ORIGINAL ARTICLE

Somatic comorbidity in Polish patients with epilepsy

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ABSTRACT

INTRODUCTION   A wide spectrum of somatic and psychiatric disorders occurs frequently in patients with epilepsy, which adds to the burden of this disease.

OBJECTIVES   The aim of the study was to estimate the prevalence and risk factors of somatic comorbidities and analyze somatic comedication in adult patients with epilepsy.

PATIENTS AND METHODS   This study involved patients with epilepsy treated in university epilepsy clinic. Data on epilepsy, antiepileptic drugs (AEDs), somatic comorbidities, and their treatment were collected from a structured interview and from medical records.

RESULTS   The sample population consisted of 636 patients (mean age, 35.3 years); 380 (59.7%) were female and 241 (37.9%) had well-controlled epilepsy. At least 1 comorbid somatic condition was found in 216 patients (34%). The most prevalent somatic comorbidities were cardiovascular diseases, allergies, migraine, hyperlipidemia, thyroid disorders, and chronic lower respiratory diseases. Furthermore, 200 patients (31.4%) were prescribed at least 1 medication for somatic disorders. Logistic regression analysis revealed several independent risk factors for the occurrence of somatic comorbidities: older age, shorter duration of epilepsy, lower seizure frequency, and lower number of AEDs.

CONCLUSIONS   Somatic comorbidities and comedication with non-AEDs were found in one-third of the relatively young cohort of adult patients with epilepsy. Patients with pharmacoresistant epilepsy may be at risk of underdiagnosis and undertreatment of somatic comorbidities. The presence of comorbidities may have implications for the diagnosis and treatment of seizure disorder and coexisting condition.

INTRODUCTION   Epilepsy is one of the most common chronic neurological disorders. The point prevalence of the active disease is 6.38 per 1000 persons in Poland; thus, it is estimated to affect approximately 250 000 people in Poland (Statistics Poland).[1,2] The burden of epilepsy is associated not only with seizures and antiepileptic medication but also with a wide range of somatic and psychiatric comorbidities and their treatment.[3] The term "comorbidity," originally coined by Feinstein, refers to the greater than coincidental co-occurrence of 2 conditions in the same person.[4] Several mechanisms of the association between epilepsy and comorbid conditions have been proposed: causative (eg, stroke and brain tumor), resultant (eg, seizure-related fractures and treatment-related psychiatric disorders), shared risk factors (eg, migraine and cerebral palsy),

bidirectional (depression), and co-occurrence by chance.[5]

A number of population-based and case-control studies have reported an inceased risk of medical and psychiatric conditions in patients with epilepsy.[6-9] Such patients with comorbidities are at higher risk of poor seizure outcome, pharmacokinetic interactions, reduced quality of life, increased health care needs, and premature mortality.[5] Early identification and adequate treatment of comorbid conditions are indispensable for the appropriate management of both epilepsy and comorbidities. Geographic, environmental, and socioeconomic factors (eg, ethnicity, the geographic distribution of the disease, and quality and availability of health care services) may influence the nature and prevalence of somatic comorbidities in patients with epilepsy.

TABLE 1 General characteristics of studied patients with epilepsy and current treatment of epilepsy

Variable		Value
Female sex		380 (59.7)
Age, y, mean (SD)		35.3 (13.6)
Age at onset of epilepsy, y, mean (SD)		19.5 (14.6)
Mean duration of epilepsy, y, mean (SD)		15.8 (11.7)
Epilepsy type	Generalized	139 (21.8)
	Focal	478 (75.2)
	Combined (generalized and focal) or unknown	19 (3)
Frequency of seizures	>1 per month	229 (36.0)
	1–12 per year	166 (26.1)
	<1 per year	241 (37.9)
Number of currently used AEDs	1	350 (55.0)
	2	208 (32.7)
	3	72 (11.3)
	4	9 (1.0)
Number of currently used AEDs, median (range)		1 (1–4)
The most commonly used AEDs (in mono- or polytherapy)	Valproate	316 (49.7)
	Levetiracetam	215 (33.8)
	Lamotrigine	141 (22.2)
	Carbamazepine	127 (20.0)
	Topiramate	67 (10.5)
	Oxcarbazepine	49 (7.7)

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: AEDs, antiepileptic drugs

Epilepsy classification, according to the history, neurological examination, electroencephalography, and neuroimaging (magnetic resonance imaging or computed tomography).[11] Antiepileptic drugs (AEDs) and their doses used at the time of the interview were recorded.

