SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Epilepsy associated with biological events

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1. INTRODUCTION AND BACKGROUND

The prevalence of epilepsy in the general population is estimated to be between 0.3 and 1%, making it the most common neurological disease. Based on this, there are 50–60,000 patients with epilepsy in Hungary alone. It is a chronic disease, oftentimes meaning life-long treatment, affecting every aspect of patients' lives, and it can possibly become life-threatening as well. Although it affects many patients, the pathomechanism of the disease cannot be clarified in all cases. Even if the aetiology of the disease is known, it may need lifelong treatment. Nowadays numerous studies help the work of the epileptologist studies on real-world scenario are important. In the thesis two groups challenging epileptologists were chosen: status epielpsticus and women with epilepsy.

Status epilepticus (SE) is an emergency in neurology, needing acute treatment and examinations. The incidence of SE falls in the range of 10–41/100,000. Its treatment is time-sensitive and delay may result in death or long-term consequences. Referring to the new classification scheme of SE, there are two operational dimensions of the definition: time point 1 (T1) is associated with abnormally prolonged seizure, when therapy should be initiated, while time point 2 (T2) is related to the time of on-going seizure activity involving a risk of long-term consequences. Treatment is urgent also because GABA sensitivity decreases and the sensitivity to excitotoxic neurotransmitters increases rapidly, leaving only a short time interval for effective treatment. SE may also have life-time consequences and, especially in refractory SE, the probability of becoming epileptic is higher. Cases of reported refractory and super-refractory SE (SRSE) are uncommon but very important clinical problems due to treatment difficulties, consequences, and high case fatality. Despite the newer generation of antiseizure medications (ASMs), the management of epilepsy and SE has not yet been resolved.

Epilepsy affects the of women with epilepsy (WWE) many times in different ways than male patients, there are special aspects of their lives to consider if one is determined to give the best of care. Considering that the female-male ratio is about 1.1/1.7, this indicates that there are ~ 30,000 women with epilepsy (WWE) in Hungary. This substantial population of patients needs special care and consultation throughout the course of their disease.

The female hormonal cycle can affect seizure frequency and vice versa: epilepsy can contribute to hormonal changes. Disorders of fertility are more frequent in the WWE than in the normal population. The hypothalamus-hypophysis axis can be altered both as an adverse reaction to antiseizure medications (e.g. valproate = VPA) or by the disease itself. Cases of

polycystic ovarian syndrome (PCOS) are more often found in temporal lobe epilepsy. As for social factors, WWE has to face a social stigma that is still present today. These patients are also exposed to irrational fear due to a lack of proper consultation about the actual risks and the effects seizures and ASMs might have on their foetuses. For most women with active epilepsy, continuing treatments during pregnancy is necessary, as ongoing seizure activity poses a risk on both foetus and mother. However, prenatal exposure to ASMs is associated with increased risks of growth restriction and congenital malformations. More information is needed to support WWE and their physicians in making a well-informed decision regarding medication use during pregnancy, specifically about newer ASMs, as most studies were conducted well-before the newer types were introduced.

2. AIM OF THE STUDY

Our goal was to investigate special aspects of this large patient population with the help of real life clinical data.

1. First of all, due to its significant morbidity and mortality, we directed our attention to the study 1of status epilepticus, which has the highest mortality rate among epileptic patients. We focused on the outcome of SE (short and longterm mortality, seizure freedom), in view of antiepileptic therapy during SE and in the follow-up period, risk factors such as age, co-morbidity, pre-existing epilepsy, as well as the underlying pathology, first in the East-Hungarian region.
2. We also investigated a special subpopulation, pregnant women with epilepsy (PWWE). We aimed to follow the changes in the number and outcome of pregnancies over a thirty year period, with the possible role of newer type ASM regarding these changes. This is the first study in our region to evaluate the experience of treatment and outcome in this fertile patient population.

