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PH.D. THESIS

BIOMARKERS, FUNCTIONAL EXPLORATION, and GENOTYPE-PHENOTYPE CORRELATIONS (SCN1A GENE SEQUENCING) in FEBRILE SEIZURES in CHILDREN SUMMARY

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Content

APPENDIX

- DNA = deoxyribonucleic acid
- FH = family history
- ASLO = antistreptolisin O antibodies
- BBB = blood-brain barrier
- Ca = calcium
- FS = febrile seizures
- CFS = complex febrile seizures
- SFS = simple febrile seizures
- MCHC = mean corpuscular hemoglobin concentration
- Cl = chloride
- EEG = electroencephalogram
- SAP = serum acid phosphatase
- GEFS+ = genetic epilepsy with febrile seizures plus
- Hb = hemoglobin
- HCO_3^- = bicarbonate
- MCH = mean corpuscular hemoglobin
- IL = interleukin
- IL-R = interleukin receptor
- IL –Ra = interleukin receptor antagonist
- MRI = magnetic resonance imaging
- K = potassium
- Ly = absolute number of lymphocytes
- Na = sodium
- pCO_2 = partial pressure of carbon dioxide
- CRP = C-reactive protein
- PCT = plateletcrit

- PDW = platelet distribution width
- pH = hydrogen potential
- P-LCR = platelet large cell ratio
- PLT = platelets
- EVP = endovenous perfusion
- RBC = red blood cells
- RDW = red cell distribution width
- RDW- CV = red cell distribution width – coefficient of variation
- RDW- SD = red cell distribution width – standard deviation
- NLR = neutrophil / lymphocyte ratio
- CNS = central nervous system
- SNP = single nucleotid polymorphism
- SNV = single nuclotid variant
- T^0 = temperature
- AST = aspartate amino transferase (oxalic glutamic transferase)
- ALT = alanine amino transferase (pyruvic glutamic transferase)
- TNF = tumor necrosis factor
- MCV = medium corpuscular volum
- MPV = medium platelet volume

INTRODUCTION

The study of febrile seizures, the most common types of seizures, is a continuous and current concern.

The awareness of a particular and persistent inflammatory process in the pathogenesis of FS possibly involved in promoting epileptogenesis arouses the special interest of researchers.

In this sense, the study of these mechanisms and the identification of new predictive potential biomarkers for recurrence or epilepsy are not only attractive research concepts but also essential elements for individualized therapy of patients.

The anxiety-inducing potential of FS for the entourage, concerning the risk of recurrence and/or epilepsy, the potential impact on cognitive and behavioral status, further motivate the complex approach to FS and promote the interest of researchers.

In addition, if some biomarkers have been researched as individual factors for prognosis and differentiation of FS types, the innovation element of the study is their interdependent approach and evaluation.

Another window of opportunity was represented by the identification of certain anamnesis and clinical features and biomarkers in the case of the first FS, relevant both for the pathogenesis of FS and for their prognosis.

Moreover, we aimed at the integration in clinical practice of SCN1A gene mutations, in individualized cases, from the perspective of the diagnostic, therapeutic approach and the prognosis.

At the same time, I aimed to highlight the effect of SCN1A gene mutations in association with phenotypes other than Dravet and the correlations between mutation type and phenotype.

In the GENERAL PART, the **first chapter** contains details about the history, updated definitions, epidemiological data, etiopathogenetic mechanisms in febrile seizures, a particular interest being addressed to risk factors for recurrence of FS, epilepsy or comorbidities, all elements that constitute the research premises.

Febrile seizures are systemic, multifactorial events, secondary to the interaction between 1.) the genetic factors determining the alteration of the inflammatory response, hypothalamic thermoregulation, respectively of the cortical hyperexcitability and, 2.) between the precipitating environmental factors of the infectious-inflammatory context, represented mainly by viral infections with neurotrophic properties, promoting inflammation or metabolic imbalances [453]. The results of studies on the involvement of oligoelements in promoting FS are contradictory [314, 356].

Literature data support the complex interaction between the central nervous system, the vegetative nervous system, endocrine and immune mechanisms in the genesis of febrile seizures. Studies place certain IL-gene polymorphisms, the imbalance between prostaglandins and cytokines involved in both fighting infection and pathological inflammation (predominantly IL-1β) and anti-inflammatory cytokines (predominantly IL-1RA), the alteration of blood-brain barrier and imbalance in neuroinhibition in the etiopathogenesis of FS. At the same time, neuroinflammation, secondary to altered blood-brain barrier and activation of the inflammatory cascade, is incriminated in epileptogenesis associated with prolonged febrile seizures, therefore placing the recurrence of FS in association with an increased risk of comorbidities [453, 422].

In **the second chapter**, the focus is on the impact of the SCN1A gene in medical practice, starting from details on the structure and function of the SCN1A gene and the encoded Nav1.1 channels, continuing with the phenotypes associated with the SCN1A gene and genotype-phenotype correlations and concluding with details on the impact of genetic diagnosis in optimizing therapy and prognosis.

The clinical picture secondary to the alteration of the function of Nav1.1 channels in the CNS varies from epilepsy [659], mesial sclerosis [658], movement disorders, gait and posture abnormalities [138, 183, 221, 302, 479, 601, 700], migraine [181, 211, 299], alteration of cell proliferation and tumor migration [295, 372, 684, 701], autism [53, 261, 376, 563], mental retardation [43, 604, 691], Alzheimer's dementia [420], sleep disorders / circadian rhythm or thermoregulation, up to cardiac arrhythmias and sudden death syndrome in epilepsy [213, 245, 303, 431, 504, 198]. Psychiatric comorbidities have varied clinical expression from stereotypical behavior, social integration disorders, to spatial memory deficiencies and attention deficit [213, 539].

