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EPILEPSIA LA FEMEI DE VÂRSTĂ REPRODUCTIVĂ. STUDIU CLINIC, IMAGISTIC, ELECTROENCEFALOGRAFIC

EPILEPSY IN WOMEN OF REPRODUCTIVE AGE. CLINICAL, IMAGISTIC, ELECTROENCEPHALOGRAPHIC STUDY

321.05 – NEUROLOGIE CLINICĂ

321.05 – CLINICAL NEUROLOGY

Rezumatul tezei de doctor în științe medicale
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CONTENTS

INTRODUCTION

Actuality and importance of the issue addressed

Three important aspects can be highlighted, which outline the research directions of the work: (a) the issue of prevalence, clinical, electroencephalographic and imagistic semiology of epilepsy in women of reproductive age, taking into account the age of onset of the disease and its evolution over time (after a follow-up of patients for 5 years); (b) to identify and describe (parameterise) correlations between the semiological picture, EEG or MRI descriptions, with the possibility of using them to guide the exact diagnosis and adaptation of antiepileptic treatment; (c) attempt to find an answer regarding possible scenarios of disease evolution (e.g. worsening, remission, resistance to antiepileptic drugs, occurrence of status epilepticus), preferably - objective, based on simple, reproducible observable indicators that can be included in a mathematical probability estimation model. It is believed that these three aspects, if known, would significantly improve the quality of life of patients with epilepsy of reproductive age and increase the effectiveness of prescribed treatments.

Description of the situation in the field and identification of the research problem

Despite remarkable advances in neuroscience, pharmacology and imaging technologies, epilepsy continues to have a high prevalence and remains an important public health problem. In Republic of Moldova, according to data from the National Bureau of Statistics, about 60,000 people suffer from epilepsy, of which 13,500-15,000 are women of reproductive age. The prevalence of epilepsy in Republic of Moldova is 16 cases per 1000 inhabitants (2015 data) [1]. The incidence of epilepsy in women is variably reported in the literature, being considered rarer in women than in men (41 vs. 49 cases per 100,000 population and prevalence: 6.0 vs. 6.5 cases per 1000 population, respectively). However, the given disease is considered to be underestimated in women due to the stigma of the disease, its non-reporting or the natural variability of the actual prevalence of the disease throughout life [2-5]. In addition to the lack of knowledge of the true prevalence of epilepsy in women of reproductive age, an important problem is the lack of a complete description of the seizure itself (aura, semiology, circumstances, triggers, duration, postictal signs, EEG tracings or MRI images, involving specific structural changes). This prevents the correct classification of seizure type (subtype). It was not until 2017-2021 that the consensus definition of epilepsy syndrome was given by the International League Against Epilepsy, ILAE [6, 7].

Contemporary electroencephalographic examination allows the differentiation of cortical areas involved in abnormal electrical activity in the brain (seizure initiation area, epileptogenic area, as well as symptomogenic, irritative and epileptogenic lesion areas), as well as distinguishing the phases of the given activity (ictal wave front, followed by excitation and inhibition wave propagation front) [8, 9].

Equipping hospitals in the Republic of Moldova with high-performance nuclear magnetic resonance machines opens up new possibilities for identifying and differentiating brain lesions with epileptogenic potential. Contemporary MRI imaging algorithms can identify and classify these lesions automatically, thus becoming important tools in diagnosis, choice of treatment tactics or prognosis of disease evolution [10, 11]. This trend in the use of MRI imaging in epileptology is nowadays current internationally, and the corroboration with clinical and neurophysiological results opens new paradigms of approach.

All these descriptions allowed the formulation of the research hypothesis, the purpose of the work and the research objectives.

Purpose. To describe the interrelationships over time between clinical, neurophysiological and imagistic features of epilepsy in women of reproductive age, with the development of predictive mathematical models for the most important clinical events.

Research objectives

1) Characterization of the evolution over time of the clinical, neurophysiological and imaging features of epilepsy in women of reproductive age, according to the age of onset of the disease;
2) Identification and parameterization of clinically important clinico-neurophysiological and clinico-imaging correlations in women with epilepsy of reproductive age, according to the age of onset of the disease.;
3) Argumentation, development and characterization of predictive mathematical models for the most important clinical events (worsening of the condition over time, risk of progression to status epilepticus, development of resistance to antiepileptic drugs and stable remission of the disease) in patients of reproductive age with epilepsy.

Research hypothesis

Epilepsy in women of reproductive age has distinct and possibly different clinical, imaging and neurophysiological features that may correlate with each other, depending on the age of onset or progression of the disease, and the likelihood of clinically important events can be estimated by mathematical models based on the features identified.

General research methodology

The study in the thesis was a prospective-retrospective, cohort, descriptive-analytical study, with approval of the research protocol by the Research Ethics Committee (minutes no. 55 of 03.06.2016). Data were collected for 5 years (primary visit and the 3 annual conclusive follow-up visits of patients, neurophysiological and neuroimaging examinations) in the Institute of Neurology and Neurosurgery "Diomid Gherman", State Hospital of the Republic of Moldova and Private Medical Institution "Excellence". After the numeration of the primary data, the database was imported into the statistical analysis software GraphPad Prism, v. 9 trial (Graph Pad Software, Boston, USA). The data were analyzed both in terms of age categories of onset of illness (3 groups, group 1 - 0-11 years; group 2 - 12-18 years; group 3 - 19-49 years) and in terms of time course of illness (visits 1-4). From these perspectives, the clinical, electrophysiological and imaging features of epilepsy were characterized using the Fisher or extended Mantel-Haenszel test. After generalizing the results and obtaining the general characteristics, a correlational analysis (Pearson's r-test) was performed; the given analysis allowed the identification of those data, which correspond to a statistically significant degree of clinical-neurophysiological and clinical-imaging correlation, from which clinically significant correlations were selected. The results obtained allowed to argue, develop and characterize probabilistic models for 4 clinically important outcomes (worsening of the condition over time, risk of progression to status epilepticus, development of resistance to antiepileptic drugs, stable remission of the disease). The selection of clinical, electroencephalographic and imaging parameters that entered the probability formula was based on multivariate analysis, testing for multicollinearity (variance inflation factor calculation) and the contribution of each parameter in the formula using the Akaike informativeness criterion. The performance of the predictive models developed was expressed by the area under the ROC curve, positive and negative prognostic power. Based on the results obtained, practical recommendations were developed.

Scientific innovation of the obtained results

1. For the first time, some patterns of evolution over time and the interrelationships between clinical, neurophysiological and imaging parameters in women of reproductive age with epilepsy were characterized according to the age of onset of the disease.
2. Several statistically significant correlations between clinical, neurophysiological and imaging parameters were found to exist, but only some of them have real clinical significance.
3. Also, as a result of our own research, it has been possible to develop, for the first time, mathematical models that can accurately predict the worsening of the condition over time, the risk of developing status epilepticus, the development of resistance to antiepileptic drugs and stable remission of the disease in patients of reproductive age with epilepsy.
4. The particularities of the evolution over time of clinical, neurophysiological and imaging features and their interrelationships in patients of reproductive age with epilepsy were identified, which made it possible to develop predictive mathematical models for the 4 important events listed.
5. The paper provides an elaborated, adapted methodology for the clinical and instrumental investigation, documentation and monitoring over time of patients of reproductive age with epilepsy, allowing the identification of clinical, neurophysiological and imaging features over time, according to the age of onset of the disease. The paper also provides the theoretical and methodological support for the development and application of predictive mathematical models for 4 important events (worsening of the condition over time, risk of developing status epilepticus, development of resistance to antiepileptic drugs and stable remission of the disease).

The applied value of the work. The research results provide simple practical solutions for neurologists in assessing, risk stratifying, monitoring patients of reproductive age with epilepsy. Clinically significant correlations between clinical, neurophysiological and imaging features (brain lesions with epileptogenic potential, identifiable on MRI) were identified. The mathematical models developed make it possible to predict with a significantly higher accuracy the 4 important events identified in the study (worsening of the condition over time, risk of progression to status epilepticus, development of resistance to antiepileptic drugs, stable remission of the disease) specific to women of reproductive age with epilepsy.

Implementation of scientific results. The research results were implemented in the current clinical practice (part of the institutional clinical protocol, standard operating procedure of the workplace) in the Neurology Department of the State Hospital, Chisinau, Republic of Moldova.

Approval of the results. The results of the study were presented and discussed in the following national and international scientific fora: 3rd Congress of the European Academy of Neurology (24-27 June 2017), Netherlands, Amsterdam; Congress dedicated to the 75th Anniversary of the founding of USMF "Nicolae Testemitanu", Chisinau, Republic of Moldova; World Congress of Neurology, XXIV edition of 2019 (27-31 October, 2019), Dubai, United Arab Emirates; Congress of Young Researchers "MedEspera" (3-5 May, 2018), Chisinau, Republic of Moldova; Conference "Days of the University USMF Nicolae Testemitanu", section no. 8 "Current problems of neurology and neurosurgery" (October 19, 2017), Chisinau, Republic of Moldova; Conference "Days of the University USMF Nicolae Testemitanu", section no. 8 "Current Problems of Neurology and Neurosurgery" (20 October 2016), Chisinau, Republic of Moldova; 4th Congress of the European Academy of Neurology (16-19 June 2018), Lisbon, Portugal; European Stroke Association Conference, 4th edition (16-18 May, 2018), Gothenburg, Sweden; European Congress of

Epileptology, 13th edition (26-30 August 2018), Vienna, Austria; European Academy of Neurology Congress, 5th edition, (June 2019), Oslo, Norway.

Publications on the thesis topic. The basic materials of the thesis have been published in 12 scientific papers, including, 6 articles in nationally indexed journals, 6 abstracts published in collections of papers at scientific events (including, 4 abroad); 4 intellectual property objects, 10 presentations and oral communications at various international scientific events (4 in the country and 6 abroad).

Volume and structure of the thesis. The text of the thesis is set out on 119 computer-processed basic text pages, consisting of: list of abbreviations, introduction, 4 chapters, synthesis of the chapters, general conclusions, practical recommendations, bibliography of 245 sources and 8 appendices. Illustrative material includes 28 tables, 21 figures.

Keywords. Epilepsy, women, reproductive age, clinico-neurophysiological correlations, clinico-imaging correlations, long-term monitoring, predictive mathematical models.

1. EPILEPSY IN WOMEN OF REPRODUCTIVE AGE: CLASSIFICATION, EPIDEMIOLOGICAL, CLINICAL, NEUROPHYSIOLOGICAL AND IMAGISTIC ASPECTS IN CONTEMPORARY VIEW (LITERATURE REVIEW)

1.1. The problem of epileptic seizure classification: evolution of concepts and principles of approach

The difficulty in classifying epilepsy lies in the multiplicity of clinical manifestations, some of which are discrete, unnoticed by the patient or the seizure witness, the association of clinical features with EEG changes and their location, and the presence or absence of structural changes on the brain MRI image. For this reason, after multiple previous versions, it was not until 2017-2021 that the consensus definition of epilepsy syndrome was given, as well as the classification of epileptic seizures by the International League Against Epilepsy, ILAE [6, 7].