At a baseline visit, patients were asked to complete the questionnaire related to the comorbidities and chronic use of medications. They were also requested to bring all their current medications and available medical records for the subsequent visit. These data were used to verify and to supplement previous information recalled by the patients. Comorbid conditions were classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; medications were classified according to the Anatomical Therapeutic Chemical classification system.[12,13] Mental and behavioral disorders, diseases of the eye and adnexa, and diseases of the ear and mastoid process were excluded from the analysis.

In this study, we followed the principles of the Helsinki Declaration, and the protocol was approved by the Bioethical Committee of Jagiellonian University, Kraków. Each patient was informed about the aims and methods of this study, and they provided their written consent to participate in this study.

Statistical analysis Qualitative variables were presented as numbers and percentages. Quantitative variables were described using descriptive statistics: mean, median, standard deviation (SD), minimum, and maximum. Significant differences between the subgroups for quantitative variables were verified using the nonparametric Mann–Whitney test. Verification of dependencies between categorical variables was calculated using the Pearson χ^2 independence test. The significance of differences between percentages for specific pairs of cases was verified using the significance test of differences for the structured index. The second part of the analysis included the analysis of the logistic regression model for those factors that in the univariate analysis showed significant differences between the groups having at least 1 somatic comorbidity and that without somatic comorbidity. The model was created using backward stepwise regression. A significance level of 0.05 was assumed. Statistical analysis was performed using the Statistica version 12.5 software (StatSoft Inc., Tulsa, Oklahoma, United States).

RESULTS **Sample characteristics** A total of 636 adult patients participated in this study. The mean (SD) age of patients was 35.3 (13.6) years. Of these, 380 (59.7%) were female and 241 (37.9%) were in remission (less than 1 seizure per year). The mean (SD) age at onset of epilepsy was 19.5 (14.6) years. The clinical characteristics of the studied group, including age, sex, age at onset of epilepsy, type of epilepsy, frequency of seizures, and currently used AEDs, are shown in **TABLE 1**.

To the best of our knowledge, Polish centers have not evaluated chronic medical disorders in patients with epilepsy. Therefore, we decided to study somatic comorbidities, their prevalence, and risk factors and to analyze the extent of somatic comedication in a large adult cohort of such patients.

PATIENTS AND METHODS **Study participants** We recruited consecutive patients with epilepsy who visited the outpatient epilepsy clinic at least twice at the Department of Neurology, University Hospital, Kraków, Poland, between January 2017 and November 2018. The inclusion criterion was the diagnosis of epilepsy established according to the guidelines of International League Against Epilepsy.[10] The exclusion criteria were lack of informed consent and coexistence of psychogenic nonepileptic seizures.

Methods This study had a cross-sectional design. Data from medical history were collected and then updated prospectively. An initial interview was structured and comprised the questionnaire that included information on age, sex, age at the diagnosis of epilepsy, duration of epilepsy, as well as the type(s) and frequency of seizures. The types of epilepsy (focal, generalized, combined, or unknown) were defined in line with the recent International League Against

Chronic somatic comorbidities	Value
Allergies	131 (20.6)
Hypertensive disorders	101 (15.9)
Migraine	59 (9.3)
Hyperlipidemia	49 (7.7)
Thyroid disorders	42 (6.6)
Chronic lower respiratory diseases	41 (6.4)
Brain tumors	33 (5.1)
Other types of heart disease	31 (4.9)
Disorders of the esophagus, stomach, and duodenum	26 (4.1)
Stroke	24 (3.8)
Ischemic heart disease	15 (2.4)
Chronic kidney disease	15 (2.4)
Neurocutaneous syndromes	11 (1.7)
Dermatitis and eczema	9 (1.4)
Diabetes mellitus	9 (1.4)
Comorbidities prevalent in <1% of patients (in alphabetic order)	
Acromegaly and pituitary gigantism	
Addison disease	
Chronic viral hepatitis	
Dementia	
Gaucher disease	
Hemophilia A	
Human immunodeficiency virus infection	
Prostatic hyperplasia	
Hyperprolactinemia	
Osteoarthritis	
Parkinsonism	
Polycystic ovary syndrome	
Psoriasis	
Sarcoidosis	
Systemic connective tissue disorders	
Vitamin B_{12} deficiency anemia	

Data are presented as number (percentage).