Pathogenic variants of SCN1A have been documented in a wide range of epileptic syndromes and especially with severe childhood myoclonic encephalopathy (Dravet syndrome). Mutations in the SCN1A gene have autosomal dominant inheritance, with

incomplete penetrance and variable expressiveness [216]. In general, mutations with protein truncation and missense mutations in the pore-forming regions of sodium channels are determinants of a severe phenotype (Dravet syndrome) therefore that missense mutations in other regions are more frequently associated with the spectrum of FS-FS plus- Genetic Epilepsy with FS plus [137, 246, 416, 418]. However, the predictive value of the type of mutation for the severity of the phenotype has not been confirmed, probably due to other modifying genes and the polygenic determinism of the FS-FS plus-Dravet spectrum [203, 418, 459].

The SPECIAL PART includes four chapters dedicated to personal research, respectively aspects related to the motivation, objectives and methodology of the research, the results and discussions of the study and finalizing with the conclusions and the global evaluation of the research project.

PERSONAL RESEARCH

Motivation

The present research aimed both the individual evaluation and especially, as an element of innovation, the interdependent evaluation of the inflammatory, metabolic, martial and electroencephalographic context as differentiating factors between FS types and as risk factors for FS recurrence, as well as the identification of certain anamnesis and clinical features and biomarkers for first FS relevant to their pathogenesis. The study aimed to identify easy, cost-effective biomarkers that would require minimally invasive maneuvers with practical applicability for establishing risk models and for prognosis.

If some biomarkers have been researched as individual factors for prognosis and differentiation of FS types, their interdependent approach and evaluation have not been performed so far.

This window of opportunity was decisive in choosing the research topic.

On the other hand, in the second part of the study, the integration of FS in a new concept, of the FS-FS plus-Dravet syndrome spectrum, the perspective of identifying new mutations of the SCN1A gene with the FS-FS plus-Dravet spectrum or with other types of epilepsy not yet associated with this gene and current trends in individualized therapy based on genomic

factors, have been a strong motivation for research. Gene exploration of subjects with the FS-FS plus-Dravet phenotype could have practical applicability in the early optimization of antiepileptic therapy and the improvement of late prognosis (both for seizures and for possible comorbidities).

The main objectives of the research were represented by:

• complex, individual and interdependent assessment of the inflammatory, metabolic, martial and electroencephalographic context as factors of discrimination between FS types and as risk factors for late recurrence;
• identification of the presence of SCN1A mutations in association with phenotypes other than Dravet and of correlations between the type of mutation and the phenotype;
• highlighting the differences between the efficiency of the SCN1A sequencing in the case of subjects with a typical phenotype associated with SCN1A mutations (FS-FS plus-Dravet spectrum) and in the case of subjects with another phenotype;
• identification of genetic testing criteria relevant to the etiological diagnosis involving the patient and his family, including aspects related to prognosis, family planning and therapeutic intervention.

As secondary objectives, we aimed to identify certain anamnestic-clinical features and biomarkers in the case of the first CF, relevant both for the pathogenesis of CF and for their prognosis.

Methodology

I proposed and performed a prospective study conducted in the Sibiu Pediatric Clinical Hospital, between October 2013 and January 2019.

Patients were included in the study in 2 stages, following the objectives of the study stated above.

In the first stage exclusively subjects with FS were included in the study represented by 208 hospitalized children with 305 FS. In the second stage, 54 subjects with FS-FS plus-Dravet phenotype and 25 subjects with other epilepsy phenotypes and history of fever-induced seizures were selected and included in the study group.

All patients with a history of febrile seizures were included in the study.

In the first stage of the study, the following patients were excluded from the study group: patients with CNS infections, with possible traumatic and metabolic causes suggestive of symptomatic acute seizures, patients with a history of unprovoked seizures, those with more than 2 hours postictal laboratory samples, who received pharmacological treatment and/or ENP with the potential to change the metabolic status, those who received emergency antiepileptics who modified the EEG trace or who underwent laboratory tests with different reference values in another medical unit.

From the second stage of the study (study group with SCN1A sequencing) were excluded patients who did not meet the quality criteria of DNA extraction.

In the first stage of the study, the entire study group included 208 patients with 305 seizures divided into study group and control group according to the rank of the seizure, the FS type and the presence of FS recurrence.

In the second stage of the study, 79 subjects who benefited from SCN1A sequencing were integrated into the whole study group, distributed in the study group and control group according to the presence of SCN1A mutations and phenotype.

Finally, the following groups resulted: study group that included patients with first FS (196 cases), compared to a control group with patients with other FS rank (109 cases); study group including patients with complex first febrile seizures (CFS) (30 cases) compared to patients with first simple febrile seizures (SFS) (166 cases); study group that included CFS patients (69) compared to SFS patients (236 seizures) from the total number of patients admitted; study group with first FS with late recurrence (82 seizures) compared to first FS without late recurrence (114 seizures); study group with SCN1A mutations (68 subjects) compared to a control group without SCN1A mutations (11 subjects) and study group dedicated to patients who benefited from SCN1A sequencing with phenotype from the FS-FS plus-Dravet spectrum (54 subjects) and group control consisting of patients with other phenotypes (25 cases).

In the first stage of the study for the whole group of subjects with FS, the anamnestic, clinical, biological and electroencephalographic evaluations were performed.

