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ORIGINAL ARTICLE

Which clinical and neuropsychological factors are responsible for cognitive impairment in patients with epilepsy?

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Abstract

Objectives The study aimed to assess the effect of demographic and clinical features of epilepsy, anxiety, depressed mood, sleep, and quality of life on the prediction of cognitive decline in patients with epilepsy.

Methods Two hundred and six consecutive patients with epilepsy (age 41.8 ± 15.6 years, mean, SD) out of 279, were included in this cross-sectional study. We used simple linear regression to calculate the results.

Results Objective cognitive status was predicted by anxiety and depression mood changes (Beck Anxiety Inventory (BAI), $p = 0.03$, Beck Depression Inventory (BDI), $p = 0.005$), language subdomain of Quality of Life Inventory in Epilepsy-89 (QOLIE-89) ($p = 0.003$), and total QOLIE-89 ($p = 0.001$). No significance was shown in demographic and clinical features of epilepsy (gender, age at onset, epilepsy duration, type, etiology of epilepsy, and antiepileptic treatment), except frequency of generalized epileptic seizures ($p = 0.03$), which also served as an independent predictor of anxiety (BAI) and depression (BDI).

Conclusions Our findings point at the role of mood changes in the cognitive status of patients with epilepsy, which should be used as an essential therapeutic target apart of seizure control.

Keywords Cognition · Epilepsy · EpiTrack · Cognitive impairment · Depression · Anxiety

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Introduction

The risk of cognitive decline caused by epilepsy was first described more than 100 years ago (Wallin 1912). The dominant model of cognitive impairment in epilepsy emphasizes structural bases for cognitive deficits (Dodson and Pellock 1993). Morphological factors refer to the presence of developmental or acquired cerebral lesions causing both epilepsy and cognitive impairment. Current theories point at the importance of disturbed network interactions as a pathophysiological basis of cognitive dysfunction in patients with epilepsy (PWE) (Tailby et al. 2018). Dynamic factors are epileptic seizures, interictal epileptic activity, and antiepileptic drugs (AEDs) (Trimble 1988). Patient's reserve capacities and age and sex-dependent neural plasticity should be considered as well (Witt and Helmstaedter 2015). The presence of epilepsy is negatively reflected in a patient's mood and cognitive performance (Witt and Helmstaedter 2015). Cognitive and psychiatric comorbidities have a strong impact on patients' quality of life. Therefore, apart from the treatment of

epileptic seizures, prevention, and reversal of the comorbidities of epilepsy with an impact on cognition, it should become an important area for the care of PWE. Understanding of reciprocal relations, e.g., AEDs with the negative impact on mood changes and possible negative pharmacological interactions of antidepressants with AEDs, tasks for complex and multidisciplinary management of PWE.

The aim of our study was to examine cognitive performance in PWE and identify its cofactors raising of epilepsy characteristics, comorbid mood changes, and subjective evaluation of role limitations due to seizure disorder. EpiTrack, a screening instrument for the detection of cognitive dysfunctions in PWE, was chosen as an easily administered tool for routine practice.

Methods

The study was set as a cross-sectional analysis of data from PWE over 18 years of age, coming for a visit to our department from January to December 2018, who provided written informed consent. PWE, who had signs of disability that would not allow understanding/seeing/writing the self-administered questionnaires, was excluded from the study.

1. The clinical data were reviewed for demographic features (age, gender) and epilepsy type (focal temporal, focal extra temporal, generalized epilepsy, etiology, number of taken AEDs). The patients were interviewed for clinical features (age of seizure onset, duration of epilepsy, seizure frequency). We quantified the numbers of epileptic seizures expressed as generalized epileptic seizures (GES), e.g., focal onset to bilateral tonic–clonic seizures or generalized tonic–clonic seizures and other epileptic seizures (OES), e.g., focal aware/impaired consciousness epileptic seizures, absences, myoclonic seizures.
2. Questionnaires were used to asses: patients' cognitive performance by EpiTrack, sleep by The Pittsburgh Sleep Quality Index (PSQI), daytime sleepiness by Epworth Sleepiness Scale (ESS), mood by Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and quality of life by Quality of Life (QoL) Inventory in Epilepsy-89 (QOLIE-89).