1.2. General and particular epidemiological aspects for women of reproductive age

The prevalence in the general population of epilepsy is reported differently from author to author. Epileptic disease is considered to affect between 1% and 3% of the population. In the Republic of Moldova, according to NBS data, the prevalence is between 14.2-16.0 cases per 1000 population. In Romania - 6.4 cases per 1000 population [12], in Ukraine - 26.4 cases per 1000 population [13], in the Russian Federation - 22.0 cases per 1000 population [14]. The European average is estimated at 8.2 cases per 1000 population. The accuracy of the estimate depends a lot on the organization of epileptology service, stigmatization of patients in society. The incidence of epilepsy in women is variably reported in the literature and is considered rarer in women than in men (41 vs. 49 cases per 1000 population and prevalence: 6.0 vs. 6.5 cases per 1000 population,respectively) [2-5].

1.3. Mechanisms of epileptogenesis in contemporary view

Neural networks, located in cortical areas, are connected to each other both locally and remotely. The neural network is functionally assisted by an astrocytic network, with its own configuration. Neuronal synapses are in fact tripartite (neuron, astrocyte, neuron). Astrocytes have the

function of maintaining the constancy of the neuronal microenvironment, metabolizing used or excess neuromediators, providing energy and nutrients to neurons [15]. On the membrane surface of neurons and astrocytes there is a large diversity of ion channels, biochemical receptors, intracellular messaging systems. All of them are genetically determined, with different phenotypic variants, sometimes - mutations (e.g. voltage-dependent Ca++, K+ or Na+ channels, underlying different forms of epilepsy) present in the population [16]. An important role is played by AMPA receptors, NMDA, KA, GABA-A, ATP-ases, efflux pumps, redox mechanisms, neuroinflammation and neuroplasticity - each of which are subject to genetic and epigenetic variability [17]. Eventually, abnormal electrical activity occurs, localized or widespread, up to generalization, where the clinical symptomatology depends on the function that the respective network of neurons performs, involvement by activation or inhibition of adjacent or distant areas [18].

1.4. Clinical features of epilepsy in women of reproductive age

With the discovery of the involvement of oestrogens and progesterone in epileptogenesis, the premises for the study of the clinical peculiarities and evolution of epileptic disease in women, according to age (children, adolescents, reproductive age, pregnancy, pre- and post-menopause) have been outlined. The peculiarities have argued for the use of hormonal treatment of epilepsy, the development of the social dimension of the disease [19, 20].

Catamenial epilepsy

The identification of the correlation of the frequency and clinical manifestations of epileptic seizures with the dynamics of hormone levels and the phases of the menstrual cycle has led to the separation of a new clinical entity - catamenial epilepsy, with specific diagnostic and treatment features [20, 21].

Role of electroencephalography in the diagnosis, monitoring and prognosis of epilepsy in women of reproductive age

EEG examination allows differentiation of cortical areas involved in abnormal electrical activity in the brain, as well as distinguishing the phases of the given activity (ictal wave front, followed by excitation and inhibition wave propagation front) [8, 9].

Role of brain nuclear magnetic resonance imaging in the diagnosis, monitoring and prognosis of epilepsy in women of reproductive age

MRI can identify brain lesions relevant to epileptogenesis, thus providing important tools in diagnosis, choice of treatment tactics or prognosis of disease progression. The correlation of imagistic data with clinical and neurophysiological findings opens new paradigms of approach [10, 11].

2. RESEARCH METHODOLOGY AND STATISTICAL ANALYSIS

2.1. General research design

The study in this thesis was a prospective-retrospective, cohort, descriptive-analytic study. The accumulation of primary material took place during 2016-2020 in the consultative outpatient departments of the Institute of Neurology and Neurosurgery "Diomid Gherman", the

State Hospital of the Republic of Moldova and the Private Medical Institution "Excellence", on the basis of collaboration contracts, signed with each institution, respecting bioethical clauses, confidentiality and protection of personal data, informed consent of patients. The study protocol was approved by the Research Ethics Committee of USMF "Nicolae Testemitanu" (minutes no. 55 of 03.06.2016). The study subjects were women of reproductive age with epilepsy, where the first epileptic seizure started in the age range 0 to 49 years. The general characteristics of the patients studied (all series and by batches) are shown in Table 2.1.

Table 2.1. General characteristics (whole series and by batches) of the patients enrolled in the study.

Parameters	All patients (n=159)	Batch 1 (0-11 years) (n=52)	Batch 2 (12-18 years) (n=54)	Batch 3 (19-49 years) (n=53)	F or $\chi 2$	p
Age of disease onset, years	14,0±6,3 [2-34]	7,0±6,4 [2-11]	14,0±6,3 [12-16]	21,0±6,4 [19-34]	295,8	0,0000
Age of first referral to specialist, years	24,0±7,2 [2-46]	25,0±7,2 [15-46]	22,0±7,2 [15-38]	28,0±7.3 [19-45]	9,46	0,0001
Studies □ primary □ secondary □ higher	 4 (2,5%) 100 (62,3%) 56 (35,2%)	 4 (7,8%) 38 (73,0%) 10 (19,2%)	 0 (0,0%) 15 (27,8%) 39 (72,2%)	 0 (0,0%) 27 (54,7%) 24 (45,3%)	 3,27 21,90 29,90	 0,1952 0,0000 0,0000
Living environment □ rural □ urban	 84 (52,8%) 75 (47,2%)	 37 (71,1%) 15 (28,9%)	 23 (42,6%) 31 (57,4%)	 24 (45,3%) 29 (54,7%)	 10,50	 0,0053
Family status □ single □ married □ divorced □ widowed	 109 (68,6%) 45 (28,3%) 5 (3,1%) 0 (0,0%)	 42 (80,7%) 8 (15,4%) 2 (3,9%) 0 (0,0%)	 43 (79,6%) 11 (20,4%) 0 (0,0%) 0 (0,0%)	 24 (47,2%) 24 (47,2%) 3 (5,6%) 0 (0,0%)	 17,82 15,03 1,07 NA	 0,0001 0,0005 0,5858 NA
Social class □ workers □ rural workers □ intellectuals	 83 (52,3%) 61 (38,3%) 15 (9,4%)	 24 (46,2%) 25 (48,0%) 3 (5,8%)	 24 (44,4%) 21 (38,9%) 9 (16,7%)	 35 (66,0%) 15 (28,3%) 3 (5,7%)	 6,13 4,35 5,00	 0,0466 0,1136 0,0818
Vulnerabilities □ unemployed* □ degree of disability**	 12 (7,6%) 11 (6,9%)	 6 (11,5%) 6 (11,5%)	 4 (7,4%) 2 (3,7%)	 2 (3,8%) 4 (7,6%)	 2,27 2,33	 0,3214 0,3118
Reproductive function □ no. pregnancies □ no. births	 40 (25,2%) 33 (20,8%)	 8 (15,4%) 7 (13,5%)	 8 (14,8%) 6 (11,1%)	 24 (45,3%) 20 (37,7%)	 17,11 14,03	 0,0001 0,0009

Note: Calculations on general patient characteristics are based on data collected at visit 1 (study enrolment). Statistical tests performed between groups L1, L2, L3. Data for age are expressed as mean and standard deviation, with presentation of extreme values; statistical test applied - ANOVA. Category data are presented as absolute and relative values. Applied statistical test: Mantel-Haenszel for linear trends. * - patients with official unemployment status; ** - patients with disability degree, granted by the National Disability Determination Council of the Republic of Moldova.

The criteria for inclusion in the study were: (1) women of reproductive age (15-49 years); (2) who gave informed consent to be enrolled in the study; (3) with no predetermined duration of illness before enrolment, regardless of the type of epileptic seizure; (4) absence of chronic acute or decompensating comorbidities; (5) onset of illness - from childhood to late reproductive age (49 years).

Exclusion criteria from the study were: (1) lack of agreement to be enrolled in the study or desire to withdraw from the study; (2) age of patients evaluated for enrollment outside the age

range of 15-49 years; (3) undocumented or unconfirmed epileptic seizures; (4) patients with persistent epileptic encephalopathy**.**

The general research design of the thesis is shown in Figure 2.1.

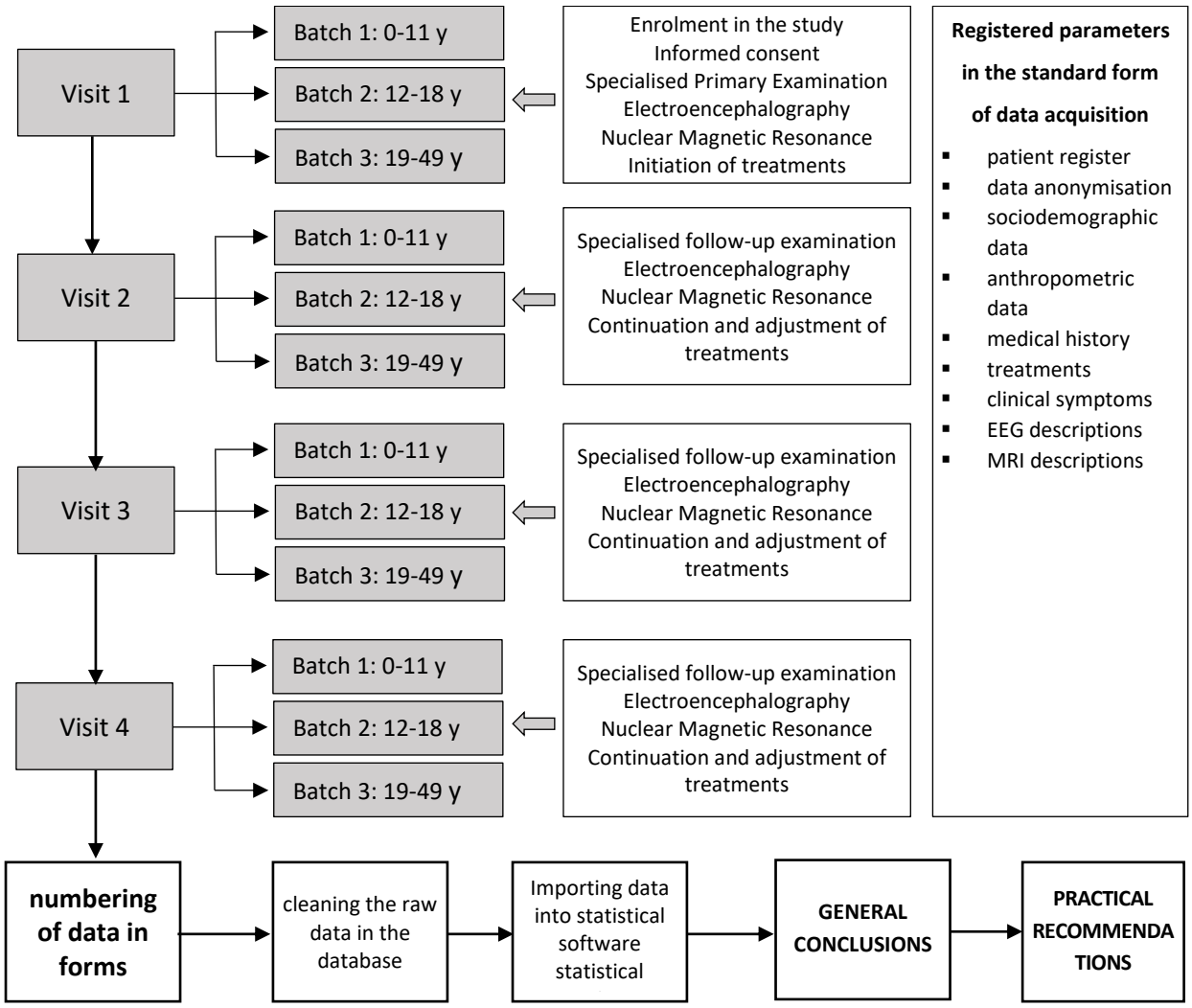

Figure 2.1. General study design.