3. METHODS AND PATIENTS

I. Status epilepticus

Patients, databases

Data were retrieved from the patients' files, covering the period between 01.01.2013 and 31.12.2017 in a retrospective view. The subjects had been treated for SE at the Neurointensive

Unit of the Department of Neurology, University of Debrecen. The patients were coded with status epilepticus diagnoses in accordance with the International Classification of Diseases by the World Health Organization. Each admission of the same patient was considered a single case. In this study, the patients were followed-up until 30.06.2018. In every case, data collection included issues as follows: age, gender, cause, history of previous epilepsy, former intracranial surgery, treatment with antiepileptic drugs before, during and after SE, and other medicines regularly taken for CNS, MRI scans, EEGs, and comorbidities. The 21 EEG electrodes were placed according to the International 10–20 system, and digital recording was used. All EEGs were evaluated by a board-certified clinical neurophysiologist. In the case of convulsive SE, EEG was done to classify the type of the seizure (focal, or generalized). According to the recommendations, and if it was clinically reasonable (e.g., impairment of consciousness), a post-SE EEG was done in order to exclude a transition to NCSE and to monitor the effectiveness of the therapy. NCSE was diagnosed according to Beniczky et al.. Depending on the therapy and response to it, EEG was repeated 24–48 h later. Unfortunately, continuous EEG monitoring was not available at the time of the study. The following age groups were considered for pooling:

1. 18–39,
2. 40–64,
3. 65–80,
4. over 81-years-old.

Regarding the status epilepticus, the following data were collected: type of seizure (focal, focal to bilateral, generalized, non-convulsive, and unknown seizures according to the ILAE definition, ASM treatment, and in case of survival, ASM used for maintenance therapy. New onset status epilepticus (NOSE) was considered if the patient did not have known seizures previously. Refractory SE (RSE) was diagnosed if the patients did not respond to standard SE treatment, i.e., receiving adequate doses of initial benzodiazepine followed by a second ASM. In case of SRSE, the definition of Shorvon et Ferlisi was used, i.e. SE could not be terminated or it recurred within 24 h; also, when propofol or midazolam were necessary, including cases in which SE recurred on the reduction or withdrawal of these drugs.

Statistics

Statistical analysis was carried out using the SPSS for Windows 19.0 (SPSS Inc. Chicago, USA) and Microsoft Office Excel 2007. Beside the basic statistics, two-sample T-test, and Fisher's exact test were used to analyse our patients' data. Categorical variables were assessed using Pearson $\chi 2$ test. Odds ratios were calcul5ated. Significant differences were considered if

$p < 0.05$. Ethical approval was obtained from the Regional and Institutional Ethics Committee (DE KK RKEB/IKEB: 5037-2018).

II. Women with epilepsy

Patients, database

Data were retrieved from the prospective Epilepsy Database of the Outpatient Clinic of the Department of Neurology at the University of Debrecen, containing encrypted data of all patients appearing in our Epilepsy Outpatient Clinic for the retrospective analysis of pregnant women with epilepsy (PWWE). The files selected are from the period between 1 January 1992 and 31 December 2020. Each pregnancy of the same patient was considered a single case. The criteria for recruiting participants for this study were either a diagnosis of epilepsy and/or the presence of an ICD code, specifically G40-41, documented in the patient's medical file. Patients with a presumed drug-provoked seizure, psychogenic seizure, or cardiogenic etiology were excluded. Patients undergoing epilepsy surgery were also excluded. In every case, data collection included: age at the onset of epilepsy, seizure type in accordance with the ILAE definitions, age at giving birth, family history of epilepsy, ASMs taken before, during, and after pregnancy, amount of ASM doses used, ASM serum levels, seizure frequency before and during pregnancy, other medicines regularly taken for the CNS, MRI scans, EEGs, and co-morbidities. The ILAE definitions were modified in 2017, we used the latest version, although most files included here used previously common expressions. A certified epileptologist diagnosed and provided care for these patients, and the ASM used in each case was prescribed by that specialist.

• Four groups were formed for comparison (time of pregnancy):

G1: Before 1992

G2: 1992–2001

G3: 2002–2011

G4: 2012–2020.

The first group (G1) included patients who reported having pregnancies before 1992, which is the year the epilepsy outpatient unit in our department was established. In the second group (G2), the patients were treated with older-generation ASMs; newer ASMs became available on the market after the millennium (i.e., in Hungary, LTG was allowed to be used during pregnancy around 2002–2003). In the third group (G3), LTG and newer drugs were used more commonly, becoming the drugs of choice in the G4 pregnant population.

• Providing care was another point of view in forming groups for comparison, which is as follows (care groups):

I. Patients with epilepsy (PWE) who were treated at our Epilepsy Care Center

II. Patients who first acquired seizures during pregnancy and stayed in our Epilepsy Care Center

III. Patients were sent only for consultation by their gynecologist.

We collected data about seizure types, the number and type of ASMs used, the outcome of pregnancies, rates of spontaneous and induced abortions, complications during pregnancy, and foetopathies.

