Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
Tome 77, No 2, 2024

MEDICINE
Neurology

NEUROPHYSIOLOGICAL METHODS FOR DIAGNOSTICS AND TREATMENT MONITORING IN PATIENTS OF ADVANCED AGE WITH EPILEPSY

Diana Betsinska✉, Pencho Kolev, Rumyana Kuzmanova

Received on February 3, 2021
Presented by B. Petrunov, Member of BAS, on February 26, 2021

Abstract

Through the last decades the duration of life and the number of elderly people is rapidly growing. In this age group morbidity of epilepsy is increasing very fast. Neurophysiological methods play an important role in diagnostics, classification of the disease and the type of the seizures, and in treatment monitoring in the elderly with epilepsy. The aim of the present study was to establish the significance of neurophysiological methods for diagnostics and treatment monitoring, as well as their relation with particular clinical characteristics of the disease in elderly patients. The study group consisted of 297 consecutive patients with epilepsy (average age 69.25 ± 5.00 years). The methods used were documentary analysis, an interview of clinical factors, EEG (basic and control), video-EEG and statistical methods. Patients with longer duration of the disease were with significant worse neurophysiological results, higher seizure frequency and more in number antiepileptic medications. Epilepsy in the elderly is a major and growing issue. The results of the study will be useful in diagnostics and treatment monitoring in this age group.

Key words: epilepsy, elderly, EEG, video-EEG

Introduction. In the recent decades life expectancy and the population of elderly people around the world, is growing. According to the World Health Organization (WHO) 65 years and more is designated as "old age" (advanced age) [1]. In this age range a sharp increase is observed of epilepsy incidence,

https://doi.org/10.7546/CRABS.2024.02.16

being the third-ranking neurological disease after cerebrovascular disease and dementia [2–5]. Making the right diagnosis in the case of such patients is difficult because of numerous factors: the non-specific and short-term complaints, the lack of memory about the accident on behalf of the patient and in many cases, the absence of witnesses of seizures [6–8]. EEG plays an important role in diagnostics and classification of epilepsy, as well as in defining the type of epileptic seizures (ES) [9]. The video EEG-examination is being used for making differentiated diagnosis between the epileptic and non-epileptic seizures, assessment of the ES resistant to treatment, in the case of atypical clinical picture, no witnesses and incomplete anamnesis [9, 10].

The aim of the present study is to establish the significance of neurophysiological methods for diagnostics and treatment monitoring in the elderly with epilepsy, and their relation to particular clinical disease features.

Clinical contingent and methods. The present research work was performed in the University Multiprofile Hospital for Active Treatment in Neurology and Psychiatry "Saint Naum" in Sofia, from January 2014 to January 2019. Among the total of 545 selected patients with specified diagnosis "epilepsy", the research work included 297 patients aged above 65 and 193 people of the same age, but without anamnestic and clinical data about neurological and psychiatric diseases. All the procedures related to the research work, were run in conformity with the requirements for "Good Clinical Practice".

The criteria for inclusion are as follows: people aged above 65; availability of more than two non-provoked epileptic seizures; duration of the epileptic disease more than one year; treatment with one, two, three or more anti-epileptic medications, and without change of the antiepileptic therapy in the last three months. The criteria for exclusion are as follows: alcohol abuse, medications and drug misuse; severe or progressive somatic and neurological disease; psychiatric disease, including diagnosed mood and emotion disorders; dementia syndrome verified via MMSE test (result < 19 points); use of psychotropic medications, including antipsychotics, antidepressants, hypnotics and anxiolytics.

For the purposes of the research work, we used the following methods:

1. Clinical methods – detailed anamnesis by the patients and their relatives.

2. Documentary analysis.

3. Neurophysiological methods: EEG (basic and controlled – three months after the start or modification of AEM and tittering to adequate daily dose), video-EEG was held for 27 patients of the research group.

4. Mini-Mental Scale Examination (MMSE) whereas most often we use screening test for rapid quantitative assessment of the comprehensive cognitive functioning, we have included the patients whose results are ≥ 19 points.

5. Statistical methods: descriptive and correlation analysis, non-parametric Mann–Whitney analysis, and Independent sample test. The data have been entered and processed via the statistical package SPSS 13.0, STATISTICA 8.0 for Windows and Excel. In view of the significance level whereas we reject the zero hypothesis, we have accepted $p < 0.05$.