2.2. Description of the general clinical and neurological examination

The clinical and general neurological examination was carried out according to the usual methodology and standards, in accordance with the National Clinical Protocol "Epilepsy in adults". The following were recorded: anamnestic, epidemiological, demographic data: age, residence, profession (working conditions), level of education (studies), personal and hereditary medical history (presence of epilepsy in first and second degree relatives), vicious habits, sexual history (menarche, menstrual cycle characteristics, obstetric and gynaecological history, sexual activity and menopause). Objective general clinical examination by systems and neurological examination was applied inter-generally. General and focal neurological symptoms, possible psychiatric, cognitive disorders were identified and entered in the standardized data recording form. For clarification of some events, relatives and eyewitnesses of seizures were interviewed

with the patients' consent. Patients also completed a diary (paper format) of epileptic seizures. The examination was performed repeatedly (visits 1-4).

2.3. Methodology of EEG investigation and brain MRI in study patients

EEG examinations were performed with electroencephalograph model BMS1-5000 and BMS1-6000 (manufacturer - Nicolet, USA) by monopolar and bipolar method using the international "10-20" electrosurgical application scheme. EEG was performed on awake patients in a relaxed state with eyes closed for 20-30 minutes. During the examination, the functional tests were performed: photostimulation, by exposure to intermittent light with the frequency of light flashes from 2 Hz to 30 Hz and hyperventilation, when patients had to breathe deeply with a breathing rate of 40-60 per minute for 2-3 min. EEG method associated with sleep deprivation was performed in cases, when epileptic focus was suspected on a standard EEG tracing. Video recording was performed with two cameras, day and night view, and data were stored either on videotapes or - on computer hard disk.

Long-term EEG recordings were made using the Coherence system long term recording equipment (manufacturer - Deltamed SA, Natus Medical Incorporated, France) in a semi-darkened room for a minimum of 8 hours of continuous night-time recording. For each patient, initially, standard video-EEG recording with functional samples was performed, followed by extended video-EEG recording. For this purpose, extra-cranial electrodes (manufacturer - Astro-Med Inc Product Group) were used. Electrodes were placed according to international standards (10-20 intonational system), with digital sampling rate of 256 Hz and electrode contact impedance below 10 kΩ. The recording parameters used were: high frequency filter of 70 Hz, and low frequency - of 0.3 Hz. Simultaneously, oculography, electrocardiography, electromyography of the deltoid muscle and respiration (respiratory movements of the chest and abdomen) were recorded.

For brain MRI (1.5T or 3.0T, with and without contrast), "the essential six" protocol was applied, upon availability - HARNESS (According to ILAE Neuroimaging Task Force, 2019).

2.4.Descriptive and inferential statistical analysis carried out within the thesis

The required number of patients was calculated using GPower 3.1 software (authors: Faul F. et al. Behaviour Research Methods, 2007; 39: 175-191). Since the main outcome parameters of the study are categorical, with non-Gaussian (non-normal) distribution, with 3 data sets, the Kruskall-Wallace test was selected for the calculation. Background information was entered: 95% confidence interval for the significance of the results, statistical power - 80%; outcome difference f=0.25; number of groups n=3; number ratio between data series - 1:1.

Calculation results: noncentrality parameter $\lambda = 9.94$, critical F-value = 3.05. Total, required number of patients for research = 159. Mathematical and statistical calculations were performed according to the hypothesis formulated and the number of data sets considered. In the paper, the following statistical tests were applied: exact Fisher, $\chi 2$ for linear trends (extended Mantel-Haenszel), unpaired two-tailed t-Student, ANOVA (Kruskall-Wallace post-test). Correlation analysis: *Pearson* (r) test.

Data are presented as absolute or relative (%) values. Continuous data or data reflecting *Pearson correlation (r)* are presented as mean and 95% confidence interval (95CI). A weak correlation was considered when (r) <0.3; intermediate - when (r) = 0.3-0.6 and strong - when (r) >0.6. For all cases, statistical significance was considered as obtaining a $p<0.05$.

2.5 Multivariate statistical analysis and probabilistic modelling

Of the 366 unique parameters that were recorded for the 159 patients enrolled in the study at each visit (total of 4 visits), 10 parameters were selected for multivariate analysis as relevant for predicting clinically meaningful outcomes. Relevance criteria were: reaching a $p \leq 0.1$ in univariate analysis, can be easily identified and recorded, have been identified in the literature.

The parameters on which the probabilistic mathematical models were built were: (1) age of onset of illness (by age categories 10, 20 and 30 years); (2) dropout or poor adherence to prescribed antiepileptic treatment; (3) presence of a brain lesion on brain MRI examination; (4) prolonged confusional state after an epileptic seizure (postictal sign); (5) focus of activity on electroencephalography without seizure symptoms; (6) anxiety; (7) depression; (8) duration of seizure over 6 minutes; (9) status epilepticus event; (10) seizure frequency (discrete quantitative variable).

The clinically relevant outcome parameters for which the models were constructed were: (1) failure of drug treatment (onset of drug resistance); (2) worsening course of the disease; (3) occurrence of status epilepticus; (4) stable remission of the disease ("stabilization" of the disease).

$$P = \frac{e^{\beta 0 + \beta 1X}}{1+e^{\beta 0 + \beta 1X}} \quad (2.1)$$

For each model, the final number of parameters remaining were selected according to the results of the collinearity test, the variance inflation factor (VIF) and the Akaike informativeness criterion. All the analysis was performed with the help of *Graph Pad Prism software, version 9* test). Within the models, the calculation of probabilities was performed using the formula (2.1), where ($e\beta 0$) represents the interceptor value, and ($\beta 1$X, as appropriate - $\beta 2$X2 and so on) - represents the contribution of each parameter to the final probability of occurrence of the outcome event. For practical convenience, the same results were also reflected by Odds ratios.

3. PREVALENCES, TRENDS AND CORRELATIONS BETWEEN CLINICAL, IMAGISTIC AND ELECTROENCEPHALOGRAPHIC SEMIOLOGY ACCORDING TO AGE OF ONSET AND TIME COURSE OF EPILEPTIC SEIZURES IN WOMEN OF REPRODUCTIVE AGE

3.1. Prevalence of types and subtypes of epileptic seizures by age group and time course of the disease

The types of epileptic seizures have a stable prevalence and correlation between them, irrespective of the age category of onset or duration of the disease (Table 3.1). Only the prevalence of epileptic seizure subtypes in the categories complex focal EC ($\chi 2=18.6$, $p=0.005$), primary generalized EC (i.e., absences) ($\chi 2=67.5$, $p=0.0001$) and secondary generalized EC (i.e., FSEC with transition to generalized) ($\chi 2=20.34$, $p=0.016$) change significantly, mainly due to the applied treatment and/or brain remodeling, produced over time (Table 3.2).

Table 3.1. Types and subtypes of epileptic seizures according to the age of onset of the disease.

ES type on debut	Whole Batch	Batch I (0-11 years)	Batch II (12-18 years)	Batch III (19-49 years)	χ^2	p
Focal aware seizures	**741 (26,5%)**	**255 (26,1%)**	**258 (27,0%)**	**228 (26,4%)**		
▪ Motor onset focal seizures	118 (15,9%)	39 (15,3%)	42 (16,3%)	37 (16,2%)	10,4	0,235
▪ Sensory onset focal seizures	172 (23,2%)	60 (23,5%)	64 (24,8%)	48 (21,1%)		
▪ Autonomic onset focal seizures	43 (5,8%)	16 (6,3%)	18 (7,0%)	9 (4,0%)		
▪ Cognitive, behavior arrest, sensory focal onset seizures	66 (8,9%)	28 (11,0%)	25 (9,7%)	13 (5,7%)		
▪ Unclassifiable seizures	342 (46,2%)	112 (43,9%)	109 (42,2%)	121 (53,0%)		
Focal impaired awareness seizures	**714 (25,5%)**	**250 (25,6%)**	**236 (24,7%)**	**228 (26,4%)**		
▪ Motor onset focal seizures	162 (22,7%)	60 (24,0%)	65 (27,5%)	37 (16,2%)	18,6	0,005
▪ Cognitive, behavior arrest, autonomic, sensory focal onset seizures	77 (10,8%)	33 (13,2%)	23 (9,8%)	21 (9,2%)		
▪ Focal onset with automatisms	195 (27,3%)	76 (30,4%)	50 (21,2%)	69 (30,3%)		
▪ Unclassifiable seizures	280 (39,2%)	81 (32,4%)	98 (41,5%)	101 (44,3%)		
Focal to bilateral tonic-clonic	**653 (23,3%)**	**228 (23,3%)**	**221 (23,1%)**	**204 (23,6%)**	**8,30**	**0,217**
Generalised onset seizures	**690 (24,7%)**	**245 (25,0%)**	**240 (25,2%)**	**205 (23,6%)**		
▪ Absence seizures	44 (6,4%)	28 (11,4%)	12 (5,0%)	4 (2,0%)	67,5	0,0001
▪ Myoclonic seizures	66 (9,6%)	29 (11,8%)	37 (15,4%)	0 (0,0%)		
▪ Tonic-clonic seizures	103 (14,9%)	43 (17,6%)	38 (15,8%)	22 (10,7%)		
▪ Atonic seizures	14 (2,0%)	8 (3,3%)	0 (0,0%)	6 (3,0%)		
▪ Unclassifiable seizures	463 (67,1%)	137 (55,9%)	152 (63,8%)	174 (84,3%)		
Total per batch, no. of seizures	**2798 (100%)**	**978 (35,0%)**	**955 (34,1%)**	**865 (30,9%)**		

Note: Statistical analysis: $\chi 2$ for linear trends (Mantel-Haenszel extended, calculated between groups I, II, III, for each seizure type and subtype). Percentages are calculated "vertically". Here, Chi-square between SFES, CFEC, SGS, PGS is not significantly different ($\chi 2=1.16$, $p=0.997$).

Table 3.2. Types and subtypes of epileptic seizures according to follow-up visits.

