).

Comorbid conditions were systematically analyzed in the following categories: cardiovascular diseases, including arterial hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), ischemic heart disease (confirmed by ECG and echocardiography), and various arrhythmias (supraventricular and ventricular). Endocrine disorders, including diabetes mellitus (blood glucose ≥7.0 mmol/L or HbA1c ≥6.5%), thyroid disorders (according to TSH, T3, T4 levels), and osteoporosis (based on densitometry results). Gastrointestinal disorders, including chronic gastritis (confirmed by endoscopy and histology), peptic ulcer disease (endoscopically verified), and drug-induced hepatopathy (elevated liver enzymes ≥2-fold above normal).

Laboratory investigations were conducted using standard methods. Biochemical tests measured glucose, creatinine, urea, total bilirubin, ALT, AST, GGT, and alkaline phosphatase. Hormonal evaluation included TSH, T3, T4, cortisol, and insulin measurements. Cardiac assessment involved 12-lead ECG, echocardiography, and, when necessary, Holter monitoring. Gastroenterological examination included fibrogastroduodenoscopy and abdominal ultrasound.

Data were collected using a standardized questionnaire that covered demographic information, epilepsy history, current medications, and comorbid conditions. All records were reviewed and verified by two independent researchers.

Statistical Analysis. Statistical data processing was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was applied to check normality of data distribution. Categorical variables were presented as absolute numbers and percentages. Differences between groups were assessed using Student's *t*-test, with degrees of freedom calculated as $df = n_1 + n_2 - 2$. A p-value <0.05 was considered statistically significant. All tests were two-tailed. Results were expressed as mean ± standard error (M±m), and effect size was evaluated using Cohen's *d* index.

Research Results.

The demographic characteristics of the 103 epilepsy patients included in the study were as follows. The 18–44-year-old group consisted of 69 patients (66.9%), while the 45–59-year-old group included 34 patients (33.1%). By gender distribution, in the younger group there were 38 men (55.1%) and 31 women (44.9%), while in the older group there were 19 men (55.9%) and 15 women (44.1%). No statistically significant difference was found between groups regarding gender distribution ($p>0.05$).

The distribution of epilepsy types was as follows: focal epilepsy was identified in 45 patients (65.2%) in the 18–44-year group and in 26 patients (76.5%) in the 45–59-year group. Generalized epilepsy was observed in 24 (34.8%) and 8 (23.5%) patients, respectively. The mean disease duration was 8.4±2.1 years in the younger group and 15.7±3.8 years in the older group ($p<0.001$).

Regarding antiepileptic therapy, monotherapy was administered to 42 patients (60.9%) in the 18–44-year group and 18 patients (52.9%) in the 45–59-year group. Polytherapy was used in 27 (39.1%) and 16 (47.1%) patients, respectively. The most commonly used drugs were carbamazepine (34.0%), sodium valproate (28.2%), lamotrigine (18.4%), and levetiracetam (19.4%).

The following table presents the frequency of cardiovascular diseases among epilepsy patients and their distribution by age groups (Table 1).

Table 1.

Frequency of cardiovascular diseases among epilepsy patients by age group

Cardiovascular Diseases	18–44 years (n=69)			45–59 years (n=34)			t test	p
	n	M±m	%	n	M±m	%		
Arterial hypertension	5	0.072±0.031	7.2	12	0.353±0.084	35.3	-3.12	<0.01
Ischemic heart disease	2	0.029±0.020	2.9	8	0.235±0.074	23.5	-2.68	<0.01
Arrhythmias	4	0.058±0.028	5.8	7	0.206±0.071	20.6	-1.98	<0.05
Total cardiovascular diseases	9	0.130±0.041	13.0	16	0.471±0.088	47.1	-3.50	<0.001

Arterial hypertension accounted for 7.2% in the younger group and increased to 35.3% in the middle-aged group. Statistical analysis revealed a significant difference ($t=-3.12$; $p<0.01$), indicating that hypertension is much more common among middle-aged patients with epilepsy. Ischemic heart disease was recorded in 2.9% of patients aged 18–44 and rose to 23.5% among those aged 45–59. The difference was statistically significant ($t=-2.68$; $p<0.01$), confirming that autonomic and hemodynamic alterations in epilepsy may contribute to the development of cardiac ischemia. Cases of arrhythmia were observed in 5.8% (M±m=0.058±0.028) of younger patients and 20.6% (M±m=0.206±0.071) of older ones. The difference ($t=-1.98$; $p<0.05$) was statistically significant, showing that cardio-neurological interactions change with age. The total rate of cardiovascular pathologies was 13.0% in younger patients and increased to 47.1% in middle-aged ones, which was highly significant ($t=-3.50$; $p<0.001$). These results suggest that with aging, additional pathological changes develop in the cardiovascular system of epilepsy patients. In summary, almost all types of cardiovascular diseases were more frequent among epilepsy patients aged 45–59, which may be explained by combined cardiometabolic and

neurovascular mechanisms. Early diagnosis and preventive strategies for these age-related comorbidities are of considerable clinical and social importance.

