THERAPEUTIC-EVOLUTIVE CHARACTERISTICS IN INFANTS AND CHILDREN'S EPILEPTIC ENCEPHALOPATIES

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Keywords: *resistance to treatment, treatment failure, antiepileptic drugs, epileptic encephalopathies, seizure control*

Abstract: *The objective of the study. Starting from the well known fact that one of the defining characteristics of epileptic encephalopathies (EE) is the resistance to treatment, involving combinations of antiepileptic drugs (AED) in bitherapy and most often polytherapy, we attempted to identify, on one hand, the factors which contribute to this mechanism, and on the other hand the treatment protocols that have proven effective in the most common forms of EE: the West syndrome (WS), Lennox-Gastaut syndrome (LGS) and Lennox-Gastaut syndrome evolved from the West syndrome (WS-LGS). Materials and methods. The study group included 28 patients aged from 2 months to 6 years old. The study was conducted over a period of 10 years, between 1999 and 2009, the patients being admitted regularly, mostly at intervals of 3 months, to the Child Neuropsychiatry Clinic of Târgu Mure. On each admittance, the patients received complete neuropsychiatric examination, EEG recordings, all types of seizures and their measurable parameters were determined as accurately as possible, AED schemes were adjusted to each particular case, blood tests were done to evaluate the toxicity potentiality of AED, especially of their combination. To achieve our goals, we applied univariate statistical analysis methods and where the coefficient p was not statistically significant, multivariate regression was used. The obtained information was organized in eloquent graphics. Results and conclusions. The results showed, even before applying the statistical rigors, a very significant involvement of valproic acid (VPA) in any associations with the other MAE. A good frequency was noticed in associations of nitrazepam (NTZ), lamotrigine (LTG) and topiramate (TPM). With all this involvement, very difficult situations were temporarily solved by the association of corticosteroids. It is already a fact clearly demonstrated that the West syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, electrical status epilepticus in slow wave sleep, is the medication of choice. The conclusion that emerges relates to a great variability regarding both clinically and EEG of these forms of EE, very resistant to treatment.*

Cuvinte cheie: *rezistență la tratament, eșec terapeutic, medicamente antiepileptice, encefalopatii epileptice, controlul crizelor*

Rezumat: *Obiectivul studiului. Plecând de la faptul bine cunoscut că una dintre caracteristicile de definire a encefalopatiilor epileptice (EE) o reprezintă rezistența la tratament, implicând asocieri ale medicamentelor antiepileptice (MAE) în bi şi cel mai des politerapie, am încercat să identificăm pe de o parte factorii care contribuie la acest mecanism, iar pe de altă parte schemele de tratament care şi-au dovedit eficacitatea în cele mai frecvent întâlnite forme de EE: sindromul West (SW), sindromul Lennox-Gastaut (SLG) şi sindromul Lennox-Gastaut evoluat din sindromul West (SW-SLG). Material şi metodă. Lotul studiat a cuprins 28 de pacienți cu vârste între 2 luni şi 6 ani. Studiul s-a desfăşurat pe o perioadă de 10 ani, între 1999 şi 2009, pacienții fiind internați periodic, în cea mai mare parte la un interval de 3 luni, în Clinica de Neuropsihiatrie pediatrică din Tîrgu-Mureş. Cu ocazia fiecărei internări pacienții au beneficiat de examen neuropsihic complet, înregistrare/înregistrări EEG, stabilirea cât mai exact posibil a tipurilor de crize şi tuturor parametrilor cuantificabili ai acestora, ajustarea schemelor de MAE în funcție de caracteristicile definitorii ale fiecărui caz, analize de sânge care să evalueze potențialitatea de toxicitate ale MAE, dar mai ales a combinării acestora. Pentru a atinge obiectivele propuse s-au aplicat metode de analiză statistică univariate, iar acolo unde coeficientul p nu a fost semnificativ statistic s-a folosit regresia multivariată. Informațiile obținute au fost organizate în reprezentări grafice elocvente. Rezultate şi concluzii. Rezultatele au evidențiat chiar şi înainte de aplicarea rigorilor statistice o implicare foarte semnificativă a preparatelor de acid valproic (VPA), în oricare dintre asocierile pe care le-a realizat cu celelalte MAE. După VPA s-a constatat o frecvență bună în asocieri a nitrazepam (NTZ), lamotriginei (LTG) şi topiramatului (TPM). Cu toată această implicare, situațiile foarte dificile au fost ameliorate temporar de asocierea corticosteroizilor, fiind un fapt deja clar demonstrat că în SW, sindromul Lennox/Gastaut (LGS), Landau-Kleffner (SLK), statusul epileptic electric în somnul cu unde lente, reprezintă medicația de elecție. Concluzia care se desprinde se referă la marea variabilitate a controlului atât din punct de vedere clinic cât şi EEG a acestor forme de EE foarte rezistente la tratament.*