Seizure type at onset	Whole Batch	V1	V2	V3	V4	χ^2	p
Focal aware seizures	**741 (26,5%)**	**202 (26,8%)**	**193 (26,9%)**	**182 (26,3%)**	**164 (25,8%)**		
▪ Motor onset focal seizures	118 (15,9%)	38 (18,8%)	31 (16,0%)	26 (14,3%)	23 (14,0%)	12,84	0,381
▪ Sensory onset focal seizures	172 (23,2%)	54 (26,7%)	43 (22,3%)	36 (19,8%)	39 (23,8%)		
▪ Autonomic onset focal seizures	43 (5,8%)	11 (5,5%)	13 (6,7%)	10 (5,5%)	9 (5,5%)		
▪ Cognitive, behavior arrest, sensory focal onset seizures	66 (8,9%)	24 (11,9%)	16 (8,3%)	15 (8,2%)	11 (6,7%)		
▪ Unclassifiable seizures	342 (46,2%)	75 (37,1%)	90 (46,7%)	95 (52,2%)	82 (50,0%)		
Focal impaired awareness seizures	**714 (25,5%)**	**189 (25,0%)**	**182 (25,4%)**	**175 (25,3%)**	**168 (26,5%)**		
▪ Motor onset focal seizures	162 (22,7%)	54 (28,6%)	37 (20,3%)	35 (20,0%)	36 (21,4%)	8,65	0,470
▪ Cognitive, behavior arrest, autonomic, sensory focal onset seizures	77 (10,8%)	19 (10,1%)	20 (11,0%)	19 (10,9%)	19 (11,3%)		
▪ Focal onset with automatisms	195 (27,3%)	56 (29,6%)	47 (25,8%)	46 (26,3%)	46 (37,4%)		

▪ Unclassifiable seizures	280 (39,2%)	60 (31,7%)	78 (42,9%)	75 (42,8%)	67 (29,9%)		
Focal to bilateral tonic-clonic	**653 (23,3%)**	**175 (23,2%)**	**164 (22,9%)**	**167 (24,2%)**	**147 (23,2%)**	**8.30**	**0,217**
Generalised onset seizures	**690 (24,7%)**	**189 (25,0%)**	**178 (24,8%)**	**167 (24,2%)**	**156 (24,5%)**		
▪ Absence seizures	44 (6,4%)	15 (7,9%)	12 (6,7%)	7 (4,2%)	10 (6,4%)		
▪ Myoclonic seizures	66 (9,6%)	19 (10,1%)	18 (10,1%)	15 (9,0%)	14 (9,0%)		
▪ Tonic-clonic seizures	103 (14,9%)	36 (19,1%)	26 (14,6%)	20 (12,0%)	21 (13,5%)	10,95	0.533
▪ Atonic seizures	14 (2,0%)	6 (3,2%)	2 (1,1%)	2 (1,2%)	4 (2,6%)		
▪ Unclassifiable seizures	463 (67,1%)	113 (59,7%)	120 (67,5%)	123 (73,6%)	107 (68,5%)		
Total per batch, no. of seizures	**2798 (100%)**	**755 (100%)**	**717 (100%)**	**691 (100%)**	**635 (100%)**	0.89	0.999

Note: Statistical analysis: $\chi 2$ for linear trends (Mantel-Haenszel extended), calculated between data series V1-V4, for each seizure type and subtype.

In general, with age the probability of disease onset is significantly reduced around the age of 30 (*Pearson's r* = 0.2393).

3.2. Clinical semiology of epileptic seizures in women of reproductive age. Approach according to age groups

A number of EC triggers were documented in two-thirds of patients (discontinuation of antiepileptic treatment (44.7%), stress (38.4%), sleep deprivation (31.4%), fever (8.8%) and menstrual cycle (7.5%) and light flashes (5.7%), the last two causes virtually disappearing towards maturity (Table 3.3).

Table 3.3. Seizure triggers by age category.

Debut parameters (calculated based on visit 1)	Whole Batch	Batch I (0-11 y)	Batch II (12-18 y)	Batch III (19-49 y)	χ^2	p
Health status at the onset of seizures						
▪ febrile	16 (10,1%)	8 (13,8%)	3 (5,4%)	5 (9,1%)	2,86	0,2390
▪ ill	7 (4,4%)	3 (5,2%)	1 (1,8%)	3 (5,5%)	1,26	0,5313
▪ exposed to the disease	50 (31,4%)	18 (31,0%)	14 (25,0%)	18 (32,7%)	1,16	0,5596
▪ insomnia	10 (6,0%)	3 (5,2%)	2 (3,6%)	5 (9,1%)	1,53	0,4663
▪ other factors	20 (12,6%)	4 (6,9%)	11 (19,6%)	5 (9,1%)	4,59	0,1009
▪ no other conditions	66 (41,5%)	22 (37,9%)	25 (44,6%)	19 (34,5%)	1,22	0,5426
Trigger factors						
▪ interruption of AED	71 (44,7%)	23 (25,0%)	25 (28,0%)	23 (28,0%)	0,10	0,9528
▪ sleep deficit	50 (31,4%)	21(23,0%)	14 (16,0%)	15 (19,0%)	2,93	0,2037
▪ fever	14 (8,8%)	10 (10,9%)	1 (1,1%)	3 (3,7%)	10,94	0,0042
▪ menarche	12 (7,5%)	3 (3,3%)	5 (5,6%)	4 (4,9%)	0,46	0,7936
▪ stress	61 (38,4%)	22 (24,0%)	17 (19,0%)	22 (27,0%)	1,65	0,4392
▪ flashes of light	9 (5,7%)	5 (5,4%)	4 (4,5%)	0 (0,0%)	5,01	0,0816
▪ other factors	30 (18,9%)	6 (6,5%)	13 (14,6%)	11 (13,6%)	2,90	0,2341
▪ no trigger factors	15 (9,4%)	2 (2,0%)	10 (11,0%)	3 (4,0%)	8,00	0,0183
Total patients per batches	159 (100%)	52 (32,7%)	54 (34,0%)	53 (33,3%)	-	-

Note: Some patients had more than one health condition or trigger, so the sum of percentages per batch exceeds 100%. Statistical analysis: $\chi 2$ for linear trends (Mantel-Haenszel extended).

Almost always (98-99%), epileptic seizures experienced by patients of reproductive age end with post-seizure signs, the most common being drowsiness (25.5%), amnesia (29.8%), confusion (13.3%) and headache (16.5%). Although statistically significant variability in the frequencies of postictal signs was observed, depending on the age of onset of the disease, these do not reach the

magnitude of clinical significance but are rather the result of the influence of antiepileptic medication and/or brain remodelling. The trend is also observed over time (Table 3.4).

Table 3.4. Postictal signs after sustained epileptic seizures by age category.

Postictal signs	Whole Batch	Batch I (0-11 y)	Batch II (12-18 y)	Batch III (19-49 y)	χ^2	p
Drowsiness	435 (25,5%)	135 (22,1%)	180 (34,1%)	120 (23,0%)	9,21	0,0099
Confusion	227 (13,3%)	95 (15,5%)	82 (14,3%)	50 (9,6%)	7,33	0,0255
Agitation	39 (2,3%)	18 (2,9%)	12 (2,1%)	9 (1,7%)	4,64	0,0981
Gait deficit	43 (2,5%)	27 (4,4%)	4 (0,7%)	12 (2,3%)	27,39	0,0001
Amnesia	509 (29,8%)	200 (32,7%)	157 (27,4%)	152 (29,1%)	2,30	0,3170
Headache	281 (16,5%)	85 (13,9%)	86 (15,0%)	110 (21,2%)	8,35	0,0154
Speech disorders	94 (5,5%)	37 (6,1%)	27 (4,7%)	30 (5,7%)	5,11	0,0776
Other signs	57 (3,3%)	10 (1,6%)	8 (1,4%)	39 (7,5%)	49,45	0,0001
No postictal signs	22 (1,3%)	4 (0,7%)	18 (3,1%)	0 (0,0%)	9,63	0,0019
Total	1707 (100,0%)	611 (35,8%)	574 (33,6%)	522 (30,6%)	-	-

Note: Statistics performed on all documented summed postictal signs in all patients for all visits. Statistical analysis: $\chi 2$ for linear trends (Mantel-Haenszel extended).

It seems that the frequency of epileptic seizures does not depend on the age of onset of the disease, but there is a statistically significant trend that at early onset of the disease (0-11 years) epileptic seizures are predominantly weekly (26.7%, $\chi 2 = 7.37$, $p = 0.0251$), and with increasing age of onset of the disease, the frequency of seizures tend to occur less frequently. With the initiation of antiepileptic treatment, seizures become rarer (annual, multi-year frequency) or absent, mainly on account of seizures with previous weekly and daily frequency (Table 3.5).

Table 3.5. Recorded frequency of sustained epileptic seizures by age category.

Frequency of ES	Whole Batch	Batch I (0-11 y)	Batch II (12-18 y)	Batch III (19-49 y)	χ^2	p
Daily	18 (7,7%)	9 (11,0%)	5 (6,0%)	4 (5,9%)	2,84	0,2421
Weekly	46 (19,7%)	22 (26,7%)	14 (16,9%)	10 (14,8%)	7,37	0,0251
Multi-weekly	15 (6,4%)	3 (3,7%)	10 (12,0%)	2 (2,9%)	8,02	0,0181
Monthly	38 (16,3%)	14 (17,1%)	12 (14,5%)	12 (17,5%)	0,39	0,8224
Multi-monthly	32 (13,7%)	11 (13,4%)	14 (16,9%)	7 (10,3%)	2,74	0,2538
Multi-annual	53 (22,9%)	13 (15,8%)	19 (22,9%)	21 (30,8%)	0,65	0,2656
Annual	18 (7,7%)	7 (8,6%)	5 (6,0%)	6 (8,9%)	0,17	0,9183
Status epilepticus	2 (0,9%)	0 (0,0%)	1 (1,2%)	1 (1,5%)	0,03	0,9845
Unspecified frequency	11 (4,7%)	3 (3,7%)	3 (3,6%)	5 (7,4%)	0,78	0,6760
Total recorded frequencies	233 (100,0%)	82 (35,2%)	83 (35,6%)	68 (29,2%)	-	-

Note: Statistical analysis: $\chi 2$ for linear trends (extended Mantel-Haenszel). Percentages calculated according to epileptic seizure frequency ("vertical").

Table 3.6. Recorded duration of sustained epileptic seizures by age category.