Objective cognitive functioning

EpiTrack is a concise and easily administered screening tool for the detection of dysfunctions of attention, memory, language problems, psychomotor performance, and executive control caused by epileptic disorders or AEDs, and to track cognitive performance parallel to changes in medical therapy. Attentional functions include the ability to attend to stimuli, concentrate on task demands, and self-monitor responses. Executive control comprises such skills as strategy formation, planning, and motor programming that are involved in the organization of complex behavior. The 15-min screening tool consists of six subtests: The Trail-Making Test (parts A and B), a test of response inhibition, digit span backward, written word fluency, and a maze test (Lutz and Helmstaedter 2005). EpiTrack divides the population of PWE epilepsy into four subgroups depending on their performance category: 1: excellent ($\geq$ 39 points), 2: average (32–38 points), 3: mild (29–31 points) and 4: significant ($\leq$ 28 points) disorder (Halmsteter 2015).

Anxiety

BAI was developed to discriminate anxiety from depression while displaying convergent validity reliably. The final scale consists of 21 items, each describing a common symptom of anxiety. The respondent is asked to rank how much was he bothered over the past week by each sign on a 4-point scale ranging from 0 (not at all) to 3 (severely—I could barely stand it). Summing the items will create a total score that can range from 0 to 63. A total score of 0–7 is interpreted as a minimal level of anxiety, 8–15 as mild, 16–25 as moderate, and 26–63 as severe (Beck et al. 1988).

Depression

BDI was developed to identify depressive syndromes. It consists of 21 categories of symptoms and attitudes. The statements are ranked to reflect the range of severity of the trait from neutral to maximal severity. Numerical values from 0 to 3 are assigned each report to indicate the degree of seriousness. Summing the items will give a final score of 0–13 points which stand for minimal depression, 14–19 points for mild depression, 20–28 points for moderate depression, and score of 29–63 for severe depression (Beck 1961).

Sleep quality

PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. Nineteen items create seven "component" scores: subjective sleep quality, sleep duration, habitual sleep efficiency, sleep latency, sleep disruptions, use of sleeping prescription, and daytime dysfunction. Summing the scores for these seven components provides one global number. A global PSQI score > 5 distinguishes poor from good sleepers (Buysse et al. 1989).

Daytime sleepiness

ESS is a self-administered questionnaire that is providing a measurement of the subject's general level of daytime sleepiness. They rated the chances that they would doze off or fall asleep in eight different situations commonly encountered in daily life. Summing the total score will give us a picture of the presence of sleepiness, which is considered to be excessive above 10 points (Johns 1991).

Quality of life

The QOLIE-89 is the most widely used and most comprehensive instrument specifically developed for the evaluation of QoL in PWE. The instrument can be completed in about 15 min. Higher scores indicate better QoL. It consists of 89 questions assessing 17 individual items totaling a score ranging between 0 and 100. The QoL concepts are the following: health perception, seizure worry, physical function, medication effects, role limitations—physical, role limitations—emotional, pain, emotional well-being, energy/fatigue, attention/concentration, memory, language, social support, work/driving/social function, social isolation, health discouragement, and overall QoL (Devinsky et al. 1995).

Statistical analysis

The Shapiro–Wilk test was used to assess the normality of distribution of independent variables. Continuous variables were expressed as medians, and interquartile ranges (IQRs) and categorical variables were expressed as absolute and relative frequencies (%). For the purpose of primary analysis, Fisher's exact test and Kruskal–Wallis test were used to examine differences in demographic, clinical, and psychometric characteristics among patients in different EpiTrack subgroups. Univariate ordinal logistic regression analyses were then performed to search for associated factors with EpiTrack subgroups. For this purpose, categorical variables were recoded into set of dummy variables. Simple analyses were first performed, and significantly associated independent variables were then included in the multiple model. Parallel regression assumption was confirmed using brant function. Influence analysis was performed by calculating Cook's distance. Collinearity of independent variables was determined by calculating variance inflation factors (VIF). Results of ordinal logistic regression models are presented as p values, odds ratios (OR) with 95% confidence intervals (95% CI) and standard error (SE) of regression coefficients. All tests were two-sided and performed at a 95% significance level. Data were analyzed using R language (version 3.6.1).

Results

We examined all patients with epilepsy, who were followed up at our department in 2018. Out of 279 patients, 73 patients were excluded either due to meeting some exclusion criteria or due to not consenting to trial participation. Furthermore, we excluded 30 more patients who refused to complete one or more questionnaires during the examination. Only patients with complete data (176 patients) were included in the final statistical analysis.