Results. For the purposes of the research work, the clinical contingent is separated in view of the following indicators:

1. *Epilepsy duration*: patients with disease duration of below 10 years ($n = 170$; 57.24%) and disease duration of over 10 years ($n = 127$; 42.76%).

2. *Type of epilepsy* (according to the International classification of Epilepsy (1989) and the National consensus for diagnostic and treatment of epilepsy (2020)) [11,12]: genetic, of unknown reason and structure/metabolic epilepsy.

3. Type of ES [11, 12]: focal seizure with/without impairment of conscience, focal seizure with evolution to bilateral tonic-clonic seizure, and primary generalized seizures.

4. Average frequency of ES in the last 6 months: without seizures of unknown frequency, patients with up to one seizure monthly, with two to three, and with over three seizures monthly.

5. Number of taken AED: patients that take 1, 2, 3 or more AED.

6. Type of AED: classic (CBZ, VPA) and new AEM (OxCBZ, TPM, LEV, LTG, LCM, GBP, PGB).

7. Type of changes in EEG and video-EEG – normal EEG finding, slight diffuse changes (SDC), moderate diffuse changes (MDC), focal or generalized paroxysmal activity (FA or GPA).

The research work includes 56% women ($n = 166$) and 44% men ($n = 131$). The average disease duration in the case of men is 10.83 ± 12.07, and in the case of women – 13.31 ± 13.99 years. Additionally, the research work covers a control group of 193 at the ages from 65 to 92: 98 men at the average age of 69.8 (SD = 3.06) and 95 women at the average age of 70.07 (SD = 5.04). Both sexes are relatively evenly represented with the ratio of men/women 0.78:1. When it comes to the comparative assessment of analysed main clinical indicators in the researched patients we did not find statistically significant sex differences ($p < 0.05$).

Within the group with epilepsy duration less than ten years most patients are with monthly frequency of 23 seizures – 81 (47.1%); forty-two are without seizures (24.71%); 31 patients (18.23%) who have more than three seizures monthly and

16 (9.96%) have up to one seizure monthly. Within the group of longer epilepsy duration once again, the highest share is attributable to patients whose ES frequency is up to 2–3 monthly ($n = 56$; 44.09%), yet the number of those with more than three seizures monthly increases ($n = 32$; 25.20%). The number of patients without seizures decreases ($n = 24$; 18.9%), the participants with frequency of up to one seizure monthly remain the same ($n = 10$; 7.87%); we observe patients that cannot specify the seizure frequency ($n = 5$; 3.94%).

Neurophysiological tests*: *EEG. *Frequency of the background activity.* In the initially performed EEG among the examined patients with epilepsy, the highest number is of those with background alpha activity ($n = 213$, 71.72%). The background theta activity is observed in 57 patients (19.2%), and the background beta activity – in 27 (9.10%). During the performed control EEG, the background alpha activity is observed in 222 patients (74.10%), the background beta activity is observed in 18 (6.07%), and the ones with background theta activity are 57 patients (19.2%). On the grounds of the performed EEG of the control group ($n = 193$), the background alpha activity is observed in 153 ($n = 79.28\%$), the background beta activity could be seen in 13 (6.74%), and the background theta activity – in 27 participants (13.98%). Delta activity was not observed in the researched patients.

Organization of the background activity. In the initial EEG, the background activity is well-organized in the case of 245 of the patients suffering from epilepsy (82.5%), in 52 (17.5%) it is disorganized. When performing control EEG, organized rhythm is reported in 254 (85.53%), disorganized – in 43 epileptic patients (14.47%). Within the control group of patients without epilepsy, organized rhythm is observed in 188 (97.41%), and in the case of five patients (2.59%) the background activity is disorganized.

Presence of hemispheric asymmetry (*HA*). In the initially performed EEG HA we observed in 22 patients with epilepsy (7.44%), whereas in the controlled EEG we found in 14 patients (4.72%). Within the control group HA is observed in 5 participants of the research (1.69%).