Duration of ES	Whole Batch	Batch I (0-11 y)	Batch II (12-18 y)	Batch III (19-49 y)	χ^2	p
≤10 sec	107 (6,4%)	58 (8,9%)	35 (5,8%)	14 (3,4%)	17,64	0,0001
11-30 sec	175 (10,5%)	80 (12,3%)	73 (12,2%)	22 (5,3%)	13,43	0,0012
31-60 sec	344 (20,6%)	124 (19,0%)	138 (23,0%)	82 (19,7%)	2,20	0,3323
2-5 min	578 (34,6%)	199 (30,5%)	199 (33,2%)	180 (43,2%)	8,90	0,1166
6-10 min	343 (20,5%)	134 (20,5%)	104 (17,3%)	105 (25,2%)	6,05	0,0485

11-30 min	104 (6,2%)	52 (8,0%)	42 (7,0%)	10 (2,4%)	63,90	0,0001
≥30 min	19 (1,1%)	6 (0,9%)	9 (1,5%)	4 (1,0%)	2,13	0,3543
Total ES recorded	1670 (100%)	653 (39,1%)	600 (35,9%)	417 (25,0%)	-	-

Note: Statistical analysis: $\chi 2$ for linear trends (Mantel-Haenszel extended).

Although the maximum prevalence is found in the medium seizure durations (every second patient, irrespective of age of onset, had a seizure duration between 31 sec - 5 min), there is a significant difference between short (under 30 sec) and long (over 11 min) durations, where the prevalence decreases significantly ($\chi 2$=17.64, p=0.00001 and $\chi 2$=63.9, p=0.0001, respectively) with increasing age of onset. Antiepileptic treatments significantly reduce the previously long epileptic seizure durations (starting at 6 min and longer) ($\chi 2$=107.7, p=0.0001), but without clinically significantly affecting the prevalence of medium and short seizure durations) (Table 3.6).

3.3. Clinical semiology of epileptic seizures in women of reproductive age. Approach according to the time course of the disease

Nocturnal epileptic seizures were recorded in practically every second patient (43.1% to 45.3%). Although there is significant variability in the frequency of sleep-related seizures over time, the proportions and correlations reported do not appear to have any clinical significance in this regard (Table 3.8). Epileptic seizures related to certain phases of the menstrual cycle are called catamenial seizures or catamenial epilepsy. It should be noted that the incidence of catamenial epilepsy varies widely, ranging from 12% to 72%, depending on the definition applied. From the data presented in Table 3.8, it appears that in the patients in the study, in about 15% of cases there was a correlation between seizures and menstrual cycle.

Table 3.7 Relationship of epileptic seizures to sleep according to the time course of the disease.

Time of seizure onset	Visit I	Visit II	Visit III	Visit IV	χ^2	p
During sleep	103 (45.3%)	82 (43.6%)	69 (43.1%)	68 (44.4%)	12.5	0.0050
During wakefulness	84 (37.0%)	65 (34.6%)	50 (31.3%)	53 (34.6%)	13.1	0.0045
Waking up	19 (8.4%)	16 (8.5%)	16 (10.0%)	14 (9.2%)	0.31	0.9584
Variable, independent	21 (9.3%)	25 (13.3%)	25 (15.6%)	18 (11.8%)	0.61	0.8934
Total per visit	227 (100%)	188 (100%)	160 (100%)	153 (100%)	-	-

Note: Statistical analysis: $\chi 2$ for linear trends (extended Mantel-Haenszel). Calculated for the number of epileptic seizures recorded in relation to sleep.

Table 3.8 Relationship with the menstrual cycle of epileptic seizures according to the time course of the disease.

Time of seizure onset	Vizita I	Vizita II	Vizita III	Vizita IV	χ^2	p
C1	11 (6,8%)	11 (6,9%)	12 (7,7%)	7 (5,1%)	0,92	0,8212
C2	6 (3,7%)	7 (4,4%)	6 (3,8%)	2 (1,5%)	2,90	0,4070
C3	6 (3,7%)	4 (2,5%)	4 (2,6%)	4 (2,9%)	0,50	0,9182
Uncorrelated	139 (85,8%)	138 (86,2%)	134 (85,9%)	124 (90,5%)	1,10	0,7770
Total per visit	162 (100%)	160 (100%)	156 (100%)	137 (100%)	-	-

Note: Statistical analysis: $\chi 2$ for linear trends (extended Mantel-Haenszel). Calculated for number of epileptic seizures recorded in relation to menstrual cycle.

The proportion of epileptic seizures associated with the menstrual cycle (sum of C1, C2, C3 events) had statistically insignificant variability over the dynamic monitoring (visits I-IV). The given

study did not show any correlation of epileptic seizures with the phases of the menstrual cycle, in time or according to the age of onset of the disease.

3.4. Electroencephalographic semiology of epileptic seizures in women of reproductive age

The EEG seizure pathway is similar in terms of most parameters, i.e. the seizure-related brain electrical abnormalities identified in the study show a similarity or analogy to those well known in epileptology and applied in medical practice, and nothing new was found in the statistical correlation applying the r (Pearson) correlation test, which would be significant and show something new in the diagnosis of seizure type or to assess prognosis based on this correlation, according to the age of onset of the disease, with the exception of the dominant alpha rhythm and the disorganized pattern, more common in younger people (Table 3. 9).

Table 3.9. EEG parameters characterizing the onset of epileptic seizures.

Registered parameters	Whole Batch	Batch I (0-11 y)	Batch II (12-18 y)	Batch III (19-49 y)	χ^2	p
Epileptic focus on the right	76 (7,0%)	26 (6,7%)	28 (7,7%)	22 (6,7%)	1,30	0,7299
Epileptic focus on the left	77 (7,1%)	23 (5,9%)	30 (8,2%)	24 (7,3%)	1,68	0,6425
Epileptic multifocal activity	85 (7,8%)	32 (8,2%)	30 (8,2%)	23 (7,0%)	3,60	0,3059
Diffuse epileptic activity	38 (3,5%)	19 (4,9%)	11 (3,0%)	8 (2,4%)	7,20	0,0659
Bilateral epileptic activity	73 (6,7%)	25 (6,4%)	25 (6,9%)	23 (7,0%)	0,24	0,9715
Organised pattern	39 (3,6%)	12 (3,1%)	19 (5,2%)	8 (2,4%)	3,49	0,3216
Disorganised pattern	111 (10,2%)	48 (12,3%)	40 (11,0%)	23 (7,0%)	9,82	0,0202
Dominant alpha rhythm	139 (12,8%)	60 (15,2%)	58 (16,0%)	21 (6,3%)	14,30	0.0008
Intricate tetha waves	113 (10,4%)	42 (10,8%)	35 (9,6%)	36 (10,8%)	4,75	0,1911
Tetha	113 (10,4%)	33 (8,5%)	24 (6,6%)	56 (16,9%)	3,83	0,2805
Delta	66 (6,1%)	18 (4,6%)	12 (3,3%)	36 (10,8%)	2,70	0,4454
Spike-wave complex 3Hz	9 (0.8%)	3 (0,8%)	3 (0,8%)	3 (0,9%)	0,01	1,0000
HV FS amplified	146 (13,6%)	49 (12,6%)	49 (13,5%)	48 (14,5%)	0,51	0,9172
Total characteristics	1085 (100%)	390 (100%)	364 (100%)	331 (100%)	-	-

Note: Statistical analysis: $\chi 2$ for linear trends (Mantel-Haenszel extended).

3.5. Brain imaging semiology in patients of reproductive age with epilepsy

Consistent with the data in Table 3.10, 3 types of brain lesions were more frequently recorded: cerebral atrophy (generalised and focal), hippocampal sclerosis and non-specific structure lesions (gliosis, leukoaraiosis). Cerebral atrophy was recorded in 17.2% of cases and was considered to be a change in brain structure with potential for epileptogenesis, regardless of age and statistically insignificant between groups.

Table 3.10. Structural brain lesions on MRI images in patients with epilepsy, by age category.

Recorded parameters	Whole Batch	Batch I (0-11 y)	Batch II (12-18 y)	Batch III (19-49 y)	χ^2	p
Hippocampal sclerosis	25 (12,3%)	13 (17,6%)	9 (13,4%)	3 (4,8%)	7,46	0,0585
Brain abnormalities *	5 (2,5%)	4 (5,4%)	0 (0,0%)	1 (1,6%)	5,56	0,1351
Brain tumours	6 (2,9%)	0 (0,0%)	4 (6,0%)	2 (3,2%)	4,00	0,2612
Vascular anomalies **	1 (0,5%)	0 (0,0%)	1 (1,5%)	0 (0,0%)	1,92	0,5902
Cerebral atrophy	35 (17,2%)	16 (21,6%)	8 (11,9%)	11 (17,5%)	4,00	0,2613
Non-specific lesions	31 (15,2%)	7 (9,5%)	9 (13,4%)	15 (23,8%)	2,77	0,4292
Other lesions	15 (7,4%)	9 (12,2%)	5 (7,5%)	1 (1,6%)	7,93	0,1170
No structural lesions	86 (42,2%)	25 (33,8%)	31 (46,3%)	30 (47,6%)	50,70	0,0000
Total characteristics	1085 (100%)	390 (100%)	364 (100%)	331 (100%)	-	-

Note: * - gliosis, leukokaryosis. **- arteriovenous malformation; cavernoma. Statistical analysis: $\chi 2$ for linear trends (extended Mantel-Haenszel).

Hippocampal sclerosis and brain atrophy was the predominant cause of early age onset of epileptic seizures; with increasing age of disease onset, the proportion of patients without identifiable brain lesions on MRI increases by half (47.6%; $\chi 2=50.7$, $p=0.0000$).

3.6.Correlations between clinical, electroencephalographic and imagistic symptoms

Since each patient has a whole spectrum of symptoms, time course of illness, neurophysiological features, imagistic features, personal history, lifestyle and living conditions, treatments, etc., a mosaic of features emerges that determine the unique, individual character of the person and their health status. As the possible combinations of symptoms are many, they are nevertheless a finite number.

Therefore, Figure 3.1 shows the correlation matrix of clinical signs of epilepsy with EEG manifestations, total and by batch (visit 1). Of the 30 combinations between clinical signs and EEG descriptions placed on the y-axis, where each combination reflects the 4 sets of data (both the whole group and the 3 age categories) - in total, a matrix of 120 r (Pearson) coefficients, a strong degree of correlation showed only the combination of primary generalized EC with 3 Hz slow wave spike complex for group III (age 19-49 years), and primary generalized EC with primary generalized epileptic activity for group II (age 12-18 years). The trends also remain the same for the correlation matrices performed for visits 2, 3 and 4, for this reason they were not shown the images.