We report differences in demographic and clinical characteristics of PWE among different EpiTrack subgroups in Table 1. Expected frequencies of GES were lower in PWE with better cognitive performance ($p = 0.03$). Neither gender, age at epilepsy onset, duration of the disease, type of epilepsy, the prevalence of other epileptic seizures, nor the number of AEDs antiepileptic drugs were significantly related to EpiTrack (Table 1).

Furthermore, we also report differences in BAI, BDI, ESS, PSQI, and QOLIE-89 among PWE from different EpiTrack subgroups (Table 2). Patients who scored higher levels on both BAI and BDI performed significantly worse in EpiTrack ($p = 0.03$, $p = 0.005$, respectively). On the side, patients who scored higher levels on total QOLIE and the language subdomain of QOLIE reported better scores in EpiTrack ($p = 0.001$, $p = 0.003$, respectively) (Fig. 1). ESS and PSQI scores in all subjects were within the normal range.

In addition to the primary analysis, we also performed ordinal logistic regression analysis to evaluate the relationship, its direction, and the magnitude between independent variables and EpiTrack score. In simple models, the monthly frequency of GES was found to be significantly associated with EpiTrack (OR 4.276, 95% CI 1.150–17.647). Patients who scored higher levels in BAI (OR 1.058, 95% CI 1.020–1.100) and BDI (OR 1.097, 95% CI 1.047–1.155) also performed worse in EpiTrack. Interestingly, patients with better results on total QOLIE (OR 0.975, 95% CI 0.964–0.986), attention subdomain of QOLIE (OR 0.977, 95% CI 0.963-0.991), language subdomain of QOLIE (OR 0.967, 95% CI 0.947–0.985), and memory subdomain of QOLIE (OR 0.982, 95% CI 0.971–0.992) reported better results in EpiTrack as well (Table 3). These variables were then used in multiple ordinal logistic regression as independent variables; however, due to high degree of multicollinearity between independent variables (VIF > 5), we were not able to fit any multiple ordinal logistic regression model.

Table 1 Demographic and clinical characteristics of patients from different EpiTrack subgroups (Slovakia 2018)

		EpiTrack subgroup				*p*
		1	2	3	4	
Patients	Number (%)	25 (14.20)	86 (48.86)	21 (11.93)	44 (25.00)	–
Gender						
Male/female	Number (%)	11/14 (6.3/8)	37/49 (21/28)	13/8 (7.4/4.5)	17/27 (9.6/15.3)	0.36
Age at epilepsy onset (years)	Median (IQR)	18 (25)	16 (14.5)	14.5 (12)	21 (40)	0.50
Epilepsy duration (years)	Median (IQR)	19 (18)	16 18.25)	21 (18)	11 (23)	0.36
Age (years)	Median (IQR)	45 (19)	36 (21.25)	37 (10.25)	40 (33)	0.09
Type of epilepsy						
Focal temporal	Number (%)	4 (2.27)	17 (9.66)	6 (3.40)	7 (3.98)	0.82
Focal extratemporal	Number (%)	14 (7.95)	41 (23.30)	11 (6.25)	25 (14.20)	
Generalized	Number (%)	7 (3.98)	28 (15.90)	4 (2.27)	12 (6.82)	
Etiology of epilepsy						
Structural lesion	Number (%)	11 (6.25)	36 (20.45)	11 (6.25)	26 (14.78)	0.61
Genetic predisposition	Number (%)	9 (5.11)	25 (14.20)	6 (3.40)	10 (5.68)	
Other	Number (%)	5 (2.84)	25 (14.21)	4 (2.27)	8 (4.54)	
Generalized epileptic seizures						
Never	Number (%)	21 (11.93)	67 (38.07)	15 (8.52)	28 (15.91)	0.03*
More than 2 years without a seizure	Number (%)	3 (1.70)	10 (5.68)	1 (0.57)	6 (3.40)	
1 per year	Number (%)	1 (0.57)	3 (1.70)	1 (0.57)	3 (1.70)	
1–11 per year	Number (%)	0	6 (3.40)	0	5 (2.84)	
More than 1 seizure per month	Number (%)	0	0	4 (2.27)	2 (1.14)	
Other epileptic seizures						
Once in a lifetime	Number (%)	1 (0.57)	4 (2.27)	0	3 (1.70)	0.20
More than 2 years without a seizure	Number (%)	15 (8.52)	55 (31.25)	11 (6.25)	21 (11.93)	
1–11 seizures per year	Number (%)	4 (2.27)	9 (5.11)	0	2 (1.14)	
1–4 seizures per month	Number (%)	4 (2.27)	10 (5.68)	5 (2.84)	9 (5.11)	
> 5 seizures per month	Number (%)	0	5 (2.84)	2 (1.14)	8 (4.54)	
Daily	Number (%)	1 (0.57)	3 (1.70)	2 (1.14)	2 (1.14)	
Number of used AEDs						
No treatment	Number (%)	0	3 (1.70)	1 (0.57)	1 (0.57)	0.19
1 AEDs	Number (%)	14 (7.95)	43 (24.43)	8 (4.55)	22 (12.5)	
2 AEDs	Number (%)	11 (6.25)	22 (12.5)	9 (5.11)	14 (7.95)	
3 and more AEDs	Number (%)	0	18 (10.22)	3 (1.70)	7 (3.98)	