Provocation procedures:

1. Eye opening and eye closing (EO/EC). During the basic EEG of 202 patients with epilepsy (68.01%) we observed good reactivity, and in 95 patients (31.99%) – poor reactivity. Within the control EEG 240 patients (81.1%) are with good reactivity at EO/EC, and 57 (18.9%) – with poor reactivity. Within the group of healthy controls the participants with good reactivity at EO/EC significantly prevail ($n = 175$, 90.50%), and 18 (9.5%) demonstrate poor reactivity. In neither of the researched patients we observed photoparoxysmal reaction in the performed procedures.

2. Photic stimulation (PS). In the initially performed EEG in 51 patients (16.84%) we observed photoparoxysmal reaction at PS, and 246 patients

(83.16%) are without photoparoxysmal reaction. Within the control EEG the number of patients with photoparoxysmal reaction decreases ($n = 27$, 9.43%), and in 270 patients (90.57%) – it is missing. Within the control group we did not observe photoparoxysmal reaction at PS in any participant.

3. Hyperventilation (HV). In the basic EEG of 85 patients (28.62%) we observed slowing of the background activity, in the case of 212 patients (71.38%) the background activity does not change. Within the control EEG we observe certain improvement – the background activity slows in the case of 70 patients (23.6%) and does not change in 227 (76.4%) of the patients with epilepsy. In the control group, only in the case of 39 persons (20.3%) we found slowing, and the rest 154 (78.7%) are without change of the background activity. In terms of the excitatory changes during HV, in the initially performed EEG we took into account manifestation of sharpened theta waves in 109 patients with epilepsy (38.05%), manifestation of sharp waves – in 35 (11.8%), and manifestation of complexes sharp-slow wave – in 38 patients (12.0%). Within the control EEG the abnormalities during HV decrease – manifestation of sharpened theta waves is found in 29 patients (9.4%), manifestation of sharp waves – in 17 (5.2%), and manifestation of sharp-slow wave complexes – in 9 patients (3.04%). Within the group with healthy controls, changes during HV are significantly less manifested: manifestation of sharpened theta waves is observed in 13 patients (4.38%), sharp waves – in 7 (2.39%) and comprehensive – in two patients (0.7%).

Diffusive changes. In the basic EEG, in the case of 32 patients (10.8%) with epilepsy we established normal EEG activity, in the case of 213 (71.72%) – availability of SDC, in the case of 52 (17.48%) – MDC. Within the control EEG in 32 patients (10.11%) with epilepsy we found normal EEG activity, in 222 (74.75%) – SDC, and in 43 (15.14%) – MDC. In the control group of patients, in 153 (79.30%) we observed normal EEG activity, 35 (18.14%) were with SDC, 5 (2.56%) – with MDC.

Focal activity or generalized paroxysmal activity. Within the initial EEG the availability of FA is found in 109 patients (36.71%), and GPA – in 38 patients (12.8%) with epilepsy. When performing the control EEG in 41 patients (13.5%) FA persists, and in five patients (1.7%) – GPA. Within the control group of patients FA is observed in seven patients (3.63%) and there is no GPA.

Video-EEG. Video-EEG was performed in the case of 27 patients, where we needed diagnostic verification of seizures. In the case of video-EEG examination of ten patients with epilepsy (43.39%) we found SDC, in the case of nine patients (39.41%) – MDC, in the case of four (17.3%) – normal EEG activity, in the case of eight (34.5%) – FA, in the case of three (13.00%) – GPA.

Within the control group we found only normal EEG activity (Table 1).

Table 1

Video-EEG

Patients	Normal	SDC	MDC	FA	GPA
Patients with E	4	10	9	8	3
Control group	4	0	0	0	0

SDC – slight diffuse changes, MDC – moderate diffuse changes,
FA – focal activity, GPA – generalized paroxysmal activity

While researching the *connection between the disease duration and the EEG examination results*, the patients with epilepsy and disease duration less than ten years are with statistically significant poorer results within the control EEG (significance level of over 95%), compared to the ones with disease duration of more than ten years (Table 2).