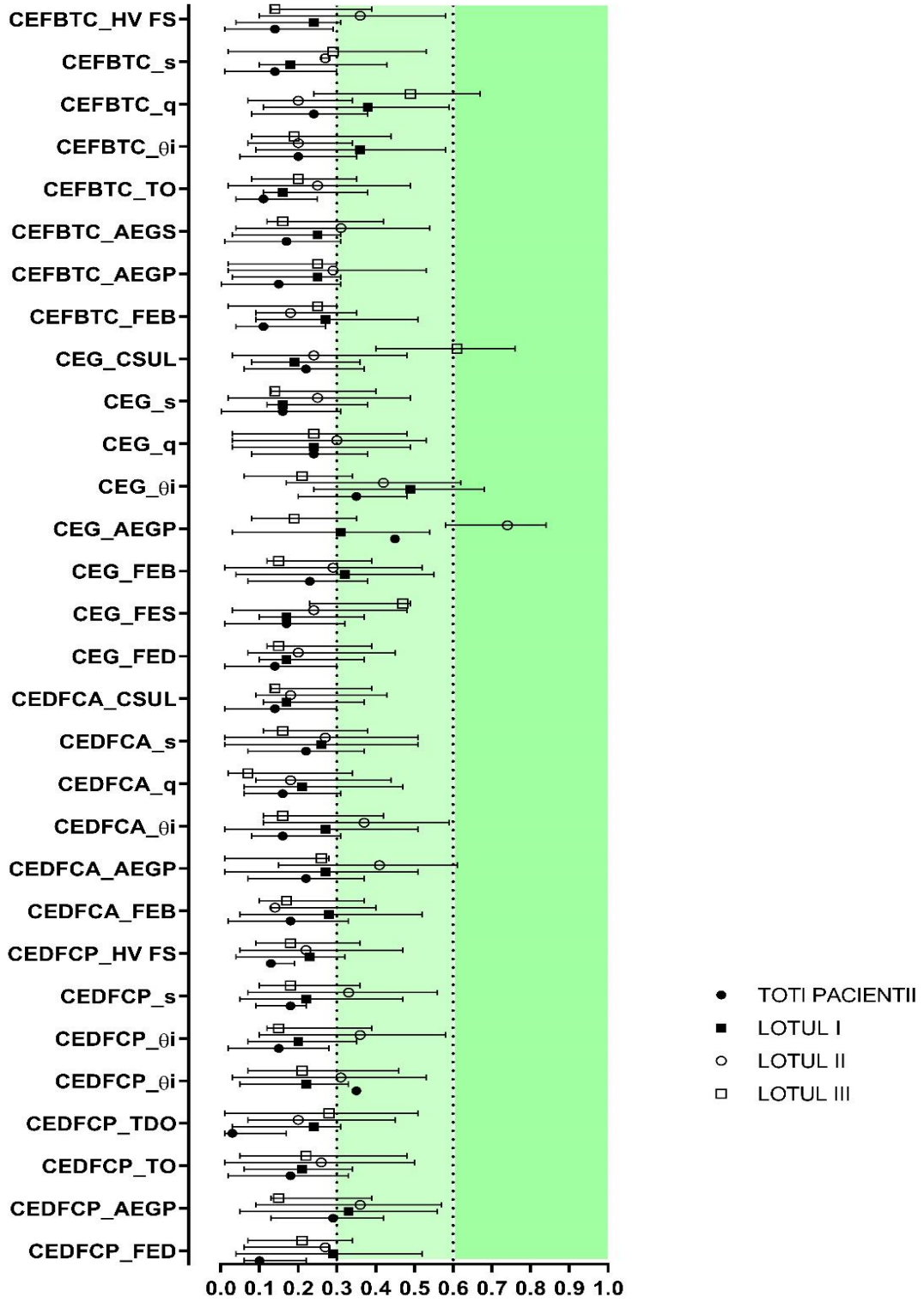

Figure 3.1 Matrix correlating epileptic seizures types with EEG manifestations, total and by batch (visit 1).

Note: FAMOFS – focal aware motor onset seisure (CEDFCP), FIAES – focal impaired awareness motor /non-motor sseizures (CEDFCA); GES – generalised ES (CEG), FBTCS – focal to bilateral tonic-clonic seizures (CEFBTC), FED – epileptic focus on the right; FES – epileptic focus on the left; MEF – multifocal epileptic focus = FEB – bilateral epileptic focus; DEA – diffuse epileptic activity= AEGP – primarily generalised epileptic activity; BEA – bilateral epileptic activity=; AEGS – secondary generalised epileptic activity;; TO – organised pattern; TDO – desorganised pattern; RαD – dominant alpha rythm; Θi – intricate tetha rythm; Θ – tetha rythm; δ – delta rythm; CSUL – *spike*-wave complex 3Hz ; HV FS – functional tests; NonEpi – non-epileptic pattern. Data presented as mean and confidence interval of 95%.

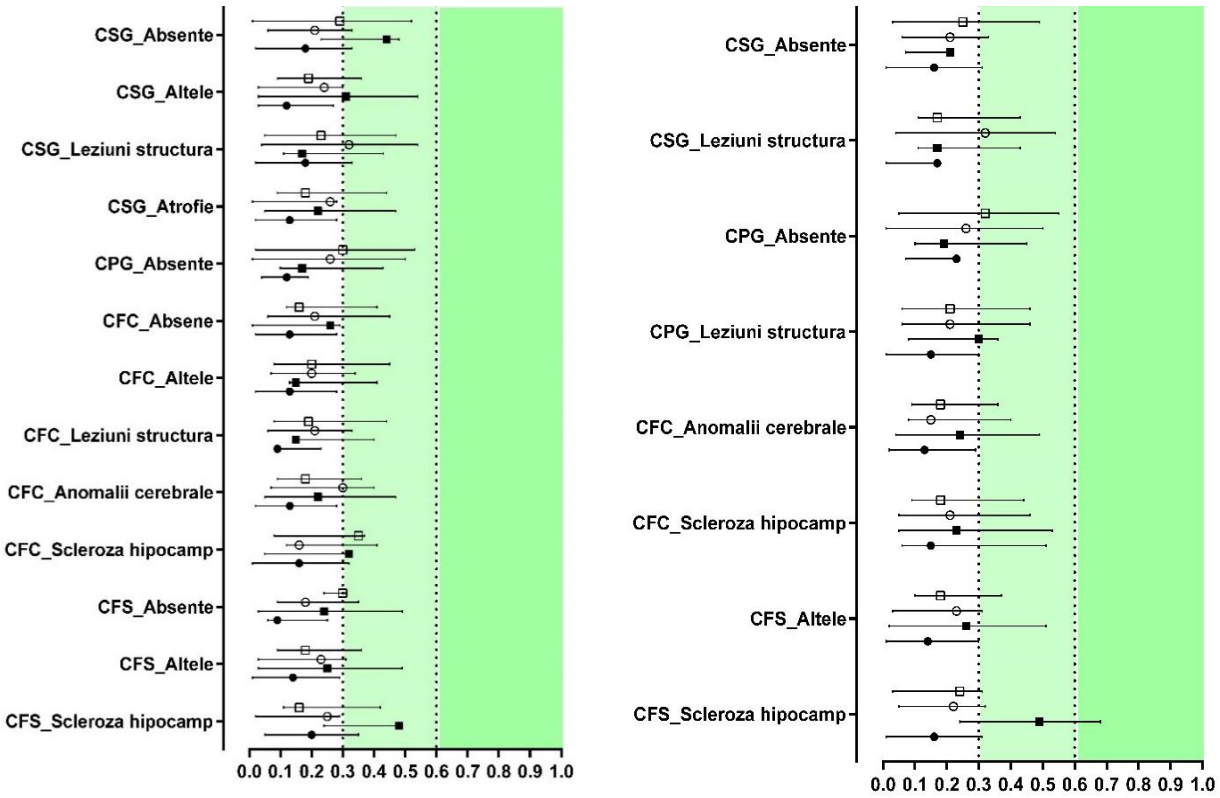

Figure 3.2. Matrix correlating epileptic seizures type with MRI manifestations, total and by batch (visits 1-2).

Note: FAMOFS – focal aware motor onset seisure =CFS – simple focal ES; FIA – focal impaired awareness motor /non-motor sseizures = CFC – complex focal ES; FBTCS – focal to bilateral tonic-clonic seizures= CSG – secondary generalised ES; MAV – arteriovenous malformation . Data presented as mean and confidence interval of 95%.

The correlation between clinical and brain imaging symptoms on MRI was found to be identified in a weak to moderate correlation range according to r (Pearson), both in terms of the age of onset of the disease and its evolution over time, the moderate degree being attributed to a correlation between hippocampal sclerosis and seizures with focal onset preserved consciousness and those with focal onset impaired consciousness (Figure 3.2). As the images relating to visits 3 and 4 are similar in appearance and parameters, they are not shown.

4. ELABORATION OF PREDICTIVE MODELLING FOR OUTCOMES RELEVANT TO THE CLINICAL PROGRESS OF EPILEPSY IN WOMEN OF REPRODUCTIVE AGE

4.1. Model predicting epilepsy worsening over time

Of the 10 parameters chosen for building prediction models for clinically important outcomes, 7 were selected to be eligible for predicting disease worsening over time. The results of the multiple logistic regression are shown in Table 4.1. Since 7 parameters in a single model is an excessive number, 2 models (named *agr_1* and *agr_2*) were constructed from this list for testing. Their predictive performance is expressed by ROC curves (Figure 4.1).

Table 4.1. Multiple logistic regression parameters for worsening condition of patients with epilepsy over time, calculated based on clinical indicators shown to be relevant.

Parameters	β (SE)	OR (95CI)	VIF	R^2	Mean probability
Interceptor (β0)	0,04 (0,31)	1,04 (0,57 – 1,91)	-	-	51%
A (β1)	-0,49 (0,25)	0,61 (0,37 – 0,99)	1,067	0,063	38%
B (β2)	-0,15 (0,20)	0,86 (0,58 – 1,26)	1,088	0,081	46%
C (β3)	-0,14 (0,23)	0,87 (0,56 – 1,37)	1,372	0,271	47%
D (β4)	-0,02 (0,24)	0,98 (0,62 – 1,56)	1,387	0,279	49%
E (β5)	0,73 (0,20)	2,08 (1,42 – 3,10)	1,070	0,066	68%
F (β6)	0,92 (0,20)	2,50 (1,69 – 3,70)	1,097	0,089	71%
G (β7)	0,39 (0,21)	1,47 (0,97 – 2,23)	1,100	0,091	60%

Note: A – depresion; B – structural abnormality on MRI image; C – age of onset of epilepsy 20 years old; D – age of onset of epilepsy 30 years old; E – discontinuation of antiepileptic treatment; F – epileptic seizure lasting more than 6 minutes; G – Confusional state after epileptic seizure. VIF – variance inflation factor; R^2 – multiple correlation coefficient.