AEDs antiepileptic drugs, *IQR* interquartile range, *p* probability value

*$p < 0.05$

Discussion

This cross-sectional study demonstrated that 37% of patients had any cognitive impairment. Symptoms of depression monitored by BDI were prevalent in 15% of patients, and symptoms of anxiety reported by BAI were found in 37% of patients. We found out that a higher BDI and BAI scores correlated with cognitive impairment seen in EpiTrack. The frequency of GES negatively influenced cognitive performance.

Cognitive dysfunction in PWE

Cognitive impairment in PWE in the present study was frequent. This finding is consistent with previous research in the field. Kampf et al. (2016) conducted a prospective study, where they screened cognitive functions in 40 PWE from Germany using EpiTrack. They found that 23.1% of patients had a cognitive deficit. Witt and Helmstaedter (2012) tested cognitive skills of 247 untreated patients from Germany with newly diagnosed epilepsy using the EpiTrack and memory (short form of the verbal learning

Table 2 Psychometric characteristics of patients from different EpiTrack subgroups (Slovakia 2018)

		EpiTrack subgroup				*p*
		1	2	3	4	
Patients	Number (%)	25 (14.20)	86 (48.86)	21 (11.93)	44 (25.00)	–
BAI	Median (IQR)	5 (6)	4 (7)	4.5 (6)	8 (10)	0.03*
BDI	Median (IQR)	3 (4)	4 (6)	5 (5.5)	6 (9)	0.005*
ESS	Median (IQR)	2 (3)	2 (4.25)	2.5 (2.50)	3 (4.00)	0.80
PSQI	Median (IQR)	3 (3)	3 (4)	4 (4.25)	4 (3)	0.33
QOLIE-89 attention	Median (IQR)	95.56 (12.22)	95.56 (20.14)	95 (11.80)	87.78 (41.11)	0.15
QOLIE-89 memory	Median (IQR)	87.78 (23.05)	89.45 (27.57)	88.75 (33.41)	71.38 (63.62)	0.09
QOLIE-89 language	Median (IQR)	100 (8)	100 (8)	96 (8)	92 (24)	0.003*
QOLIE-89 total score	Median (IQR)	92.765 (24.42)	89.485 (26.60)	87.35 (24.27)	84.475 (53.31)	0.001*

BAI Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *QOLIE-89*, Quality of Life Inventory in Epilepsy-89, *IQR*, interquartile range, *p* probability value