Regarding endocrine comorbidities, diabetes mellitus was found in 8.7% (M±m=0.087±0.034) of younger patients and increased to 32.4% (M±m=0.324±0.082) among the 45–59-year group. This difference was statistically significant (t=–2.74; p<0.01), indicating that with age, metabolic disturbances—especially insulin-related metabolic disorders—occur more frequently. Thyroid disorders were observed in 5.8% (M±m=0.058±0.028) of younger patients and 14.7% (M±m=0.147±0.062) of older ones, with a statistically insignificant difference (t=–1.35; p>0.05). This finding suggests that thyroid dysfunction in epilepsy patients is more likely associated with individual endocrine reactivity rather than solely age-related factors.

Osteoporosis was observed in 10.1% (M ± m = 0.101 ± 0.036) of younger patients and 26.5% (M ± m = 0.265 ± 0.077) of older patients, with a statistically significant difference (t = –1.98; p < 0.05). These findings confirm that with age, the reduction in bone mineral density and disturbances in calcium-hormonal balance become more pronounced among patients with epilepsy (Table 2).

Table 2.

Frequency of endocrine disorders among epilepsy patients by age group

Endocrine disorders	18–44 years (n=69)			45–59 years (n=34)			t test	p
	n	M±m	%	n	M±m	%		
Diabetes mellitus	6	0.087±0.034	8.7	11	0.324±0.082	32.4	-2.74	<0.01
Thyroid disorders	4	0.058±0.028	5.8	5	0.147±0.062	14.7	-1.35	>0.05
Osteoporosis	7	0.101±0.036	10.1	9	0.265±0.077	26.5	-1.98	<0.05
Total endocrine diseases	15	0.217±0.050	21.7	18	0.529±0.088	52.9	-3.08	<0.01

The total frequency of endocrine disorders increased from 21.7% (M ± m = 0.217 ± 0.050) in the younger group to 52.9% (M ± m = 0.529 ± 0.088) in the middle-aged group. The difference was statistically significant (t = –3.08; p < 0.01), indicating that the long-term course of epilepsy contributes to increasing loads on the endocrine system and dysregulation of the hypothalamic-pituitary axis.

The following table presents the frequency of gastrointestinal disorders among patients with symptomatic epilepsy and their comparative distribution across different age groups (Table 3).

Table 3.

Frequency of gastrointestinal disorders among epilepsy patients by age group

Gastrointestinal disorders	18–44 years (n=69)			45–59 years (n=34)			t test	p
	n	M±m	%	n	M±m	%		
Chronic gastritis	18	0.261±0.05	26.1	15	0.441±0.08	44.1	-1.82	>0.05
Peptic ulcer disease	4	0.058±0.02	5.8	8	0.235±0.07	23.5	-2.28	<0.05
Drug-induced hepatopathy	8	0.116±0.03	11.6	7	0.206±0.07	20.6	-1.15	>0.05
Total gastrointestinal disorders	25	0.362±0.05	36.2	22	0.647±0.08	64.7	-2.78	<0.01

Chronic gastritis was present in 26.1% (M ± m = 0.261 ± 0.05) of younger patients and 44.1% (M ± m = 0.441 ± 0.087) of older patients. Although the difference was not statistically significant (t = –1.82; p > 0.05), the trend suggests that longer epilepsy duration may lead to altered gastric secretory function. Peptic ulcer disease occurred in 5.8% (M ± m = 0.058 ± 0.02) of patients aged 18–44 and increased to 23.5% (M ± m = 0.235 ± 0.074) in the 45–59-year group (t = –2.28; p < 0.05). The statistically significant difference indicates that long-term antiepileptic drug use may adversely affect the gastrointestinal system, increasing ulcer risk due to medication-related stress factors. Drug-induced hepatopathy was detected in 11.6% (M ± m = 0.116 ± 0.03) of younger and 20.6% (M ± m = 0.206 ± 0.071) of older patients. Although the difference was not significant (t = –1.15; p > 0.05), the trend reflects the hepatotoxic effects of antiepileptic drugs and the age-related decline of hepatic metabolism.

Overall, gastrointestinal disturbances were recorded in 36.2% (M ± m = 0.362 ± 0.05) of younger patients and in 64.7% (M ± m = 0.647 ± 0.084) of older ones. The difference was statistically significant (t = –2.78; p < 0.01), confirming that gastrointestinal toxicity and metabolic impairment are important comorbid factors in the long-term management of epilepsy.

In older epilepsy patients, a significant increase in glucose, ALT, and AST levels confirmed the development of metabolic-hepatic dysfunction. This indicates that oxidative stress and medication load play a crucial role in the pathogenesis of epilepsy, emphasizing the need for continuous laboratory monitoring of such patients (Table 4).