The anamnestic-clinical evaluation allowed the collection of data related to the family history of FS, epilepsy or diabetes, personal physiological and pathological history (ante-, peri- and postnatal: evolution of pregnancy, gestational age, type of birth, Apgar score, birth weight, days of hospitalization in maternity), and also allowed assessments on nutritional status, the neurological status of patients, psychomotor development, psychiatric

comorbidities and details about the febrile-critical context (etiological classification of the disease-causing fever, body temperature at the time of seizure, interval from the onset of the fever to the onset of the FS and the clinical aspect of the FS, the classification of the FS (CFS / SFS), the clinical pattern of patients with complex febrile seizures), the length of hospitalization as an indicator of the severity of the disease.

The biological evaluation aimed at determining / dosing inflammatory parameters (CRP, NLR, platelet count, PCT, MPV, PDW, P-LCR), metabolic (pH, pCO_2, HCO_3^-, lactate, blood glucose, electrolytes - Na, K, Cl, ionic Ca, ASLO) and martial (RBC, Ht, Hb, MCV, MCH, MCHC, RDW-SD, RDW-CV, serum iron, ferritin). The following methods of determination were used: for CRP, ASLO immunoturbidimetric method, for other biochemical parameters (ALAT, ASAT, urea, creatinine, glycemia, calcium, ALP, etc.) the spectrophotometric method or analysis by dry biochemistry, for full blood count and flow cytometry, for the ionogram the potentiometric method ISE directly.

In the second stage of the study, the general, anamnestic-clinical, electroencephalographic and imaging parameters pending the genetic study were represented by age, gender; phenotype and defining characteristics for phenotypic classification, respectively family history of FS or epilepsy, age and aspect of the first seizure, the interval between the first seizure and recurrence, personal history of febrile seizures, neurological status before the onset of seizures and dynamics, EEG appearance at first seizure and in dynamics, brain MRI anomalies, reactivity to the regimen or drug resistance and prognosis.

The genetic exploration involved sequencing SCN1A with the nomination of the type of genetic variant depending on the impact on the protein sequence (missense, frameshift), the effect on structure (deletion, insertion and SNV), prediction of pathogenicity: probably pathogenic, possibly pathogenic and benign.

Genomic DNA was extracted from leukocytes in peripheral blood using an automated robotic DNA isolation system, using the MagCore Super HF 16 nucleic acid extractor and the MagCore Genomic DNA Large Volume Whole Blood extraction kit. The amplification of the 26 exons covering the coding regions of SCN1A and the intron-exon binding areas by polymerase chain reaction (PCR) was performed, followed by the cyclic sequencing on both chains, exclusively exonic, using the MiSeq sequencing system and the MiSeq research (Illumina, San Diego, CA, USA). The classification of the variants was performed according to the annotated and updated ACMG criteria (American College of Medical Genetics, 2015) [538].

Statistical analysis

In the data analysis process, for the variables under study, multiple elements of descriptive statistics were determined and statistical tests were used taking into account the level of significance/probability of error $p < 0.05$.

In the case of quantitative data, the normality of the data was first determined, using Shapiro-Wilk, Kolmogorov-Smirnov tests, histograms, QQ plot charts, and skewness (asymmetry) and kurtosis (excess) shape indicators. Depending on the distribution and the variant (Levene test) we applied parametric tests (Gaussian distribution) such as Student t-test (for equal variants) and Welch's t-test (for equal or unequal variants), both for independent samples and for paired samples, or nonparametric tests - Mann-Whitney test, respectively for more than two groups, the ANOVA analysis of variance test and the Kruskal-Wallis test were used.

To highlight groups that differ on average, we used Dunn-Bonferonni post-hoc analysis as a multiple comparison technique.

In the case of qualitative data, contingency tables were used, the data is analyzed using the Pearson-chi-square test or the Fisher test to verify the existence of a relationship/association between variables (qualitative). Z-tests with Bonferroni correction were performed to detail the results obtained after the contingency tables [404, 443]. To detect changes in the EEG appearance in the dynamics we used the McNemar test, which verifies the significance of the difference between two dependent samples when the variable is a dichotomous one.

In the associative analysis of the data, the following coefficients were calculated: the Pearson correlation coefficient (r) [404, 443], for dichotomous variables the / nominal Phi / Cramers V coefficients, and for ordinal variables the nonlinear association coefficient.

To predict the occurrence of late recurrence we used the logistic regression model, in which we integrated all laboratory parameters from the study that individually had a significant association with the change in the frequency of late recurrence.

Decision trees generated by the CRT (Classification and Regression Tree) method were used to study the interconnections between different markers [252].

After the individual analysis of the laboratory parameters, we used the two-step grouping procedure, in the exploratory mode, to identify subgroups of patients with FS based

on the association of the most frequently used metabolic, inflammatory and defining markers for anemia status.

Graphical representation of the analyzed data was performed using histogram diagrams, or boxplot [404, 443]. Statistical analysis was performed using IBM SPSS Statistics 25 and Microsoft Office Excel / Word 2013.

Results and discussions

Regarding the group of first FS compared to the group of recurrent FS, we found that the group with first FS is characterized by:

- lower percentages of seizures triggered by Tº less than 38ºC and higher percentages of seizures lasting between 5 and 14.9 minutes;
- significantly lower median values of CRP, NLR, MCV, MCH and HCO_3^- and higher absolute number of lymphocytes;
- lower percentages of those with low PDW values and mild hypokalemia, respectively higher percentage of those with microcytosis;
- a higher percentage of clusters defined by iron deficiency anemia using as segmentation variables: Hb + MCV + MCH + MCHC or MCV + RDW-CV;
- relatively higher chance than in the case of recurrent FS to fit in the cluster defined by the normal median values of CRP and NLR.

The association of the first FS with moderately high values of CRP, respectively significantly lower median values of CRP, the higher risk of inclusion in the cluster defined by normal median values of CRP and NLR and lower percentages of subjects with low values of PDW compared to recurrent FS, indicates a distinct inflammatory pattern probably correlated with the genetically determined low seizure threshold.