INTRODUCTION

The treatment of epilepsy, especially in epileptic encephalopathies is a challenge because of their high resistance, sometimes discouraging of the recurrent crises. It consists of

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repeated attempts, of various combinations of the AED, of bi or polytherapy. The polymorphic nature of the seizures, their variability during treatment supported by the drug control inefficient to seizures and by the maintenance for long periods of EEG patterns characteristic in most cases, make of these forms of EE, true redoubts, sometimes insurmountable.(2) The most common forms of this group are the West syndrome (WS), Lennox-Gastaut syndrome (LGS) and Lennox-Gastaut syndrome evolved from the West syndrome (WS-LGS).(2) The diagnosis in WS is based on the infantile spasms triad (symmetric, asymmetric, asynchronous, focal, combined with focal seizures or preceded by these, subtle, subclinical or preceded by short atonia), EEG characteristic pattern, hipsaritmia (classical, fragmented, asymmetrical, unilateral, atypical) and psychomotor retardation, accentuated initially or developed over time.(3,4) The diagnosis in LGS is also based on a triad, ie polymorphic seizures (mostly generalized, tonic, tonic-clonic and atonic, and atypical absence and status epilepticus), EEG characteristic pattern, discharged generalized by spike-wave complexes with periodic character, pseudo-rhythmical and psychomotor regression after the onset of seizures (some forms are evolving from WS in which both clinically and in terms of EEG, there has been a transition of the types of seizures, respectively of the EEG aspect.(5,6) Monotherapy is an utopian concept, and the bi- or polytherapy represents the rule. Drug combinations are based on objective principles, represented by compliance with the recommendations provided in epilepsy treatment guidelines developed by recognized international boards and according to rational politherapy principles which involve combining AED with different mechanisms of action.(7,8) However, there are many situations where the medical treatment has not proved fully effective, so that we need to resort to non-pharmacological methods, such as epilepsy surgery (subpial multiple transsection, section of corpus calosum, hemispherecthomy) (9), ketogenic diet, vagal nerve stimulation, cerebellar stimulation, neuromodulation of the centro-median thalamic nucleus (after previous unsuccessful attempts to stimulate the anterior thalamic nucleus).(10,11) The above-mentioned methods refer mainly to the group of resistant epilepsies, united under the term of epileptic encephalopaties. In order to adopt and observe a common language on the definition of accurate operational terms in the treatment of epilepsy, at the International Epilepsy Congress that took place in Budapest in 2009, the Executive Committee of the ILAE (International League Against Epilepsy) defined the treatment resistance by using two hierarchical levels.(12)

The first level is advancing a general scheme to include in categories the answers to each therapeutic intervention based on a minimum set of data on the need for intervention. The second level suggests the essence of the definition of treatment resistance: “failure of adequate attempts with one or two antiepileptic drugs carefully chosen, well tolerated and commonly used to obtain control over the seizure”.(12) This definition has become a necessity in order to adopt a common language, in circumstances marked by a rapid development of the therapeutic options. Defining seizure control was also an important issue under discussion and was finally defined as: “control over all types of seizures for a period of 12 months or a period equivalent to three times longer than the time between seizures, before a new therapeutic intervention, no matter what it would be”.