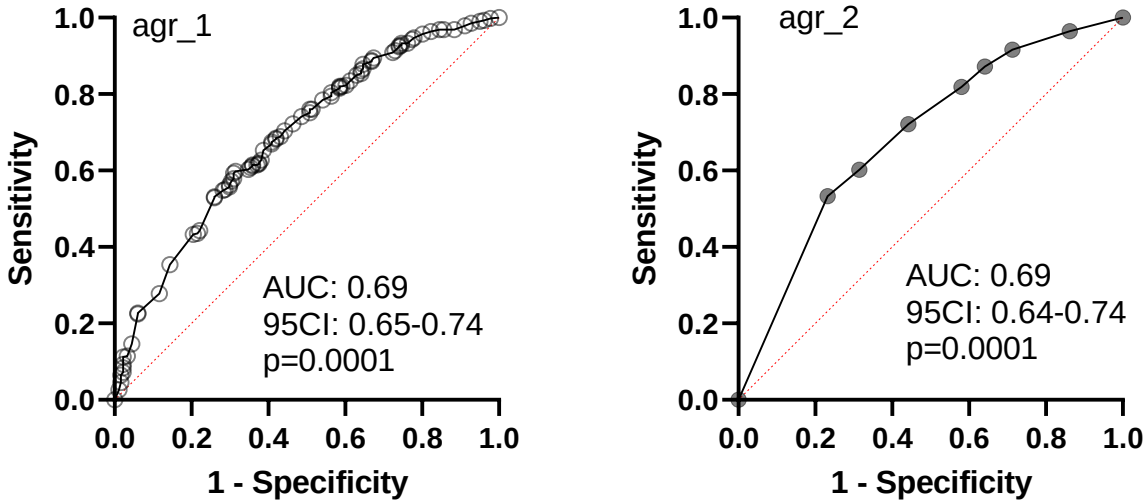

Figure 4.1. Parameters of probabilistic models for predicting the worsening of the patient's condition over time, based on the parameters identified to be the most relevant from a pre-defined list (discontinuation of antiepileptic treatments, epileptic seizure lasting more than 6 min. and confusion after seizure.

Following the multicollinearity testing exercise (R2 value in Table 4.1) and the contribution of each parameter to the utility of each model (VIF value in Table 4.1), the final version proposed for use in clinical practice is described in formula 2. Note, the intermediate calculations and formulae here are not presented.

$$P(agr\_s) = \frac{e^{-0,7+ATAE^{0,74}+CE^{0,70}+CON^{0,37}}}{1+(e^{-0,7+ATAE^{0,74}+CE^{0,70}+CON^{0,37}})} \quad (2)$$

Respectively,

$$P(agr\_s) = 0,86\ (86\%) \quad (3)$$

4.2. Model for predicting the risk of developing status epilepticus

For the construction of the model predicting the occurrence of status epilepticus over time, 4 parameters out of 10 were selected; the values of the multiple logistic regression are shown in Table 4.2.

Table 4.2. Multiple logistic regression parameters for the occurrence of epileptic status in patients with epilepsy over time, calculated based on clinical indicators shown to be relevant.

Parameters	β (SE)	OR (95CI)	VIF	R^2	Mean Probability
Interceptor (β0)	2,67 (0,74)	14,46 (3,89 – 74,13)	-	-	93%
A (β1)	0,59 (0,67)	1,80 (0,44 – 6,47)	1.068	0.06	64%
B (β2)	0,76 (0,72)	2,14 (0,56 – 10,39)	1.092	0.08	68%
C (β3)	0,10 (0,66)	1,10 (0,27 – 3,87)	1.038	0.04	52%
D (β4)	1,23 (0,63)	3,43 (0,99 – 12,42)	1.067	0.06	77%

Note: A – depresion; B – structural abnormality on MRI image; C – age of onset of epilepsy 20 years old; D – age of onset of epilepsy 30 years old; E – discontinuation of antiepileptic treatment; F – epileptic seizure lasting more than 6 minutes; G – Confusional state after epileptic seizure. VIF – variance inflation factor; R^2 – multiple correlation coefficient.

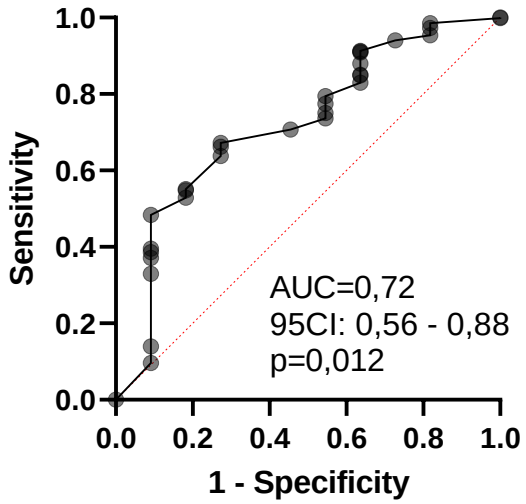

Figure 4.2. Parameters of the probabilistic model for predicting the occurrence of status epilepticus, based on the parameters identified to be the most relevant from a predefined list (depressed state; structural abnormality on MRI image; discontinuation of antiepileptic treatment; confusional state after epileptic seizure).

Subsequently, its predictive performance was tested and expressed in terms of the ROC curve, the parameters of which are shown in Figure 4.2. Since each of the four parameters made a significant contribution to the predictive ability of the final model, without showing collinearity between them, the final formula includes all of them (formula 4 and 5).

$$P(e\_stat) = \frac{e^{2,37+DEP^{0,59}+RMN^{0,76}+ATAE^{0,1}+CON^{1,23}}}{1+(e^{2,37+DEP^{0,59}+RMN^{0,76}+ATAE^{0,1}+CON^{1,23}})} \quad (4)$$

$$P(e\_stat) = \frac{0,97+0,64+0,68+0,52+0,77}{1+(0,97+0,64+0,68+0,52+0,77)} = 0,78 \quad (5)$$

4.3. Model predicting the development of resistance to antiepileptic drug treatment

For the construction of the model predicting the onset of resistance to antiepileptic medication over time, 8 out of 10 parameters were selected. The value of the logistic regression analysis for them is shown in Table 4.3.

Table 4.3. Multiple logistic regression parameters for the onset of antiepileptic drug resistance in patients over time, calculated on the basis of clinical indicators shown to be relevant.

Parameters	β (SE)	OR (95CI)	VIF	R^2	Mean Probability
Interceptor (β0)	0,78 (0,34)	2,19 (1,13 – 4,32)	-	-	69%
A (β1)	0,06 (0,24)	1,06 (0,67 – 1,70)	1.046	0.04	52%
B (β2)	0,75 (0,26)	2,11 (1,2 – 3,50)	1.066	0.06	68%
C (β3)	0,68 (0,26)	1,97 (1,20 – 3,30)	1.095	0.09	66%
D (β4)	-0,34 (0,25)	0,71 (0,43 – 1,17)	1.075	0.07	42%
E (β5)	0,24 (0,25)	1,28 (0,78 – 2,08)	1.127	0.11	56%
F (β6)	-0,43 (0,77)	0,65 (0,15 – 3,42)	1.039	0.04	39%
G (β7)	0,16 (0,25)	1,17 (0,71 – 1,91)	1.049	0.05	54%
H (β8)	-0,001 (0,001)	0,99 (0,99-1,00)	1.068	0.06	50%

Note: A – anxiety; B – depression; C – structural abnormality on MRI image; D – discontinuation of antiepileptic treatment ;E - epileptic seizure lasting more than 6 minutes ; F- status epilepticus; G – Confusional state after epileptic seizure; H – frequency of epileptic seizures; VIF – variance inflation factor; R^2 – multiple correlation coefficient.

As collinearity phenomena and modest contributions to the performance of the final model were identified, only 3 remained in the final version: the presence of depression in the patient, the presence of a brain lesion on the MRI image and the annual frequency of epileptic seizures. Model performance is expressed by the ROC curve (Figure 4.3). Of note, the probability of the installation of resistance over time to antiepileptic medication is almost directly proportional to the annual seizure frequency (Figure 4.4). This dependence makes for variable model performance - the higher the annual frequency of epileptic seizures, the higher the probability of installing resistance (formulae 6 and 7).

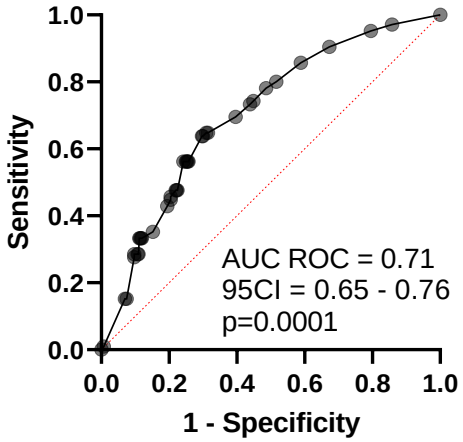

Figure 4.3. ROC curve of cases of epilepsy resistant to antiepileptic treatment by annual number of epileptic seizures.

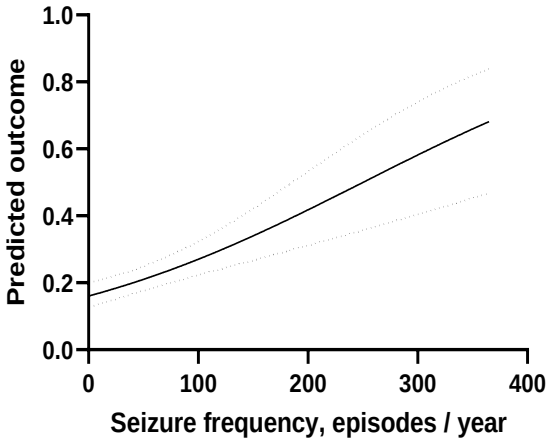

Figure 4.4. Probability of developing resistance to antiepileptic drug treatment as a function of the annual number of recorded epileptic seizures.

$$P(AErez) = \frac{e^{1,16+DEP^{-0,21}+RMN^{-0,92}+FREQ^{-0,01}}}{1+(e^{1,16+DEP^{-0,21}+RMN^{-0,92}+FREQ^{-0,01}})} \quad (6)$$

$$P(AErez) = \frac{3.19+0.81+0.40+0.99}{1+(5.39)} = 0.84 \quad (7)$$

4.4. Model predicting stable epilepsy remission

The last model developed, according to the methodology described above, was the prediction of stable remission of epilepsy. The model efficiency parameters are expressed in terms of the ROC curve (Figure 4.5). The four parameters (absence of depression, absence of brain lesions on MR imaging, onset of the disease at more than 10 years) give a prediction with a probability of 87% (formulas 15, 16).

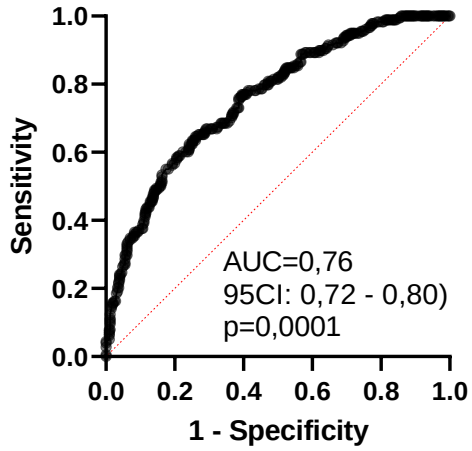

Figure 4.5. The parameters of the probabilistic model for predicting the duration of epileptic seizure recovery, based on the parameters identified to be the most relevant, described in Table 4.4.

$$P(rem\_s) = \frac{e^{-0,87+DEPabs.^{1,22}+RMN^{-0,35}+DEBUT \geq 10\ ani^{0,90}}}{1+(e^{-0,87+DEPabs.^{1,22}+RMN^{-0,35}+DEBUT \geq 10\ ani^{0,90}})} \quad (15)$$

$$P(rem\_s) = \frac{0,42+3,39+0,7+2,46}{1+(0,42+3,39+0,7+2,46)} = 0,87 \quad (16)$$

Table 4.4. Comparative characteristics of own predictive models developed.