Prevalence of somatic comorbidities At least 1 comorbid somatic condition was found in 216 patients (34%). The most prevalent somatic comorbidities were cardiovascular diseases, allergies, migraine, hyperlipidemia, thyroid disorders, and chronic lower respiratory diseases. The most common conditions directly underlying epilepsy were brain tumors, stroke, and neurocutaneous syndromes. Data on the prevalence of somatic comorbidities in the study group are provided in TABLE 2.

Use of medication for somatic disorders A total of 200 patients (31.4%) were prescribed at least 1 medication for somatic disorders. The majority of patients took 1 (87, 43.5%), 2 (55, 27.5%), or 3 (23, 11.5%) medications. TABLE 3 shows the categories of the Anatomical Therapeutic Chemical classification system of somatic medications chronically used by the studied patients. The 10 most commonly used medications other than AED(s)

included levothyroxine (40, 6.3%), metoprolol (26, 4.1%), simvastatin (25, 3.9%), atorvastatin (25, 3.9%), acetylsalicylic acid (23, 3.6%), amlodipine (19, 2.9%), perindopril (13, 2.1%), and ethinyl estradiol (15, 2.3%). In addition, 92 patients (14.5%) took antipsychotics, antidepressants, and/or anxiolytics, but they were not included in the analysis. Three patients demonstrated excessive polypharmacy with 10 AEDs or more and non-AEDs.

Somatic comorbidities in patients with epilepsy risk factors We compared patients with and without somatic comorbid conditions in terms of age, sex, age at onset of epilepsy, duration and type of epilepsy, seizure frequency, number of currently used AEDs, and type of AEDs. Variables that were significant in the univariate analysis were included in the multivariate model. Logistic regression (TABLE 4) revealed several independent risk factors for somatic comorbidities in patients with epilepsy: older age, shorter duration of epilepsy, lower seizure frequency, and lower number of AEDs.

DISCUSSION In this prospective, single-center study, we reported the frequency of somatic comorbidities in a large cohort of adult patients with epilepsy. At least one co-occurring somatic condition was found in 216 patients (3%). The most common comorbidities were allergies, hypertension, migraine, and hyperlipidemia.

Similar to a Canadian study by Tellez-Zenteno et al,[8] the most common comorbidity in our study was allergy. However, it should be considered rather as a symptom and not as a single disorder.[8] In this study, we included a wide range of food, contact, seasonal, and drug allergies. Furthermore, AEDs are a well-known class of medications causing idiosyncratic reactions.[14] The most common AEDs in this study were valproate, levetiracetam, lamotrigine, and carbamazepine. Valproate and levetiracetam are rarely culprit drugs; however, lamotrigine and carbamazepine cause rash in up to 5% of patients. The frequent use of AEDs with an aromatic ring (carbamazepine, lamotrigine, and oxcarbazepine) in the study population can partially explain the high percentage of patients with allergies.

The high frequency of cardiovascular diseases and hyperlipidemia is consistent with the results of Canadian and British studies.[6,8] The relationship between cardiovascular diseases and epilepsy may be bidirectional. Ischemic brain tissue lesions are the common cause of epilepsy and acute symptomatic seizures.[15] Furthermore, hepatic enzyme-inducing drugs are associated with the acceleration of atherosclerosis in patients with epilepsy.[16] The relatively low incidence of cardiovascular diseases in comparison with the general population can be partially explained by the young mean age of the studied patients.[17,18] The prevalence of migraine in our cohort (9.3%) was higher than that reported by Gaitatzis et al[6] (5.7% in patients in the age group of 16–64 years) and lower than that

TABLE 3 Medications chronically used by patients with epilepsy as categorized by the Anatomical Therapeutic Chemical classification system