Table 2

Connection between the epilepsy duration and the EEG results –
initial and control one with group statistics

	Duration of epilepsy	Number of patients	Mean rank	Sum of rank
Basic EEG	≥ 10 years	127	143.35	18 205.50
	< 10 years	170	153.22	26 047.50
Control EEG	≥ 10 years	127	126.98	16 126.00
	< 10 years	170	165.45	28 127.00

Statistics	Basic EEG	Control EEG
Mann–Whitney U	10 077.500	7998.00
Wilcoxon W	18 205.500	16 126.000
Z	−1.026	−4.218
Asymp. Sig (2-tailed)	0.305	0.000

Connection between the number of anti-epileptic drugs (AED) taken and control EEG. At the time of the performed examination, 114 patients with epilepsy (38.39%) are being treated with one AED, and 183 (61.61%) – with more than one AED. When surveying the connection between the result of the control EEG and the number of the taken AED, with statistical significance (significance level of over 99%) we established that the patients who have normal EEG or SDC, take fewer AED compared to the patients with MDC, FA or GPA (Table 3).

In the examined patients with epilepsy we did not establish statistically significant difference in terms of the features in EEG (frequency and organization of the background activity, HA availability, reactivity when performing the provocation procedures, availability of FA or GPA) and the type of taken AED (classic and new ones).

In the case of sought *dependency between the EEG result and the ES frequency* we established that in the case of patients with normal EEG and SDC are of lower

Table 3

Dependency between the number of AED and the result of control EEG with group statistics

Present therapy – number of AED	Control EEG	$N = 297$	Mean rank	Sum of rank
	Normal, SDC	200	140.52	28 103.50
	MDC, FA or GPA	97	166.49	16 149.50
Statistics		Value		
Mann–Whitney U		8003.000		
Wilcoxon W		28 103.500		
Z		−2.823		
Asymp. Sig (2-tailed)		0.005		

Table 4

Dependency between the EEG result and the availability of ES with group statistics

Epileptic seizures	Control EEG	$N = 292$	Mean rank	Sum of rank
	Normal, SDC	198	151.31	29 959.50
	MDC, FA or GPA	94	136.37	12 818.50
Statistics		Value		
Mann–Whitney U		8353.000		
Wilcoxon W		12 818.000		
Z		−1.511		
Asymp. Sig (2-tailed)		0.131		

ES frequency compared to the ones of more manifested violations in EEG (MDC, FA or GPA) (Table 4).

Discussion. In Bulgaria we have no systematic research of patients with epilepsy at advanced age. Despite the common belief that epilepsy impacts mainly the younger part of population, almost 25% of the newly diagnosed cases are of patients aged above 65 [3, 13].

The performance of EEG-monitoring of patients with epilepsy at advanced age and disturbed conscience and unclear disease etiology, sometimes is the only possible method for making the right diagnosis [14–17]. When researching the connection between the disease duration and the results of the EEG-examinations in our research, the patients with longer disease duration are with statistically poorer results within the control EEG, compared to the ones with disease duration of less than ten years. In our research work, the longer duration of disease correlates to the increase of ES frequency – the number of patients with more than three ES monthly increases and those with unclear seizure frequency show up (significance level 95%). Our conclusions approximate the conclusions drawn by numerous authors [18, 19]. Additionally, we establish statistically significant dependency between the number of the taken AED and the EEG results – the patients with normal EEG or SDC, take fewer AED compared to the patients

with MDC, FA or GPA. We did not establish such connection with the type of taken AED.

The neurophysiological examinations are an important method for monitoring the efficiency of anti-epileptic treatment [14–16]. The results of the performed control EEG in our patients reflect the optimization of anti-epileptic therapy with results' improvement in the main parameters of the used neurophysiological examinations: organization and frequency of the background activity, decrease of the availability of HA, severity of the diffusive changes and presence of FA or GPA, improvement of procedure reactivity EO/EC, decrease of the percentage of patients with photoparoxysmal reaction at PS. The percentage of patients with slowing of the background activity decreases, as well as the ones with provocation of exitatory changes (appearance of complexes sharp-slow wave, sharpened theta and sharp waves) during HV. According to the literature data, the disorganized background activity, HA with more than 1 Hz, the poor reactivity of activation procedures, especially in the case of procedure with EO/EC, the diffuse generalized theta activity and the appearance of delta waves are perceived as abnormal [20].