About the statistically significantly higher absolute number of higher lymphocytes respectively lower NLR in the group with first FS may be related to an increased inflammation dependent on neutrophils and on a lymphocyte-mediated anti-inflammatory response, both with probable genetic determinism, although the complex underlying mechanism has not been fully elucidated [262, 386].

The higher percentage of subjects with iron deficiency anemia in the group of first FS could on the one hand suggest the involvement of iron in the etiopathogenesis of FS through its function in neurotransmission, neural metabolic activity and immunity, and on the other

hand, it can be explained by the concordance of the maximum incidence age of iron deficiency anemia with that of the first FS [217, 240, 314].

Regarding the first CFS group compared to the first SFS group, we found that the first CFS group is characterized by:

- ❖ statistically significantly higher values of the duration of hospitalization, higher percentages of subjects with a family history of epilepsy and lower frequency of seizures occurred in sleep;
- ❖ higher percentages of subjects with stress hyperglycemia, the probability of identifying a first CFS being higher in the case of these subjects than in the absence of stress hyperglycemia;
- ❖ significantly higher percentages of the first CFS in the clusters defined by the presence of stress hyperglycemia compared to the other clusters;
- ❖ significantly higher median values of serum iron level and lower probability of low serum iron level.

The statistically significantly higher percentages of subjects with early CFS and stress hyperglycemia supports seizure activity as the main risk factor for stress hyperglycemia, but the exact contribution of FS activity or febrile/infectious context in the genesis of stress hyperglycemia remains uncertain. The results are consistent with data from the literature that associate stress hyperglycemia with prolonged seizures [368].

Statistically significant differences were identified between the degree of fever and the aspect of FS, both in the group of first FS and in the whole study group of FS: CFSs are predominantly precipitated by Tº between 40-41ºC, and SFS by Tº between 39-40ºC.

The percentages of first CFS were significantly higher in the cluster characterized by the highest median values of PDW and the lowest median values of PLT compared to the clusters defined by:

- ❖ median values of PDW by the lower normal limit and increased PLT values;
- ❖ low median values of PDW and normal median values of PLT;
- ❖ median values of PDW and normal PLT;

respectively in the case of subjects with inflammatory status defined by the highest median values of PDW, the lowest values of PLT (both within physiological limits), the highest median values of P-LCR (towards the upper limit of normal) and moderate increased CRP median values, suggestive of platelet activation.

If individually the platelet parameters have been the subject of a small number of studies aimed at differentiating FS types, the integrated "clustering" analysis offers a new perspective including the relationship with the inflammatory cascade in the case of CFS versus SFS.

Regarding the CFS group versus the SFS group, the CFS are characterized by:

- ❖ higher values of hospitalization duration, higher percentages of subjects with a family history of epilepsy and lower frequency of seizures in sleep;
- ❖ higher percentages of subjects with stress hyperglycemia which determines a higher probability of identifying a CFS in the case of these subjects than in the absence of stress hyperglycemia;
- ❖ lower percentage of subjects with normocalcemia;
- ❖ higher risk of an FS to be complex if the seizure occurs in less than an hour than in more than an hour from fever onset

The percentage of CFS was significantly higher in the cluster characterized by normal median values of platelet indices (PLT, PCT, P-LCR, MPV, PDW), slightly increased CRP and NLR compared to the cluster characterized by normal median values of PLT and PCT, low MPV, towards the lower limit of PDW, slightly higher CRP and NLR, results that reveal a distinct inflammatory pattern of FS depending on their type.

Although we did not identify statistically significant differences between the individual acid-base parameters to the FS type, we found a higher percentage of patients with acidosis in the CFS group, possibly due to the longer duration of the seizure.

Regarding the group of first FS with late recurrence versus the group of first FS without late recurrence, the present study reconfirms the known risk factors for FS recurrence: low age, family history of FS, the time interval between fever onset and seizure less than one hour and low degree of Tº [587].

The late recurrence group is characterized by median values: lower CRP and pH, respectively higher pCO_2 and ionic Calcium.

In the differentiation of subjects at risk of late recurrence, moderately increased cut off point values of CRP were identified, pH cut off values pH at the limit between mild and moderate alkalosis, pCO_2 at the limit of mild/moderate hypocapnia, lactate values at the threshold of severe hyperlactatemia and lactic acidosis and cut off point of 170mg / dL for blood glucose, compatible with stress hyperglycemia.

The combined analysis of demographic and anamnestic-clinical parameters by decision trees showed that:

- the strongest risk indicators for recurrence are T^0 for the age category greater than or equal to 20 months and family history of FS for the age of less than 20 months;
- in the absence of a family history of FS, T^0 is a stronger recurrence risk factor for SFS than for CFS;
- in the presence of febrile seizure family history and T^0 less than 38 C^0, CFS was a stronger risk factor for recurrence;
- for both types of seizures the late recurrence was indirectly proportional to the time interval between fever onset and seizure, and T^0;
- the model of association T^0 with a family history of FS and time interval between fever and seizure is the best in assessing the risk of late recurrence;

About the inflammatory status, the risk of late recurrence was significantly higher in the cluster (2) defined by normal median values of CRP and lower values of NLR than in cluster (1) with increased median values of CRP and higher NLR values; the number of FS recurrences was significantly higher for subjects in cluster 2 compared to those in cluster 1.

The risk of late recurrence was significantly higher in cluster 2 defined by normal median values of CRP, elevated PCT, slightly lower RDW-SD and median NLR lower than in cluster 1 defined by elevated median CRP and PCT, normal RDW-SD and higher NLR values.