*$p < 0.05$

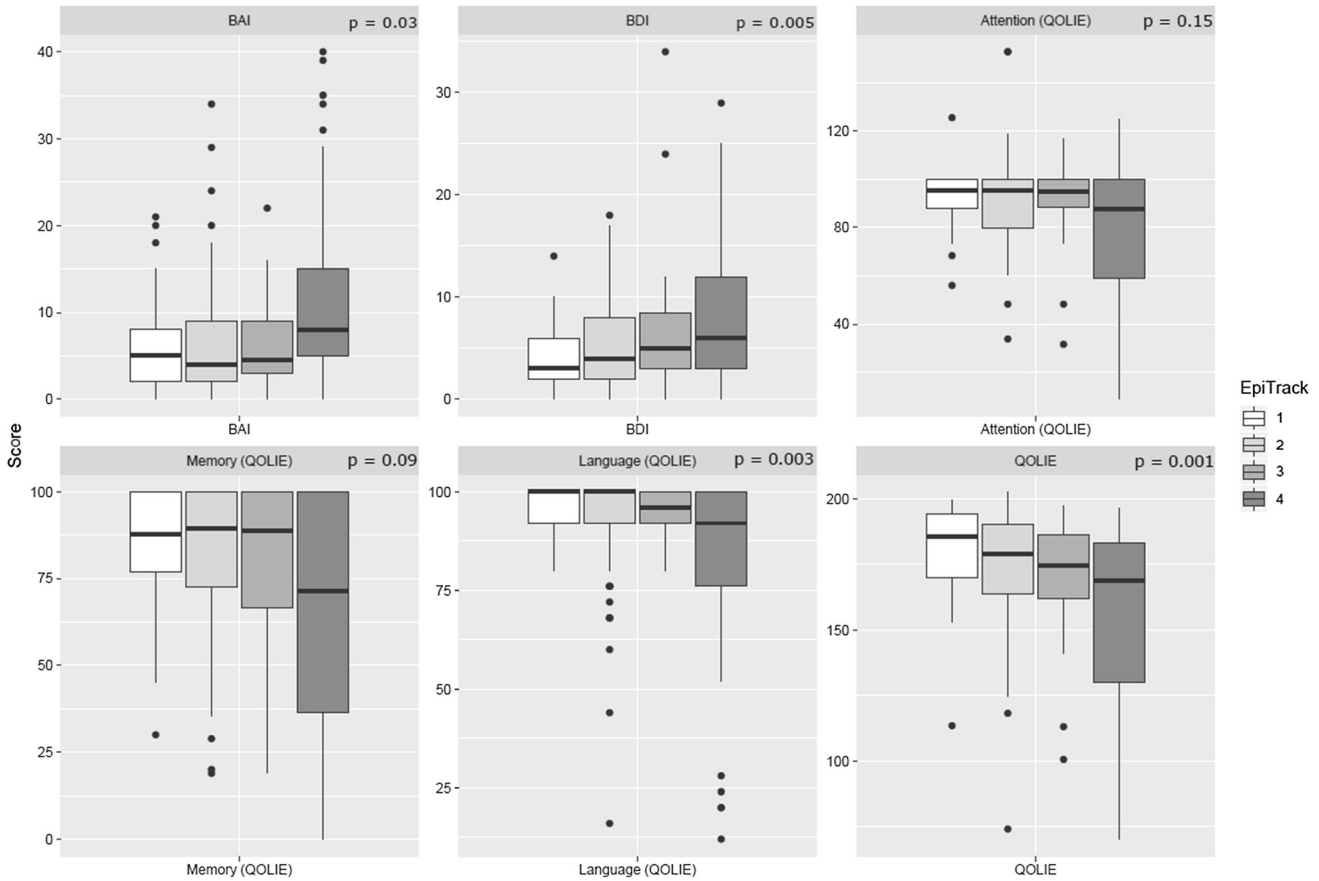

Fig. 1 Boxplots of relevant questionnaires results among different EpiTrack subgroups (Slovakia 2018). BAI Beck Anxiety Inventory, BDI Beck Depression Inventory, QOLIE Quality of Life Inventory in Epilepsy-89

and memory test). Almost half of the patients had impairments in attention and executive functions or memory deficits. Unimpaired performance in all domains was observed just in one-third of the cases. Even if used the same instrument (EpiTrack) for cognitive evaluation, differences in the proportions of affected individuals could be due to variable samples of PWE in the outpatient clinics, e.g., having a higher number of pharmacoresistant epilepsy

Table 3 Parameters for EpiTrack subgroups (simple ordinal logistic regression) (Slovakia 2018)