Statistics

Statistical analysis was carried out using Microsoft Office Excel 2021. Besides the basic statistics, categorical variables were assessed using Pearson's $\chi 2$ test with Yates' correction. A p-value of <0.05 was considered statistically significant. The odds ratio and 95% confidence intervals were calculated where needed. Ethical approval was obtained from the Regional and Institutional Ethics Committee (DE RKEB/IKEB: 5472-2020).

4. RESULTS

I. Status epilepticus

4.1.1. Basic Characteristics

The diagnosis of SE was established in 121 patients (male: 61; 50.4%). As eight patients (6.6%; male 3, female: 5) had had two or more admissions due to SE, a total of 135 episodes (male: 68, 50.4%) were evaluated. The patients' mean age was 64.1 ± 13.9 years. Based on the distribution by age, 87 (71.9%) of the patients were between 40 and 80 years old. Among them, the working/active age group included 50 (41.3%) patients. The mean follow-up time was 39.9±14.2 months. The longest follow-up was 66 months and the shortest was 7.5 months.

The prevalence of SE was in the range of 9.4–14.7/100,000 inhabitants/year. The seasonality of prevalence showed the highest occurrence in December and January followed by August. According to the classification of Trinka et al, previous epilepsy was known in 89 patients (73.6%), the mean age being 62.2 ± 14.4 years. Of the 32 patients with unknown previous epilepsy (26.4%; mean age: 70.1 ± 12.35 years), 22 died during hospitalization, all could be classified as symptomatic SE. Among the survivors (10 patients), there was only one patient

who had no symptomatic abnormality in the background. So only this one could fit the definition of the ILAE epilepsy diagnosis.

One third of the patients did not visit epilepsy outpatient units regularly. Of the 89 patients with known epilepsy, 37.1% had focal seizures without secondary generalization and 23.6% had focal seizures with secondary generalization. Among the patients with generalized epilepsy (39.3%) seizure types were as follows: generalized tonic-clonic, myoclonic and absence, i.e., 33, 1 and 1 cases, respectively. Only one patient had a history of Lennox-Gastaut syndrome. Altogether, 91% had symptomatic epilepsy among patients with a history of this disease. Among all the patients with SE, 78 and 23 patients had RSE and SRSE, respectively. New onset refractory status epilepticus (NORSE) was observed in 18 patients among those having refractory SE. The number of NOSE and NORSE cases with undetermined causes were so few (3 and 2 patients, respectively) that far-reaching conclusion cannot be drawn. All of the SE patients had hypertension.

4.1.2. Etiology, seizures

Unknown aetiology of SE was revealed in nine cases but in the majority of the patients, several causes were identified. In the different age groups, the particular causes showed varying pictures in terms of aetiology. Among patients with previously known epileptic seizures, the most common causes of status epilepticus were infections, stroke, alcoholism and non-compliance, while among patients with NOSE, infections, alcoholism, stroke and tumor were at the top of the list. Only two thirds of the people with epilepsy were regularly supervised by an epileptologist prior to SE; these patients all had refractory epilepsy. Just under 50% of cases were focal, and focal epilepsy with secondary generalization (41 patients; 30.4%; 26 patients; 19.3% respectively); generalized epilepsy was diagnosed in 34.8% (47) of patients and combined-type epilepsies amounted to 15.6% (21 patients) of status epilepticus. Nine patients were diagnosed with non-convulsive status epilepticus (NCSE). Of them, three patients had generalized seizure and four patients focal epilepsy with secondary generalization prior to NCSE.

4.1.3. Antiepileptic Drug Treatment

All known people with epilepsy took one, two, and three or more types of ASMs, 34 (52.3%), 21 (32.3%), 12 (18.5%), respectively. Interestingly, if we compare the pattern of ASM use among SE patients with a history of epilepsy with the data of people with epilepsy in our outpatient care unit (published earlier), the differences are significant ($p = 0.0014$) (34 [52.3%] vs. 894 [69.7%]; 21 [32.3%] vs. 286 [22.3%]; 12 [18.5%] vs. 102 [8%]). In order to control seizures, one, two, and three or more ASMs were used in 15 patients (11.1%); 41

patients (30.4%); and 79 patients (58.5%); respectively, subsequent to the first line benzodiazepine (diazepam or clonazepam) during SE. No significant difference was found between the number of ASMs taken before SE and the ASMs administered during SE. General anesthesia was necessary in 23 (17%) patients. Midazolam, ketamine and propofol were administered in 16 (11.9%), 4 (3%), and 9 (6.7%) cases, respectively. Seven of the patients had generalized type of epilepsy, eleven patients had focal epilepsy with or without secondary generalization (7, 4 respectively), four patients suffered from a combined type and one patient had NCSE. Certain older generation ASMs such as valproate, clonazepam, phenytoine, and carbamazepine (supp.) as well as newer type ones including levetiracetam, and lacosamid were used in the treatment of SE. Even if a nasogastric tube had to be inserted treatment with ASMs such as oxcarbazepine and lamotrigine were continued.