Conclusion. The severity of changes in the performed neurophysiological examinations of patients with epilepsy of advanced age correlates to the disease duration and the effectiveness of the performed treatment. The slighter changes in EEG of patients with epilepsy of advanced age are related to lower number of taken AED and lower frequency of ES, compared to the patients with more profound disturbances in the neurophysiological examinations.

Epilepsy in the elderly is a major and growing issue. The results of the study will be useful in the diagnostics and treatment monitoring in this age group. Additionally, there is a lack of more in-depth research works in the area studied by us in the specialized literature, not only in Bulgaria, but also globally.

REFERENCES

[1] WHO (2016) WHO Definition of an older or elderly person, `https://www.who.int/health-topics/ageing#tab=tab_1`.

[2] Brodie M. J., P. Kwan (2005) Epilepsy in elderly people, BMJ, **331**(7528), 1317–1322.

[3] Poza J. J. (2007) Management of epilepsy in the elderly, Neuropsychiatr. Dis. Treat., **3**, 723–728.

[4] Hiyoshi T., K. Yagi (2000) Epilepsy in the elderly, Epilepsia, **41**(Suppl. 9), 31–35.

[5] Lee S. K. (2019) Epilepsy in the elderly: Treatment and consideration of comorbid diseases, J. Epilepsy Res., **9**(1), 27–35.

[6] Harms S. L., L. E. Eberly, J. M. Garrard, N. A. Hardie, P. C. Bland et al. (2005) Prevalence of appropriate and problematic antiepileptic combination therapy in older people in the nursing home, JAGS, **53**, 1023–1028.

[7] Mamiya K., E. Yukawa, T. Matsumoto, C. Aita, S. Goto (2002) Synergistic effect of valproate coadministration and hypoalbuminemia on the serum-free phenytoin concentration in patients with severe motor and intellectual disabilities, Clin. Neuropharmacol., **25**, 230–233.
[8] Acharya J. N., V. J. Acharya (2014) Epilepsy in the elderly: Special considerations and challenges, Ann. Indian Acad. Neurol., **17**(Suppl. S1), 18–26.
[9] Kolev P., I. Milanov (2012) Clinical neuropsysiology. In: Neurology (Ed. I. Milanov), Sofia, Meditsina i Fizkultura, 238–243, 322—336 (in Bulgarian).
[10] Keranen T., S. Rainesalo, J. Peltolla (2002) The usefulness of video-EEG monitoring in elderly patients with seizure disorders, Seizure, **11**, 269–272.
[11] International Classification of Epilepsies and Epileptic Syndromes (ICE) (1989).
[12] National consensus on diagnosis and treatment of epilepsy (2020) Bulgarian Neurology, 13.02.2020, 1–76.
[13] Ghosh S., L. E. Jehi (2014) New-onset epilepsy in the elderly: Challenges for the internist, Cleve. Clin. J. Med., **81**(8), 490–498.
[14] Abubakr A., I. Wambacq (2005) Seizures in the elderly: Video/EEG monitoring analysis, Epilepsy Behav., **7**(3), 447–450.
[15] Javidan M. (2012) Electroencephalography in mesial temporal lobe epilepsy: a review, Epilepsy Res. Treat., `https://doi.org/10.1155/2012/637430`.
[16] McBride A. E., T. T. Shih, L. J. Hirsch (2002) Video-EEG monitoring in the elderly: A review of 94 patients, Epilepsia, **43**, 165–169.
[17] Van Cott A. C. (2002) Epilepsy and EEG in the elderly, Epilepsia, **43**(3), 94–102.
[18] McLean A. J., D. G. Le Couteur (2004) Aging biology and geriatric clinical pharmacology, Pharmacol. Rev., **56**, 163–184.
[19] Hermann B., M. Seidenberg, M. Sager et al. (2008) Growing old with epilepsy: the neglected issue of cognitive and brain health in aging and elder persons with chronic epilepsy, Epilepsia, **49**(5), 731–740.
[20] Davidson P., K. Davidson (2012) Electroencephalography in the elderly, Neurodiagn. J., **52**, 3–19.

University Hospital of Neurology and Psychiatry "St. Naum",
1 Lyuben Roussev St, 1113 Sofia, Bulgaria
e-mails: `diiva@abv.bg`, `penchokolev@gmail.com`, `rumyana kuzmanova@abv.bg`