Regarding metabolic status, the risk of late recurrence was significantly higher in the cluster with a compensated respiratory alkalosis (normal median pH values, moderately low pCO2 and slightly low HCO_3^-) versus the cluster with a decompensated respiratory alkalosis (high median values of pH, severely low pCO_2 and slightly low HCO_3^-).

The risk of late recurrence was significantly higher in the cluster (1) with compensated respiratory alkalosis, moderate hyperlactatemia and the tendency to stress hyperglycemia compared to cluster (2) with decompensated respiratory alkalosis with hyperlactatemia and mild hyperglycemia

Using decision trees to identify patterns of risk of recurrence related to the metabolic status and EEG appearance we found the maximum risk of late recurrence for the association of early epileptiform abnormalities (EEG) with the cluster - respiratory alkalosis compensated with moderate hyperlactatemia and the tendency to stress hyperglycemia. The absence of recurrence was predominantly recorded for subjects in the cluster with

decompensated respiratory alkalosis with mild hyperlactatemia and hyperglycemia and without epileptiform abnormalities at both records.

The use of the decision tree (CRT type) allows, as an element of novelty, the identification of a risk model for the presence or absence of late recurrence depending on inflammatory parameters (CRP, NLR, PCT, PDW, RDW-SD, Fe), a model that increases and decreases in depending on the association and value of these parameters.

The results of the study are in line with data from the literature that support the strong modulation of the excitability of neural circuits by pH changes [349, 643]: increased pH being associated with neuronal hyperexcitability, seizure inhibition being facilitated by acidosis. Lower pH values, respectively higher pCO_2 values in the group with late recurrence compared to the group without late recurrence, the association of the risk of recurrence especially with the cluster defined by compensated respiratory alkalosis, moderate hyperlactatemia and the tendency to stress hyperglycemia indicate a metabolic status, particularly of subjects at risk of late recurrence. The results support the involvement of the common mechanisms of hyperlactatemia and stress hyperglycemia in promoting the recurrence of febrile seizures. Thus, in FS, abnormal synchronized discharge of neurons leads to a hypermetabolic status, a high need for oxygen and energy, promoting aerobic metabolism of blood glucose and anaerobic glycolysis. Although the mechanisms of FS are still under debate, immune activity may overlap with the counter-regulation of hormonal activity and proinflammatory status described in stress hyperglycemia. A complex interaction between fever, seizure and infection may be key, in the form of combined stressors, leading to a cumulative, synergistic interaction between proinflammatory cytokines and stress-associated hormones (interleukins, growth hormone, insulin, glucagon [413].

In addition to their important role in hemostasis and thrombosis, studies show that platelets contribute to the inflammatory process and microbial defense of the host by the release of cytokines, antibacterial peptides and microbiocidal proteins, angiogenesis and remodeling [630].

Simultaneous measurement of all platelet indices and their interdependent analysis in association with other inflammatory markers, by clustering or decision trees, can provide a valid tool for assessing disease severity and a perspective on the etiology of changes in platelet indices and prognosis.

Thus, the association of the risk of late recurrence with only moderately high values of CRP, respectively with the clusters that define a mild inflammatory syndrome, in the stage

of pre-activation or early platelet activation, suggests the importance of the genetic factor in promoting FS.

Genetic study

For the genetic evaluation, the study group included 68 subjects - with SCN1A mutations and the control group 11 subjects - without SCN1A mutations.

No significant differences were identified between groups regarding anamnestic, clinical and paraclinical data.

However, subjects in the study group compared to the control group presented: a higher percentage of family history of FS, epilepsy or FS and epilepsy; normal neurological status before and after the seizure onset; clinical picture more frequently consistent with the phenotype of FS or FS plus or Dravet vs. phenotype of FS or other epilepsies not included in the spectrum febrile seizures-febrile seizures plus-Dravet; respectively higher percentages of cases with severe phenotype.

We identified 24 distinct types of mutations and 3 other synonymous variants grouped in 1 to 4 associations in the case of one of the 79 subjects with mutations.

Thus, the most frequent mutations were: NM_001202435.1: c.4793A> T, NM_001202435.1: c.182T> C, NM_001202435.1: c.3778delA and NM_001202435.1: c.4385delA; most of the mutations were of the missense type, SNVs, with a predominantly probably pathogenic clinical significance, the rest were frameshift (deletions and insertions). Pathogenic significance was reported in approximately 45% of patients.

Most mutations are found in the spectrum FS-FS plus-Dravet, the most representative mutations being: NM_001202435.1: c.4793A> T, NM_001202435.1: c.182T> C, NM_001202435.1: c.3778delA and NM_001202435.1 : c.4385delA;

The most common SCN1A mutations in subjects with epilepsy not included in the spectrum of FS-FS plus-Dravet were: NM_001202435.1: c.4793A> T, NM_001202435.1: c.182T> C, NM_001202435.1: c.4766d and NM_001202435.1: c.1024G> C.

The mutation NM_001202435.1: c.4906dupC was identified exclusively with the FS-FS plus-Dravet spectrum.

The percentage of subjects with SNVs was similar between FS-FS plus and other epilepsies; most subjects with deletions presented FS or FS plus phenotype, and those with insertions other types of epilepsy.

Significantly more frequently, subjects with deletions had a normal EEG trace, probably in the context of identifying deletion-type mutations, mainly with the phenotype of FS or FS plus.

Significantly more frequently, insertion-type mutations were associated with a severe phenotype while deletions were more frequently associated with the absence of the severe phenotype.