The benefit of these specifications lies in the possibility to choose as objectively as possible, the most favourable moments for the most effective combination of AED.(12)

MATERIALS AND METHODS

The group of patients included in this study was set up after having been diagnosed and classified in one of the forms of EE. To reach this stage, we used criteria valid for each entity, both from the clinical point of view and from the electroencephalographic one, as well as the therapeutic-evolutive criteria. A number of 28 patients were included in the group: 12 patients diagnosed with the West syndrome, 8 patients with the Lennox-Gastaut syndrome and 8 patients with the Lennox-Gastaut syndrome evolved from the West syndrome. The study was conducted over a period of 10 years, between 1999 and 2009, the patients being admitted regularly, mostly at intervals of 3 months, to the Paediatric Neuropsychiatry Clinic of the city of Târgu Mure□. During admissions, a very important objective was the accurate evaluation of possible epileptic seizures quantified parameters: seizure types, frequency, duration and intensity of each type, the behaviour including the onset, continuation, the end and the post seizure period with reference to its duration and degree of consciousness alteration.

In order to highlight the differential control of various types of seizures, we formed three categories: generalized seizures, focal seizures and infantile spasms. Each patient benefited from specific blood tests in order to achieve a control of the well known toxic potentiality of the AED. Patients underwent a comprehensive neuropsychiatry examination which evaluated the psychomotor and language performances at that time, allowing making a comparison with the previous examinations and drawing conclusions on the evolution of the patients based on the level of drug control of the epileptic seizure parameters.

EEG recordings were made with a Nihen-Koden device. We used longitudinal and referential assemblies in the 10-20 system. Records were made on 16 channels, in terms of drug-induced sleep with chloral-hydrate solution at a concentration of 10% given intrarectaly .The necessary dose was of 1 ml / kg.(13)

In the situations in which the patient was not in a proper stage of sleep necessary for achieving recordings unaltered by other factors, the recording was repeated, but sleep deprivation was added to the conditions mentioned above. For an easy analysis and as objective as possible in the dynamic aspects of EEG, 5 recordings were established, the most suggestive ones, regarding both the characteristic EEG pattern and the degree of comparison with other recordings. The captured aspects could be compared with the previous ones. This was important in taking decisions for a future objective and efficient therapeutic approach, observing the principles underlying the strategy of treatment in epilepsy in general, and in EE in particular. As previously mentioned, within the EE group, monotherapy is an utopian goal, and the bi- and especially the polytherapy make the rule irrespective of the risks implied by AED associations, potentially generators of drug interactions. The available antiepileptic drugs (with special mention for vigabatrin and clobazam) have been used in various combinations justified by objective criteria (level of seizure control, EEG pattern of appearance and patient’s quality of life parameters).

RESULTS AND CONCLUSIONS

The most accurate possible evaluation of quantifiable parameters for seizures: seizure types, frequency, duration and intensity of each type, the seizure development with all the stages: onset, duration, end and the post seizure period with reference to its duration and degree of consciousness alteration, showed variable frequency of different types of seizures, with

different and varied degrees of control regarding the above-mentioned parameters. These aspects required new therapeutic decisions, taking into account the aspects of EEG captured. The most common types of seizures in WS were the infantile spasms, whether they occurred in flexion or extension, in bursts or isolated, symmetric or asymmetric, preceded or not preceded by focal seizures, strongly manifested or with subclinical aspect, each of these features represent a valid criterion in a determined stage. Generalized tonic seizures followed, the tonic-clonic seizures, amiotonic seizures (irrespective that they referred to the head or trunk flexion and convulsivant epileptic seizures characteristic of LGS status. As it can be seen in Figures 1, 2 and 3, drug control has been shown progressively consistently favorable in infantile spasms (figure no. 2), while in the other two categories (generalized and focal seizures), the control proved variable in the different stages (Figure no. 1 and no. 3).

Figure no. 1. Dynamic control of generalized seizures in EE (SW, SLG, SW-SLG)

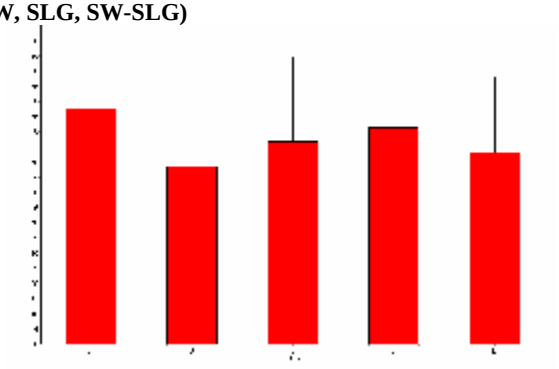


Figure no. 2. Dynamic control of infantile spasms in EE (SW, SLG, SW-SLG)