Table 4.

Comparative biochemical and hormonal laboratory indicators in epilepsy patients by age group

Laboratory Indicators	18–44 years (n=69)	45–59 years (n=34)	t test	p
Glucose (mmol/L)	5.2±0.3	6.8±0.7	-2.45	<0.05
ALT (U/L)	28.4±3.2	42.7±5.8	-2.31	<0.05
AST (U/L)	26.1±2.9	38.9±4.7	-2.54	<0.05
Total cholesterol (mmol/L)	4.8±0.4	5.9±0.6	-1.67	>0.05
TSH (mU/L)	2.1±0.3	3.4±0.8	-1.58	>0.05

This table compares the main biochemical and hormonal laboratory parameters of patients with symptomatic epilepsy by age group.

The glucose level in the younger group was 5.2 ± 0.3 mmol/L, whereas in older patients it increased to 6.8 ± 0.7 mmol/L (t = –2.45; p < 0.05). This result indicates the development of hyperglycemia associated with insulin resistance and metabolic stress, suggesting impaired glucose homeostasis due to the long-term duration of epilepsy and antiepileptic therapy.

ALT (alanine aminotransferase) activity was 28.4 ± 3.2 U/L in the younger group and 42.7 ± 5.8 U/L in the older one (t = –2.31; p < 0.05). This elevation demonstrates structural damage to hepatic cell membranes, possibly caused by antiepileptic drugs. Similarly, AST (aspartate aminotransferase) activity rose from 26.1 ± 2.9 U/L to 38.9 ± 4.7 U/L (t = –2.54; p < 0.05). This finding corresponds to hepatocellular stress and the manifestation of moderate drug-induced hepatopathy.

Total cholesterol levels were 4.8 ± 0.4 mmol/L in younger patients and 5.9 ± 0.6 mmol/L in the older group (t = –1.67; p > 0.05). Although the difference was not statistically significant, the trend reflects a slowing of lipid metabolism. This may indicate an increased atherogenic risk related to hypodynamia and pharmacological modulation in epilepsy.

The thyroid-stimulating hormone (TSH) level increased from 2.1 ± 0.3 mU/L in younger patients to 3.4 ± 0.8 mU/L in older ones ($t = -1.58$; $p > 0.05$). Even though this difference was insignificant, it points to compensatory partial dysfunction within the neuroendocrine system.

According to electrocardiography (ECG) data, rhythm disturbances were found in 6 patients (8.7%) aged 18–44 and in 11 patients (32.4%) aged 45–59 ($p < 0.01$). Echocardiographic evaluation detected left ventricular hypertrophy in 3 younger patients (4.3%) and structural cardiac changes in 9 older patients (26.5%) ($p < 0.01$).

Fibrogastroduodenoscopy results revealed erosive lesions in 12 younger patients (17.4%) and 18 older patients (52.9%) ($p < 0.001$). This finding demonstrates that age progression in epilepsy is often accompanied by a higher frequency of gastrointestinal mucosal damage, reflecting cumulative metabolic and pharmacotoxic stress.

Discussion. The obtained results showed that comorbid conditions were significantly more common in older epilepsy patients, consistent with international research data [17]. The sharp increase in cardiovascular diseases with advancing age (from 13.0% to 47.1%) can be explained by several factors. First, the natural aging process disrupts endothelial function and promotes the development of atherosclerosis [18]. Second, long-term antiepileptic therapy—particularly with phenytoin and carbamazepine—has been identified as a contributor to elevated cardiometabolic risk factors [19].

The frequency of endocrine disorders also more than doubled with age (from 21.7% to 52.9%). This outcome is associated with the long-term impact of antiepileptic drugs on the endocrine system [20]. Sodium valproate has been shown to increase insulin resistance, leading to the development of metabolic syndrome [21]. Phenytoin and carbamazepine interfere with vitamin D metabolism, resulting in osteoporosis [22].

The rise in gastrointestinal disorders (from 36.2% to 64.7%) is most likely due to the hepatotoxic influence of antiepileptic medications and the age-related decline in gastrointestinal function [23]. Phenytoin, carbamazepine, and valproate affect the cytochrome P450 enzyme system, which can impair hepatic function [24].

Conclusion. The research findings indicate that all types of comorbid conditions occur at a significantly higher frequency among older patients with epilepsy. Cardiovascular diseases were 3.6 times more prevalent (47.1% vs 13.0%), endocrine disorders 2.4 times more frequent (52.9% vs 21.7%), and gastrointestinal disturbances 1.8 times more common (64.7% vs 36.2%) in the 45–59-year age group compared to the younger group. These results emphasize the necessity of a comprehensive clinical approach for older epilepsy patients.

In addition to neurological treatment, regular cardiological, endocrinological, and gastroenterological monitoring should be integrated into clinical management. Selecting antiepileptic therapy must take into account the patient's age and existing comorbidities, while also minimizing drug interactions and adverse effects.

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