We found the presence of the same mutations in association with different phenotypes (FS, FS plus, Dravet). We detected SCN1A mutations with other types of genetic epilepsy not previously associated with SCN1A: benign rolandic epilepsy of childhood with centrotemporal spikes, epilepsy pf childhood with absence seizures and idiopathic genetic epilepsy (with adolescence onset) (genetic epilepsy with grand mal seizures on awakening, juvenile myoclonic epilepsy and Jeavons syndrome);

The lower percentage of family history of FS and the higher percentage of family history of epilepsy in the study group vs. the control group, the exclusive presence of a family history of epilepsy and FS in the study group suggests the main association of SCN1A with the GEFS spectrum plus and less with familial FS, generally correlated with other types of mutations.

Although subjects with the Dravet phenotype had more frequent frameshift mutations compared to subjects with FS or FS plus, the differences were not statistically significant due to the small number of cases with the Dravet phenotype.

We found the presence of brain MRI abnormalities in a small percentage of subjects with SCN1A mutations, however, it is difficult to establish a causal relationship of SCN1A with brain abnormalities.

Phenotypic variability found by the presence of the same mutations in association with different phenotypes, FS-FS plus-Dravet, would be explained by polygenic determinism, the existence of regulatory genes or epigenetics. Genome-wide sequencing, especially in families with different phenotypes, could provide additional explanations.

In the case of family history, the higher percentage of FS in the control group compared to the study group, the lower percentage of epilepsy in the control group compared to the study group, and the presence of a family history of epilepsy and FS exclusively in the study group could be suggestive of the association of SCN1A mutations predominantly with the GEFS spectrum plus and less with familial CF, generally correlated with other types of mutations [739].

Moreover, although data from the literature associate SCN1A mutations, predominantly with FS plus-Dravet spectrum and exceptionally with FS and other types of epilepsy, in this study SCN1A mutations were present in a small number of subjects with other types of genetic epilepsy a causal relationship could have not been certainly established.

Although subjects with the Dravet phenotype had more frequent frameshift mutations compared with FS subjects and FS plus subjects, this observation was consistent with literature associating mutations with protein truncation with severe phenotype and the variability of phenotype severity with missense mutations; the differences were not statistically significant due to the low number of cases with Dravet phenotype [137, 246, 416, 418].

Currently, it is difficult to establish a determinism between mutation and the presence of MRI abnormalities (bilateral hippocampal atrophy, gliosis, suprasellar arachnoid cyst, bilateral nodular heterotopias, frontal cortical dysplasia), in the context in which the origin of structural abnormalities (cortical focal atrophy, focal dysplasia, heterotopias and hippocampal sclerosis) reported in the literature in a minority of patients with SCN1A mutations remains unclear [232].

There does not appear to be any correlation between the presence of MRI abnormalities and the duration of epilepsy, the age at the onset of seizures, or the frequency of status epilepticus episodes. The few neuropathological studies available on Dravet's syndrome have provided inconsistent findings, including evidence of subtle brain malformations. However, the basic dysfunction of the SCN1A gene could give the brain a unique vulnerability profile whose consequences are not easily revealed by neuropathology and require specific experimental settings to be fully appreciated [232].

On the other hand, the study by Striano and colleagues in a group of patients with severe infantile myoclonic epilepsy reports MRI abnormalities more frequently in patients without SCN1A mutations [611], while Lee and the colleagues report large-scale brain changes in patients with epilepsy and SCN1A gene mutation, which may be associated with the underlying symptoms of patients [371].

Further longitudinal MRI studies with larger cohorts are needed to confirm the effect of SCN1A gene mutation on brain structural development.

Variants in the SCN1A gene are a common genetic cause for a wide range of epilepsy phenotypes, from febrile seizures to Dravet syndrome. Focal onset seizures and structural lesions may be present in these patients and the question arises as to whether epilepsy

surgery should be considered, given that data from the literature record postoperatively, in subjects with SCN1A mutations variable results and directly related to the anatomo-electroclinic phenotype of the patient Patients with Dravet syndrome had unfavorable results, and those with focal epilepsy correlated with a single structural lesion good postoperative prognosis [668].

The interpretation of the data from the genetic study was integrated into the current informational context and reported to the currently available SCN1A databases. However, the process of classifying a genetic variant is continuous and involves the identification of the genetic variant in association with a certain pathology, confirmation association through functional studies that demonstrate not only the validity of the proposed hypothesis but also that clarify the molecular mechanism.

Current data from the literature have allowed the validation of the pathogenic character of certain variants identified in this study. For the new genetic variants, the classification was performed based on the functional prediction programs, but the data validation requires the performance of functional studies and/or re-evaluation in time by reference to the updated SCN1A databases.

At the same time, to validate the pathogenicity of the mutations, it would be advisable to investigate the SCN1A of the parents, especially in cases with a family history of epilepsy and/or FS, taking into account the autosomal dominant transmission with incomplete penetrance and phenotypic variability. The investigation of the parents could be the object of a new study and would also allow the classification of the hereditary or de novo character of the mutation.

Regarding the EEG

The study supports the variability of the detection rate of EEG abnormalities depending on the time of recording, age of subjects, type of febrile seizures and types of abnormalities monitored (epileptiform and/or nonspecific), consistent with data from the literature that mentions a variable prevalence of EEG abnormalities in FS subjects, between 2% and 86% [689].

Early EEG was predominantly associated with nonspecific abnormalities and late EEG with epileptiform abnormalities stating that the timing of recording did not decisively influence the presence of epileptiform abnormalities and that nonspecific abnormalities decreased in dynamics.

The value of EEG in the differentiation of CFS from SFS is limited regardless of the time of examination although pathological EEG predominantly defined by epileptiform abnormalities (frontal or central) is more common in the CFS group.

Regardless of the time of recording, pathological EEG defined by epileptiform (frontal) or nonspecific abnormalities is less common in the group of first FS compared to the group of recurrent FS.