Model name	AUC ROC	PPP, %	PPN, %	Probability, %	Odds ratio
agr_1	0.69 (0.65 – 0.74)	76	58	93	13,3
agr_2	0,69 (0,64 – 0,74)	74	61	86	6,2
agr_s	-	-	-	86	6,2
e_stat	0,72 (0,56 – 0,88)	98	NA	78	3,5
rez_1	0,72 (0,56 – 0,88)	83	62	96	24,0
rez_2	0,74 (0,69 – 0,79)	83	59	96	24,0
AErez	-	-	-	84	5,3
remision	0,76 (0,72 – 0,80)	65	75	90	9,0
rem_s	-	-	-	87	6,7

Table 4.4 provides a summary of the comparative characteristics of all the own predictive models developed. Note the similar characteristics, determined by the natural limits of sensitivity and specificity of the clinical, neurophysiological and imagistic parameters used.

5. SUMMARY OF RESULTS

The research data established that by using the method of predictive mathematical models, in which specific clinical, neurophysiological and imaging characteristics of epilepsy in women of reproductive age, identified during 5 years of follow-up and the period of seizure onset, were applied, based on the clinical-instrumental investigations carried out, documented and monitored, it becomes possible to find an answer regarding some possible scenarios of disease evolution. This method involves taking into account simple, reproducible indicators (clinical, EEG and MRI) which can be included in a mathematical model for estimating probability. Summarising the work carried out to develop predictive models, we can highlight the main points:

1. Primary data (clinical, EEG, MRI) was digitized and the database was imported into GraphPad Prism, v. 9 trial statistical analysis software (Graph Pad Software, Boston, USA). Data were analysed both in terms of age categories of disease onset (3 groups, group 1 - 0.11 years; group 2 - 12-18 years; group 3 - 19-49 years) and in terms of time course of disease (visits 1-4). From these perspectives, the clinical, electrophysiological and imaging features of epilepsy were characterized, and the differences between the groups were estimated using the Fisher test or, where appropriate, the extended Mantel-Haenszel test. After systematizing the results and obtaining the general characteristics, a correlational analysis (Pearson's r-test) was performed between clinical parameters and those of instrumental examinations. The given analysis allowed the identification of clinical-neurophysiological and clinical-imaging correlations that are statistically and clinically significant.
2. The characteristics that entered the final probability calculation formula based on multivariate analysis were selected. Testing for multicollinearity (variance inflation factor calculation) and the contribution of each parameter in the formula using the Akaike informativeness criterion allowed the final formula to be simplified without losing its properties. Thus, out of the 370 unique parameters, which were recorded in the 159 patients enrolled in the study and at each annual conclusive visit (total of 4 conclusive visits, annually), 10 parameters were finally selected for multivariate analysis, considered relevant for predicting clinically significant outcomes. Relevance criteria were: reaching a $p \leq 0.1$ in univariate analysis, can be easily identified and recorded, or were also mentioned in the literature.
3. The features, on the basis of which the probabilistic mathematical models were constructed were: (1) age of onset of illness (by age categories, at 10, 20 and 30 years); (2) poor adherence to prescribed antiepileptic treatment; (3) presence of a brain lesion on brain MRI examination; (4) prolonged state of confusion after the seizure (postictal sign); (5) focus of activity on electroencephalography without seizure symptoms; (6) anxiety; (7) depression; (8) duration of seizure over 6 minutes; (9) status epilepticus event; (10) seizure frequency (discrete quantitative variable).
4. The probabilities were calculated according to the formula: $P = \frac{e^{\beta 0 + \beta 1X}}{1+e^{\beta 0 + \beta 1X}}$ (2.1). For each individual model, the final number of remaining parameters were selected according to the results of the collinearity test, the variance inflation factor (VIF) and the Akaike informativeness criterion. All analysis was performed using Graph Pad Prism software, version 9 trial. Within the models, the calculation of probabilities was performed using the formula (2.1), where (eβ0) represents the value of the intercept, and (β1X, as appropriate - β2X2 and so on) - represents the contribution of each parameter to the final probability of occurrence of the outcome event. For practical convenience, the same results were also reflected by Odds ratios.
5. The possible patterns of disease progression specified in the present research are: 1) worsening of the disease over time; 2) stable remission of the disease; 3) resistance to antiepileptic drugs; 4) risk of progression to status epilepticus.

6. GENERAL CONCLUSIONS

1. The important scientific problem solved in the paper was the characterization of the interrelationship in time between clinical, neurophysiological (EEG) and imaging (brain MRI) manifestations of epilepsy in women of reproductive age, with the development of predictive mathematical models for the four possible scenarios of disease progression. Thus, the data of their own research found that the prevalences of each type and subtype of EC, both in terms of age of onset of the disease and its evolution over time, had a stable prevalence and correlation between them ($\chi2=1.16$; $p=0.997$). Only the prevalences of CEDFCA ($\chi2=18.6$; $p=0.005$), generalized EC (i.e., absences) ($\chi2=67.5$; $p=0.0001$) and CEFBTC ($\chi2=20.34$; $p=0.016$) changed significantly.
2. Correlation between seizure type and electroencephalographic pattern according to age of onset or progression of the disease showed a strong relationship (Pearson's $r \geq 0.6$) between generalized EC and the 3 Hz/sec slow spike-wave complex for the 19-49 age group and for generalized epileptic activity for the 12-18 age group.
3. A fost stabilit, că scleroza de hipocamp și atrofia cerebrală au fost cele mai frecvente leziuni cerebrale care au corelat cu debutul CE la vârstă precoce a pacientelor. Odată cu vârsta, proporția pacientelor fără leziuni cerebrale identificabile la RM a crescut la jumătate (47,6%; $\chi^2=50,7$, $p=0,0000$). Corelația dintre simptomatologia clinică și RM cerebrală a fost slabă (r^2 Pearson $\leq 0,3$), atât din punctul de vedere al vârstei de debut al maladiei, cât și a evoluției ei în timp, cu excepția unei corelări de grad mediu (r^2 Pearson până la 0,48; 95%CI = 0,24-0,49, $p=0,0001$) dintre scleroza de hipocamp și CEDFCP, și CEDFCA.

4. Our own research established that a maximum prevalence (~50%) had the average duration (31 sec - 5 min) of EC. The prevalence of short (under 30 sec) and long (over 11 min) EC durations decreased significantly ($\chi2=17.64$; $p=0.00001$ and $\chi2=63.9$; $p=0.0001$, respectively) with increasing age of onset of illness. Antiepileptic treatments significantly reduced only the previously longer EC durations (starting at 6 min and longer) ($\chi2=107.7$; $p=0.0001$).

5. Based on the results obtained, predictive models were developed for the 4 likely scenarios of disease evolution. Thus, our own research has established that the most important predictive parameters of the evolution of the disease are: (a) post-cardiac confusional state; (b) reduced adherence to antiepileptic treatment; (c) EC duration longer than 6 minutes; (d) depressive state; (e) structural changes in brain MR, in particular, hippocampal sclerosis and cerebral atrophy and (f) age of onset of the disease from 10 years onwards. Proprietary probabilistic predictive models developed allowed prognosis: (a) worsening of status in dynamics (AUC ROC = 0.69; 95%CI = 0.64-0.74; OR = 6.2-13.3); (b) risk towards progression of status epilepticus (AUC ROC = 0.72; 95%CI = 0.56-0.88; OR = 3.5); (c) development of resistance to antiepileptic medication (AUC ROC = 0.74; 95%CI = 0.69-0.79; OR=5.3-24.0); disease remission (AUC ROC = 0.76; 95%CI = 0.72-0.80; OR=6.7-9.0).

7. PRACTICAL RECOMMENDATIONS

1. It is proposed to use a standardised primary consultation form or follow-up visit to check for the presence or absence of a particular feature from a set of signs and symptoms of seizures.

2. It is recommended to systematically identify the causes, such as anxiety, depression and specific barriers (territorial and financial accessibility, presence of the specialist, and possibility of investigations, etc.), which would lead the patient to abandon antiepileptic treatment.

3. It is recommended to develop a monitoring logbook for epilepsy patients (preferably electronic) to document the presence, absence or dynamics of symptoms, depending on treatments, triggers, circumstances and personal events.

4. Based on the results obtained, predictive modelling is recommended in order to estimate the risk of developing clinically important events, to inform the patient and to apply preventive measures as appropriate. For a quick and easy estimate:

    (a) Patients who have epileptic seizures lasting 6 minutes or longer, followed by confusional states and who have discontinued antiepileptic treatment on their own, are 6-13 times more likely to worsen in dynamics compared to patients who do not exhibit these characteristics.

    b) Patients who have signs of depression, have discontinued antiepileptic medication on their own, have confusional states after seizures and have documented structural lesions on MRI (in particular hippocampal lesion, brain atrophy), have a 3.5 times higher risk of entering status epilepticus.

    c) Depressed patients with documented structural lesions on MRI (in particular, hippocampal lesion, brain atrophy), and a high frequency of epileptic seizures, have a progressive, significant (5.3-24.0-fold) risk of developing resistance to antiepileptic drugs.

    d) Patients without depressive symptoms, without structural brain lesions in the MRI and in whom the illness started at an age of more than 10 years have a 6.7-fold higher chance of achieving a lasting remission of the illness.

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LIST OF ABBREVIATIONS

AED - diffuse epileptic activity
AIC(c) - Akaike informativeness criterion (with correction**)**
ANOVA - analysis of variance (statistical test)
AUC - area under the curve
CE - epileptic seizures
CEDFCA - epileptic seizure with focal onset and impaired consciousness
CEDFCP - epileptic seizure with focal onset and preserved consciousness
CEG - generalized epileptic seizure
CSUL - "spike-slow wave" complex
CT - computed tomography
MAE - antiepileptic medication
EEG - electroencephalography
ERM - drug-resistant epilepsy
FEB - multifocal epileptic focus
FED(S) - epileptic focus on the right (on the left)
HV FS - voluntary hyperventilation and photostimulation test
ILAE - International League Against Epilepsy
AVM - arteriovenous malformation
ML - machine learning
MVS - support vector machine
OR - Odds ration
PPN - negative predictive power
PPP - positive predictive power
MRI - magnetic resonance
ROC - receiver operator characteristics
SDC - clinical decision support tool
SE - status epilepticus
SE - standard error
TDO - disorganized EEG pathway
TO - organized EEG track
VIF - variance inflation factor (test statistic)

DUCA Victoria

EPILEPSIA LA FEMEI DE VÂRSTĂ REPRODUCTIVĂ.
STUDIU CLINIC, IMAGISTIC, ELECTROENCEFALOGRAFIC

EPILEPSY IN WOMEN OF REPRODUCTIVE AGE.
CLINICAL, IMAGISTIC, ELECTROENCEPHALOGRAPHIC STUDY

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321.05 – CLINICAL NEUROLOGY

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