Medications classified according to ATC		Value
Alimentary tract and metabolism (A)	Drugs for acid-related disorders (A02)	22 (3.5)
	Drugs used in diabetes (A10)	9 (1.4)
	Vitamins (A11)	5 (0.8)
	Other alimentary tract and metabolism products (A16)	7 (1.1)
Blood and blood-forming organs (B)	Platelet aggregation inhibitors (B01AC)	23 (3.6)
	Anticoagulants (B01AA or B01AE or B01AF)	10 (1.6)
Cardiovascular system (C)	Diuretics (C03)	21 (3.3)
	β-Blockers (C07)	54 (8.5)
	Calcium channel blockers (C08)	24 (3.7)
	ACEIs (C09A)	35 (5.5)
	Angiotensin II antagonists (C09C)	15 (2.4)
	Lipid-modifying agents (C10)	49 (7.7)
Genito-urinary system and sex hormones (G)	Progestogens and estrogens (fixed combinations) (G03AA)	23 (3.6)[a]
Systemic hormonal preparations excluding sex hormones and insulins (H)	Systemic corticosteroids (H02)	5 (0.8)
	Thyroid therapy (H03)	40 (6.3)
Antineoplastic and immunomodulating agents (L)		4 (0.6)
Musculoskeletal system (M)		4 (0.6)
Respiratory system (R)	Drugs for obstructive airway diseases (R03)	20 (3.3)
Various (V)		15 (2.4)

Data are presented as number (percentage).

a A total of 17 patients used hormonal contraception.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ATC, Anatomical Therapeutic Chemical classification system

TABLE 4 Risk factors for somatic comorbidities in patients with epilepsy (logistic regression)

Parameter	OR	95% CI	*P* value
Sex	0.86	0.59–1.27	0.46
Age	1.08	1.07–1.10	<0.001
Duration of epilepsy	0.97	0.96–0.99	0.003
Seizure frequency	0.76	0.59–0.98	0.03
Number of AEDs	0.66	0.48–0.91	0.01

Abbreviations: AED, antiepileptic drug; CI, confidence interval; OR, odds ratio

of Tellez-Zenteno et al[8] (17%). This discrepancy can be explained by the fact that the diagnosis of migraine in the Polish cohort was established by a neurologist (MB) according to the International Headache Society criteria and was not based on data from general practices or population--based surveys.[19]

One-third of the patients were prescribed at least 1 medication for somatic disorders. However, in this study, we aimed to evaluate the presence of comorbidities and we did not focus on non-AEDs. The number of comedications, risk of seizure aggravation, and potential interaction between AEDs and non-AEDs in Polish patients have been described elsewhere.[20,21]

Somatic comorbidities lead to premature mortality or disability and to increased health care costs in patients without epilepsy. Epilepsy itself accounts for a significant proportion of the disease burden worldwide, as well as strongly affects patients' independence, psychological health, and social life. Somatic comorbidities add to the burden of epilepsy, and their early detection and treatment may increase health-related quality of life in patients with epilepsy.[22,23]

Logistic regression analysis identified several independent risk factors for somatic comorbidities. Older patients were more likely to suffer from coexisting conditions, which is in line with the results of Gaitatzis et al,[6] Adebayo et al,[24] and Stefan et al.[25] Surprisingly, patients with shorter duration of epilepsy, less frequent seizures, and taking fewer AEDs were at higher risk of having at least 1 comorbidity. We are not able to provide a clear explanation for this finding. There may be several reasons for this association. In pharmacoresistant cases, the neurologist–patient interaction focuses on seizure frequency and treatment as well as on searching for possible coexisting conditions. However, other health care providers and patients themselves are prone to attribute all complaints to epilepsy and AEDs. Underdiagnosis and undertreatment of both somatic and psychiatric disorders is a well-known phenomenon in patients with epilepsy.[26-28]

We must acknowledge some limitations of this study. First, there was no control group. Second, we studied the population of a university epilepsy clinic, which may differ substantially from the general population of patients with epilepsy with regard to seizure frequency, treatment of epilepsy therapy, frequency of comorbidities, and use of concomitant medication. Third, some rare conditions resulting in pharmacoresistant epilepsy may be overrepresented in our cohort, and patients with multiple comorbidities seen within the university hospital are frequently referred to our clinic. Finally, we focused on somatic comorbidities. Psychiatric comorbidities and comedication in Polish patiens with epilepsy were analyzed previously.[20]

In conclusion, our findings highlight the high prevalence of somatic comorbidities and comedication with non-AEDs among patients with epilepsy. Both were found in one-third of the relatively young cohort of adult patients. Neurologists and other health care providers should increase their efforts to actively screen such patients for somatic comorbidities. Patients with pharmacoresistant epilepsy may be at greater risk of underdiagnosis and undertreatment of these comorbidities. The presence of comorbid conditions may have implications for the diagnosis and treatment of seizure disorder and coexisting condition. Further prospective studies are needed to determine risk factors for somatic comorbidities in patients with epilepsy.

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