Independent variables		OR	95% CI	St. error. of regression coeff.	*p* value
Generalized epileptic seizures	More than 2 years without a seizure	1.236	0.485–3.130	0.4757	0.65
	1 seizure per year	1.926	0.488–7.660	0.7024	0.34
	1–11 seizures per year	2.532	0.794–8.455	0.6034	0.12
	More than 1 seizure per month	4.276	1.150–17.647	0.6966	0.03*
Other epileptic seizures	More than 2 years without a seizure	0.664	0.159–2.767	0.7287	0.57
	1–11 seizures per year	0.296	0.054–1.588	0.8626	0.15
	1–4 seizures per month	1.161	0.248–5.440	0.7878	0.85
	> 5 seizures per month	2.934	0.554–16.018	0.8582	0.20
	Daily	1.078	0.166–6.925	0.9518	0.94
BAI		1.058	1.020–1.100	0.0193	0.004*
BDI		1.097	1.047–1.155	0.0250	< 0.001*
ESS		1.070	0.977–1.173	0.0466	0.16
PSQI		1.001	0.907–1.105	0.0504	0.88
QOLIE-89 attention		0.977	0.963–0.991	0.0073	0.002*
QOLIE-89 memory		0.982	0.971–0.992	0.0055	< 0.001*
QOLIE-89 language		0.967	0.947–0.985	0.0100	< 0.001*
QOLIE-89 total score		0.975	0.964–0.986	0.0058	< 0.001*

BAI Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *QOLIE-89* Quality of Life Inventory in Epilepsy-89, *IQR* interquartile range, *OR* odds ratio, *95% CI* 95% confidence interval, *p* probability value

*$p < 0.05$

or structural brain abnormalities being connected with a higher chance for cognitive decline.

Relationship between mood, cognition, and seizures

The relationship between cognition and mood changes is well known. Mood disorders are often presented by cognitive symptomatology as troubles with memory and attention, and cognitive problems may influence the mood changes. The morphological basis of epilepsy, together with the seizure frequency and adverse effects of treatment, is traditionally connected with mood changes in PWE. Novel models emphasize clinically significant distress in the background of the relation. It results in the cognitive attentional syndrome, which consists of preservative thinking (e.g., rumination, worrying, overanalyzing), unhelpful coping strategies (e.g., resting too much, avoidance of activities), and attentional strategies (e.g., monitoring for negative thoughts and feelings). The patient activates positive metacognitive beliefs about the usefulness of perseverative thinking, which prolongs low mood and anxiety. Patients believe that worry is uncontrollable, and they do not try to control it (Fisher and Noble 2017).

In our sample, moderate and severe symptoms of depression monitored by BDI were prevalent in 15% of patients, and moderate or severe levels of anxiety by BAI were found in 37% of patients. Similar results were found by Balibey et al. (2015), who measured symptoms of depression by BDI and anxiety by BAI in 41 male PWE and 48 healthy volunteers from Turkey. PWE had a high frequency of depression (34.14%) and anxiety (26.8%). Based on a nationally representative population study, almost one-third of the PWE with epilepsy had an International Classification of Diseases, Tenth Revision anxiety or depressive disorder (compared with one in six people without epilepsy) (Rai et al. 2012).

Tang et al. (2013) conducted a study on 186 PWE from Hong Kong. They described how symptoms of depression (measured with BDI), symptoms of anxiety (measured with BAI), and quality of life (measured with QOLIE-31) affect intelligence, memory, verbal and visual abilities, and executive function. Patients with more psychological symptoms tend to perform worse in neurocognitive tests. In this series, the major depressive episode was significantly associated with worse performance in the category fluency test, and verbal fluency performance was also related to seizure control in univariate analysis. Previous work has also found that depression was negatively correlated with performance on tasks of memory, fluency, and global cognition (Martin et al. 2005).

Similar results were found by Miller et al. (2016), who compared 38 adults with epilepsy and 29 healthy older adults and identified potential risk factors for cognitive

impairment. PWE performed worse across nearly all cognitive domains and was clinically impaired on more individual tests when compared with controls. Higher anxiety was associated with worse visual memory in PWE.

In the meta-analysis performed by Beaudreau and OHara (2008), the interrelationship between anxiety and cognition depended on the clinical significance of these symptoms. Patients with less severe anxiety did not have affected cognition, while individuals with clinically relevant anxiety symptoms had problems with cognition.

Among first seizure patients in Australia, cognitive complaints correlated strongly with anxiety, while there was no association between cognitive complaints and objective measures of attentional processing (Velissaris et al. 2007). A high prevalence of mood changes in PWE and a strong impact of mood changes on cognitive performance in the present study is in agreement with the previous studies.