The detection rate of the epileptiform pattern regardless of the time of recording was: higher in the elderly, family history of epilepsy, duration of FS greater than 15 minutes, early recurrence in the first 24 hours and lower in those with hyperpyrexia.

The risk of late recurrence of the first FS was higher correlated with the presence of epileptiform anomalies, especially those located frontally, in the context of mixed data available in the literature [81, 335].

The results of the study are consistent with those of most studies, which associate early recorded EEG in the first 7-10 days with the presence of nonspecific abnormalities, and late EEG with the presence of epileptiform abnormalities [292].

Our results are partially consistent with data from the literature, according to which EEG abnormalities are rarer in SFS compared to CFS [292]. In antithesis, such as data obtained by Maytal et al, other studies identify a similar rate of postictal abnormalities in the two types of FS. An explanation is provided by the inclusion in the study group only of patients with normal neurological examination and the interpretation of results based on a single sleep EEG examination (in the first postictal week) [292, 427, 716]. However, in the absence of an FS-specific EEG trace, in the context of an inconclusive history, the EEG value in differentiating CFS from SFS is limited.

The results are consistent with the data from the literature, according to which there is a low sensitivity of EEG in (unprovoked) seizures until the age of 3 years, and a lower detection rate of the epileptiform pattern at young ages [292, 316]. This result states a better EEG recording accuracy especially at older ages when the frequency of FS should be decreased. The association between the presence of localized late epileptiform abnormalities and family history of epilepsy supports the involvement of the genetic factor in the genesis of FS.

The results of this study converge, regardless of the neurological status of the subjects, with the recommendations of some authors to capitalize on EEG registration in the case of CFS, especially in the presence of other risk factors for epilepsy, which increase the detection rate of epileptiform pattern: atypical seizures, neurological abnormalities, extreme

age, family history of epilepsy [118]. So far described as predictive of EEG abnormalities are focal seizures lasting more than 15 minutes, multiple seizures (repeated within 24 hours) [292], abnormal psychomotor development, family history of epilepsy and the presence of more than one diagnosis criterion for CFS [506], delay in psychomotor development, neurological abnormalities, age under 1 year, seizures facilitated by low fever, atypical seizures and extreme ages [359].

Thus, although there are no class Ia studies about the value of EEG abnormalities for FS recurrence or epilepsy, the arguments that could recommend the appearance of EEG as a predictor for FS or epilepsy cannot be ignored. The absence of EEG abnormalities is described with a low frequency of seizures in the absence of fever so that the presence of epileptiform (focal) abnormalities, predominantly frontal, is a risk factor for later unprovoked seizures [279, 322, 335].

Conclusions

1. The present research supports the multifactorial etiology of FS, with the possible genetic factor determining the susceptibility and prognosis of FS, in the context in which the inflammatory process, through its particularities, cannot be considered a unique promoter element of FS. In the case of the first FS, especially in the case of subjects with late recurrence, there are lower values of inflammatory parameters consistent with the stage of preactivation or early platelet activation compared to recurrent FS and subjects without late recurrence. Moreover, the percentage of CFSs was statistically significantly higher in the cluster defined by values of platelet indices suggestive of initiating platelet activation.
2. The study partially supports the importance of iron in the genesis of CF and its properties to promote the growth and differentiation of immune cells and its interference with cytokine pathways, by identifying a higher percentage of clusters defined by iron deficiency anemia in the group of first FS compared to the group of recurrent FS. Its usefulness in discriminating the type of FS and as an inflammatory marker is supported by identifying a higher percentage of subjects with low serum iron levels (functional iron deficiency) in the CFS group.
3. The association of the risk of late recurrence especially with the cluster defined by compensated respiratory alkalosis, moderate hyperlactatemia and the tendency to

stress hyperglycemia indicates a particular metabolic status of subjects at risk of late recurrence, secondary to the complex interaction between proinflammatory cytokines and stress hormones.

4. The combined analysis of the demographic and anamnestic-clinical parameters, respectively of the inflammatory parameters through decisional trees allowed the elaboration of some risk models that require validation through multicenter studies.
5. The present research suggests the phenotypic variability of SCN1A by polygenic determinism, the existence of regulatory or epigenetic genes, and the association of SCN1A mutations predominantly with the GEFS spectrum plus and less with familial FS.
6. We detected the presence of SCN1A mutations with other types of epilepsy not associated so far with SCN1A mutations, but with "FS" onset; functional studies and SCN1A investigation of parents are to demonstrate the validity of the causal relationship.
7. SCN1A mutations give the brain a unique profile of vulnerability, which could also result in the presence of brain malformations.
8. The EEG exploration of subjects with CF should be individualized according to the presence of risk factors for recurrence, epilepsy or comorbidities, and the time of recording adapted to the objective. In the interpretation of EEG, the parameters that influence the detection rate of EEG anomalies must be taken into account.

Personal contributions. Limitations of the study. Recommendation

Overall evaluation of the study

The present personal research aimed at the individual as well as interdependent evaluation of the inflammatory, metabolic, martial and electroencephalographic parameters as risk factors for late recurrence and discrimination factors between FS types, as well as the integration in the FS evaluation of platelet indices, parameters explored less at the moment. The innovation element of the study is the interdependent evaluation of the above-mentioned parameters, using tree type methods and especially the Two-Step Cluster grouping algorithm.

Combined analysis of demographic and anamnestic-clinical parameters by trees

has identified different risk patterns for late-based recurrence different combinations of anamnestic-clinical parameters (age, family history of epilepsy or FS, fever-seizure onset interval, Tº, FS type).

At the same time, the use of the decision tree allowed the identification of a risk model for the presence or absence of late recurrence depending on inflammatory parameters (CRP, NLR, PCT, PDW, RDW-SD, Fe), with increasing and decreasing risk depending on the association and the value of these parameters.