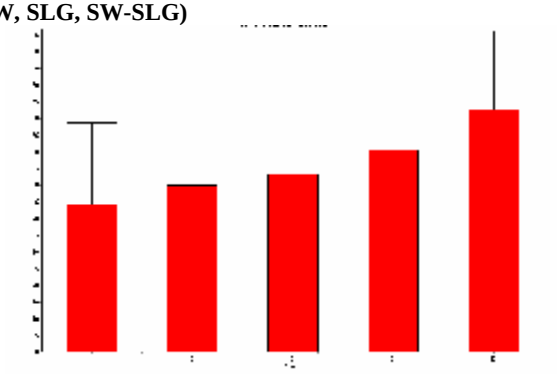
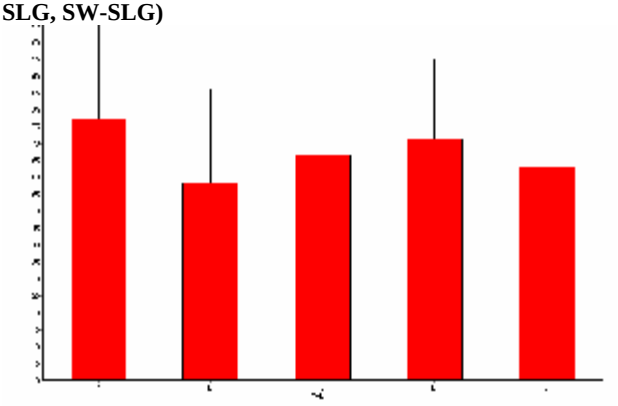


Figure no. 3. Dynamic control of focal seizures in EE (SW, SLG, SW-SLG)



EEG patterns were represented in considerable proportions in hipsarrythmia, that registered different percentages according to the moment of recording (nearly 30% at the first recording, 12% at the second, then the percentage declined below 10%) eventually replaced by the generalized discharges of spike-wave complexes, first with the percentage representation of 14%, followed by successive increases to 24%, maintenance records set at 3 and 4 and finally increased to almost 30%, the fifth record) (Figures 4-8), and one of the variant of HA (hipsaritmia fragmented, having an opposite trend, with progressively increasing percentage values to values below 10%, above) (Figures 4-8), sometimes with outbreaks in various locations, but mostly frontally and/or temporally, characteristics in the LGS. In one case, we found status epilepticus in slow wave sleep. Statistical representation of those stated before was possible by applying specific tests and by the graphical representation of the results.