Age, duration of epilepsy, AEDs, seizures, and their effect on the cognitive profile

Surprisingly, the clinical characteristics of our patients did not correlate with cognitive status. Age of epilepsy onset, epilepsy duration, and epileptic seizures (apart of generalized ones) did not affect cognitive performance in EpiTrack. These findings might be explained by the fact that we are not aware and probably cannot quantify what is an epileptogenic brain load of our participants during the time they suffered from disease (i.e., patients who suffered from the disease for a more extended period might experience fewer seizures through the years because of the less frequent occurrence of seizures than patients who have epilepsy for a shorter period). With a longer duration of the disease, there is a more significant cumulative effect of seizures. Seizures cause changes in brain cells and their metabolism, on a morphological level that can cause loss of neurons, correlate with neurogenesis, and change synaptic organization. On a metabolic level, we can observe changes in oxidative stress, regulation of growth factor expression, and inflammation. These changes that can cause cognitive decline are more pronounced with the increasing number of seizures patients overcome (Haut et al. 2004; Najm et al. 1998; Pitkänen and Sutula 2002; Lukoyanov et al. 2004; Holmes 2015). If epilepsy starts earlier, it can more influence brain development. Thus, the age of onset is an important parameter (Helmstaedter and Elger 2009; Kaaden et al. 2011), although, in the study conducted by Breuer et al. (2017) on 27 patients, there was found the correlation between older age and cognitive impairment. In the present study, the age at examination was not linked to cognitive impairment, mostly since EpiTrack has already age correction factors.

GES tends to be prolonged, thus secondarily causing hypoxia, ischemia, head trauma, and mesial temporal sclerosis (Kleen et al. 2012). In our study, we found a certain level of association between GES and cognition, showing an association between the most frequent GES and cognitive decline. A similar finding was found in a study conducted on 71 patients with refractory unilateral, mesiotemporal lobe epilepsy, who performed more poorly on memory tests if the seizure frequency was higher (Voltzenlogel et al. 2014). These findings were not confirmed by Piazzini et al. (2006), who compared 40 healthy volunteers and 40 patients with focal epilepsy from Milan and did not find any correlation between cognitive functions and seizure etiology and frequency. Miller et al. (2016) examined 38 patients and 29 healthy volunteers from Rhode Island hospital and found that cognitive parameters show no association to seizure severity and age of onset. The studies as mentioned above focused on selected smaller groups of patients with a highly specific type of epilepsy, evaluating different clinical data of epilepsy, maybe not covering the whole burden of epileptic seizures and others, that make it difficult to compare their results.

Despite documented adverse events of some AEDs on cognitive performance, the number of AEDs in our study did not affect their cognitive skills. Similarly, in the study performed in 325 Japanese PWE (Matsuoka et al. 2019), authors did not find the link between the number or type of AEDs used in the treatment of epilepsy and their cognitive outcome.

Sleep

The absence of excessive daytime sleepiness (based on ESS scores) in any of our PWE, even if scored for the inferior quality of sleep (PSQI score five and above), did not have an impact on cognitive impairment. This is similar to the result of Matsuoka et al. (2019), who examined daytime sleepiness (based on ESS scores) and quality of sleep (described by PSQI score) in 325 Japanese PWE. They found out that sleep parameters did not have an impact on daytime functioning and explain the sleep quality did not show an effect on cognitive impairments.

Quality of life in PWE

The patients who had a more pronounced cognitive deficit in EpiTrack had a significantly lower quality of life shown by QOLIE-89 in our cohort. Perrine et al. (1995) examined the relationship of objectively assessed cognitive functioning to self-reported quality of life in 257 PWE across the USA. The overall quality of life, measured by QOLIE-89 inventory, correlated with mood, psychomotor speed,

verbal memory, and language. These correlations were even more significant in some selected scales (e.g., mood) of the QOLIE-89.

Similarly, Mwangala et al. (2018) compared 63 PWE and 83 community controls; participants of these studies were found among low-literacy adults living in rural Kenya. PWE had a worse quality of life, more reduced executive functions, working memory, and I.Q. than controls. Contrary to healthy controls, 34.9% of patients could not even finish the Major Depression Inventory, which is a self-reporting measure of moods due to their cognitive problems. It shows that major cognitive impairment can be limiting while working with certain scales. In the presented study, we could not test 36% of PWE due to disability that would not allow understanding/seeing/writing the self-administered questionnaires or inability to cope with the examination, which proportion covers patients with cognitive impairment, who task for completely different clinical approach.