Finally, based on the decision trees, we identified some risk patterns of recurrence related to the metabolic status and EEG anomalies.

Moreover, the research was focused on facilitating the identification of certain anamnestic-clinical features and biomarkers in the case of the first FS (compared to other FS) relevant both for their pathogenesis and especially for prognosis.

The "genetics" chapter of the study aims to highlight the effect of SCN1A mutations in association with phenotypes other than Dravet and the correlations between mutation type and phenotype. At the same time, the identification of genetic testing criteria relevant to the etiological diagnosis would have implications for prognosis, family planning and therapeutic intervention, especially in the era of innovative gene therapies.

Regarding the genetic study in which we identified 24 distinct types of mutations and 3 other synonymous variants grouped in 1 to 4 associations in the case of one of the 79 subjects with mutations, as original findings we noted that:

- the percentage of subjects with SNVs was similar between FS-FS plus and other epilepsies;
- most subjects with deletions presented FS or FS plus phenotype, and those with insertions other types of epilepsy;
- significantly more frequently subjects with deletions had a normal EEG trace, probably in the context of identifying deletions predominantly in relationship with FS or FS plus phenotype;
- the presence of SCN1A mutations has been identified with other types of epilepsies not previously associated with SCN1A (rolandic epilepsy of childhood with centrotemporal spikes, epilepsy of childhood with absence seizures and idiopathic genetic epilepsy (in adolescence) (genetic epilepsy with grand mal seizures on awakening seizures, juvenile myoclonic epilepsy and Jeavons syndrome);
- the brain MRI abnormalities were present in a small percentage of subjects with SCN1A mutation.

We have identified several SCN1A variants not described so far in the literature, classified by the prediction software as pathogenic or possibly pathogenic.

Recommendations for research and general practice:

It would be advisable to perform multicenter studies to validate biomarkers identified as risk factors for late recurrence in the present study.

At the same time, the detection by interdependent analysis of a particular inflammatory status of the first FSs to other FSs should be explored by using more sensitive biomarkers involved in the pathogenesis of FS (cytokines).

In the case of subjects with FS in the evaluation and interpretation of EEG, the parameters that may influence the aspect of EEG must be taken into account: age, family history of epilepsy or FS, time and type of recording.

Determining the right time for EEG recording depends on the goal examination; for the differentiation of FS from other paroxysmal manifestations of nonepileptic type is potentially useful early EEG. The risk of recurrence regarding the EEG trace is not influenced by the time of recording, so that an EEG performed late (between 21-28 days postictal) does not alter the value of this instrument in evaluating the late prognosis.

Although the present study identifies a higher frequency of epileptiform abnormalities in CFSs compared to SFSs, the usefulness of EEG exploration in differentiating FS types is limited.

The benefit of EEG recording should be integrated into the clinical context and considered especially in subjects with CFSs, especially in the presence of other risk factors for late recurrence or epilepsy.

Monitoring the postictal EEG aspect in dynamics, having other temporal landmarks, as well as the integration in the analysis of the sleep EEG pathway, could be the subject of future studies on the FS prognosis.

Phenotypic variability by the presence of the same mutations in association with different phenotypes, FS-FS plus-Dravet, could be explained by polygenic determinism, the existence of genes regulatory or epigenetics. Genome-wide sequencing, especially in families with different phenotypes, could provide additional explanations. The investigation by SCN1A sequencing of the parents could be the object of a new study and would allow both the validation of the pathogenic character of the VUS type mutations and the classification of the hereditary or de novo character of the mutation.

Parental SCN1A investigation is especially recommended in cases of family history of epilepsy and/or FS, taking into account autosomal dominant inheritance with incomplete penetrance and phenotypic variability.

To be able to establish with certainty a cause-effect relationship between the genetic variants SCN1A identified in other types of epilepsy not previously associated with SCN1A mutations additional genetic explorations should be considered (SCN1A sequencing of parents, functional tests for framing the pathogenetic character of the variant, genome sequencing for proband and parents).

Considering the limitations of next-generation sequencing, CNV variants and the fact that deletions/duplications of one or more exons represent a small proportion of pathogenic variants, we recommend MLPA analysis in addition to sequencing SCN1A in cases without SCN1A mutations but with phenotype compatible with FS-FS plus-Dravet spectrum.

The interpretation of the data from the genetic study has been integrated with the current informational context and related to currently available SCN1A databases. However, it must be taken into account that the process of classifying a genetic variant is a continuous one and involves the identification of the genetic variant in association with a certain pathology, confirmation of association through functional studies that demonstrate not only the validity of the proposed hypothesis but also clarify the molecular mechanism is needed.

Current data from the literature have allowed the validation of the pathogenic character of certain variants identified in this study. For new genetic variants, the framing was performed on the basis of functional prediction programs, but data validation requires studies functional and/or reassessment over time by reference to updated SCN1A databases.

At the same time, to validate the pathogenic character of the mutations, it would be advisable to investigate SCN1A of parents especially in cases with a family history of epilepsy and/or FS, considering the autosomal dominant inheritance with incomplete penetrance and phenotypic variability. The investigation of the parents could be the subject of a new study and would also allow the classification of the hereditary or de novo character of the mutation.

In the context of identifying MRI abnormalities in association with SCN1A mutations, evaluation of the epilepsy phenotype, integrated with the understanding of the meaning of genetic variants, is essential in determining the benefit and identifying candidates for epilepsy surgery.

Thus, the value of epilepsy-oriented surgery in patients with an SCN1A variant is based on two aspects: the demonstration of the pathogenicity of the variant and the anatomo-electroclinic phenotype of the patient.

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