Figure no. 4. EEG1 patterns frequency

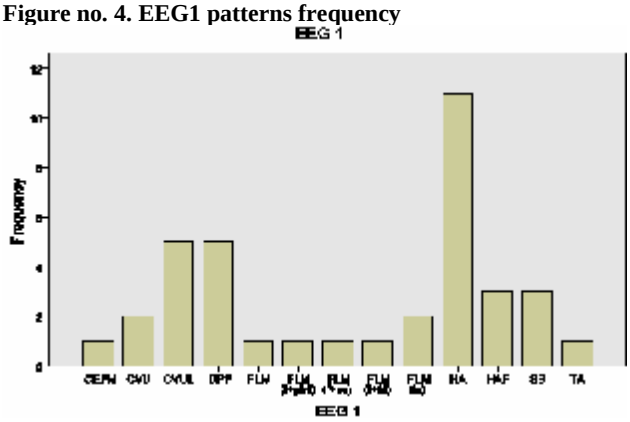


Figure no. 5. EEG 2 patterns frequency

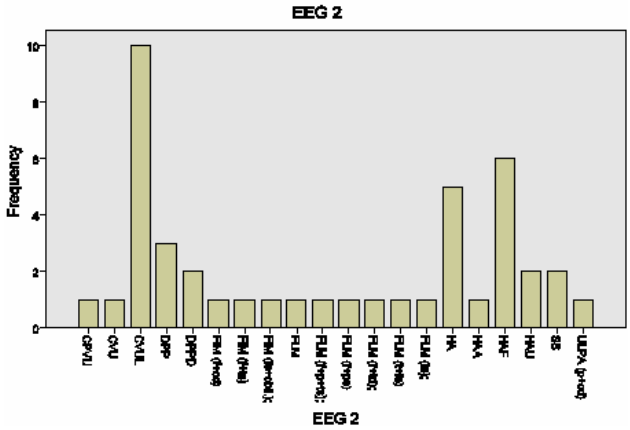
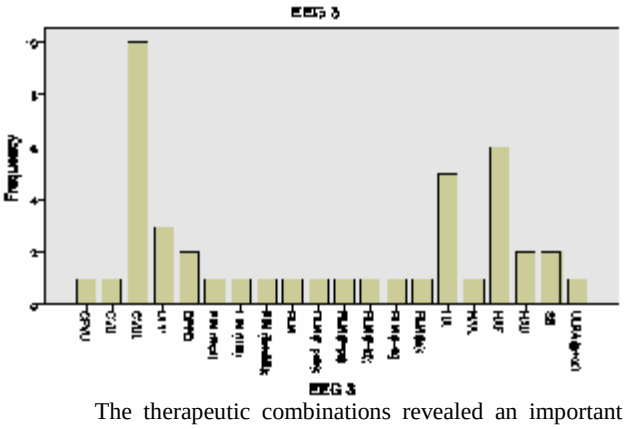


Figure no. 6. EEG3 patterns frequency



The therapeutic combinations revealed an important aspect that of the frequent involvement of valproic acid in many combinations, while other drugs such as lamotrigine and

topiramate used according to the recommendations as adjuvant medication were found in lower percentages without significant statistical importance. Based on the current results, it can be stated that the group of EE represents the powerful forms of epilepsy in the therapeutic options (at least in terms of numbers in full progress), which is reflected in the clinical pictures, too revealing almost in all the cases, mixed severe retardation in development (motor, mental and language retardation). It is largely maintained by the lack of control or by partial insufficient control on seizures (too many, too strong, too resistant). In this context, epilepsy surgery was proved very useful in the West syndrome, whereas vagal nerve stimulation, cerebellar stimulation and centromedian thalamic nucleus neuromodulation, mainly in the Lennox-Gastaut syndrome by controlling seizures in 40-42% of cases, improve these patients'quality of life.

Figure no. 7. EEG 4 patterns frequency

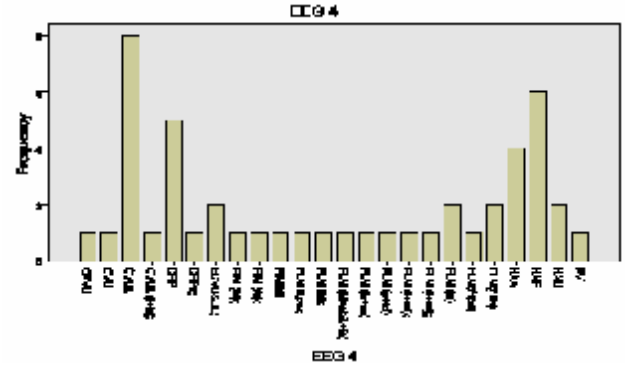
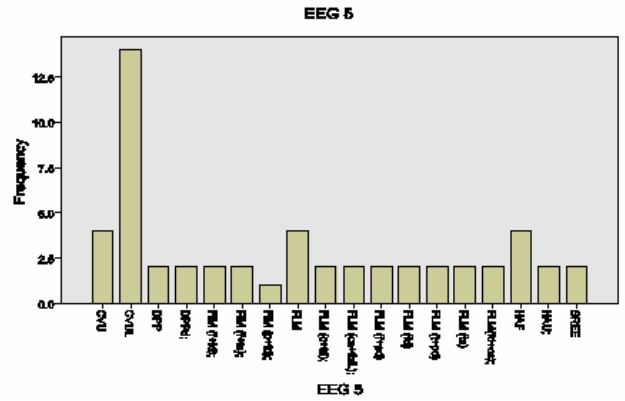


Figure no. 8. EEG 5 patterns frequency



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