Patients' self-assessment of cognitive skills

Understanding of cognitive functions by physicians and PWE is conceptually different; there might be discrepancies in between how patients subjectively feel affected by their possible cognitive decline and results of objective measurements of their cognitive skills. Current neuropsychological tests do not adequately reflect this difference.

Since sometimes patients are not aware of their cognitive decrease either due to reduced everyday cognitive demands or troubles with metacognition, we compared whether objectively measured cognitive skills (measured by EpiTrack) are correlated with their subjective complaints about their cognition (measured by memory, attention, and language subdomain of QOLIE-89). In these subdomains of QOLIE-89, patients are asked about their troubles with cognitive functions and how they affect their everyday life. In the present study, the EpiTrack score was predicted only by the language subdomain of QOLIE-89.

Samarasekera et al. (2015) investigated 100 PWE, and their caregivers in the UK EpiTrack objectively measured the cognition of the patient. Both patients and caregivers filled the A-B neuropsychological assessment schedule, which can show subjectively perceived cognitive problems. Cognitive impairment was seen in seventy two percent of the patients. Correlation between the patient or caregiver report and objectively measured cognitive performance was modest. Caregivers were more precise in reporting unimpaired patients, while patients were more able to perceive their impairment. However, some patients without cognitive impairment complained of memory dysfunction.

Feldman et al. (2018) examined 670 PWE, who visited the Cleveland Clinic Epilepsy Center. Patients were examined by the A-B neuropsychological assessment schedule (ABNAS) for subjective cognitive impairment. Clinical and demographic data were taken from their medical records. Forty percent of patients reported cognitive impairment. Sixty patients underwent complete neuropsychological testing. They had measured cognitive domains, such as intelligence, attention/working memory, verbal memory, visuomotor processing speed, language, and executive functioning. These patients also completed BDI and BAI. Forty percent of reported cognitive impairment was most strongly associated with depressive symptomatology, seizure frequency, and number of AEDs but not with most objective cognitive measures.

Similarly, Witt and Helmstaedter (2015) examined 247 untreated PWE from Germany. EpiTrack detected cognitive deficits in almost half of the patients; only 25.1% complained of these troubles. These results could be explained by patients' limited insight, or their mood problems, namely anxiety and depression, or low correlation of objective tests with everyday cognitive performance.

Limitations

Our findings may not apply to PWE in general since the study evaluated population drawn from an outpatient clinic serving as well as consultation center for refractory epilepsy. Since we did not include patients who have signs of disability that would not allow coping with the test batteries and we did not evaluate the whole clinical spectrum of PWE, we are not able to say whether our findings can predict the factor of cognitive impairment in this group of patients, and what is the role of epilepsy characteristics themselves on cognition in general. The study was set as a cross-sectional analysis of PWE over 18 years of age, coming for a visit to our department from January to December 2018. Patients, who provided written informed consent, were included. It is nearly impossible to capture these differences in one variable, such as the age of onset or seizure frequency, mainly when we have these information from the patient's retrospective report. This is because patients may have trouble remembering every seizure they overcome, and they might give us only limited information about their trouble.

Since it is not feasible to conduct long questionnaires with a large group of patients in an outpatient clinic, we did not utilize structured interviews to assess psychiatric disorders in PWE. We objectively measured cognition by screening with EpiTrack, and we did not use any other neuropsychological test battery to more profoundly evaluate undergoing cognitive impairment. It would be very interesting to examine patients who scored positively on scales, such as BDI and BAI, by the psychiatrist. But since

it would prolong the time of examination, and many patients were not willing to undergo a psychiatric examination, it was not possible. Finally, we were not able to perform multiple ordinal logistic regression to find out how different clinical variables influence cognitive skills in patients because of a high degree of multicollinearity between independent variables.

Conclusion

Cognitive deficit in PWE is frequent. EpiTrack in the presented study served as a screening tool to identify PWE with cognitive dysfunction; at the same time, the effect of mood changes on cognitive performance in PWE was found out. In order to confirm these findings, a study of the effects of anxiety and depression treatment as epilepsy comorbidities on cognitive outcome in PWE is needed in the future.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the Regional Ethics Committee of the University Hospital of L. Pasteur in Košice.

Informed consent Informed consent was obtained from all individual participants included in the study.

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