Among the patients who survived SE (101 patients), 85.1% (86 individuals) took one or two ASMs (49 and 37 patients, respectively) at discharge to maintain seizure freedom. Only 15 patients were discharged with three or more ASMs to take. The number of ASMs per patient was 1.7 ± 0.7. The number of ASMs is significantly (<0.0001) higher if the results of patients surviving SE and our previous findings (1.4 ± 0.56) of people with epilepsy at the outpatient department are compared. The prescriptions of newer type ASMs were significantly higher at discharge than at admission ($p < 0.005$), but the number of older type ASMs showed a variety as well. Among our patients, the ones taking carbamazepine, levetiracetam and/or valproate had the highest probability to achieve seizure freedom. The choice of ASM on discharge had no significant effect on mortality. The need for general anesthesia was independent of the add-on administration of levetiracetam and/or lacosamide in SRSE.

4.1.4. Outcome

The discharged patients' mean survival time was 10.44 ± 8 months. Seventy patients have survived SE (mean age: 55.8 ±14.6 years) and 25 of them achieved seizure freedom. The mean seizure free period was 6.8±6.9 months (the shortest seizure free time was 1 day and the longest one was 5 years). Sixty-five patients (53.7%) died during the period investigated, primarily due to co-morbidities especially common in the advanced age group. Case fatality rate was 25.2% among all examined SE patients 22 of which suffered from NOSE. The death rate among NOSE patients was significantly higher than the mortality among previously people with epilepsy ($p = 0.009$). Young patients had a much better chance to survive. There was no difference between male and female mortality rates. If the time course of death was examined, in-hospital case fatality was the highest and a second peak was detected at 6 months. Mortality increased by age ($p < 0.0001$). Apparently, younger patients died after

discharge. Among patients with pre-existing epilepsy, the highest mortality was observed in case the duration of epilepsy was < 1 month. The leading causes of SE among deceased patients were stroke (42.86%), tumor (33.33%) and infection (23.81%). Mortality within a co-morbidity group was due to tumor (28%), stroke (25.71%), and infection (20.83%). The probability of death increased significantly ($p = 0.0021$) with the number of comorbidities. All patients who had had cancer died. Most of the deceased patients had focal epilepsy with or without secondary generalization (61.5%), 21.5% of patients had generalized seizure. NCSE was observed in 12.3% of the SE patients. By the types of SE, NCSE showed the highest mortality, followed by focal epilepsy (59.7%) and generalized epilepsy (31.1%). The number of ASMs given to cease seizures were inconsistent with mortality. Using older and/or newer type of ASMs (administered as second- or third-line drugs) did not influence the odds of death during the status epilepticus. The ASMs used during SE did not influence mortality significantly. General anesthesia did not influence survival and seizure freedom significantly. Co-administered other drugs belonging to the ATC N05 group (47 patients) before SE did not influence the seizure freedom after SE, but the mortality among patients taking at least one drug was favorable (OR: 0.41 95%CI: 0.1969–0.8571; $p = 0.02$). They took chlordiazepoxide, alprazolam, antidepressants, etc.

II. Women with epilepsy

4.2.1. Basic characteristics

In total, we collected data on 191 pregnancies by 127 women. After data clearing, 181 pregnancies were included in the database. Ten pregnancies were excluded because of insufficient data and/or because the pregnancies happened years before the onset of epilepsy. Of all the people studied, 33 women had a positive family history of epilepsy (18.2%). Comparing the mean age in the G4 group to the other groups' (G1, G2, and G3), significantly older ages were detected ($p < 0.05$). If the mean age in care group I was compared to the mean age in group II, it was significantly lower ($p = 0.002$). The number of women becoming pregnant and the number of pregnancies and births have kept growing since the 2000s, and even though it did not reach statistical significance, a trend is clearly evident. Of all examined pregnancies, 79% happened after 2002. Nevertheless, the number of new patients also grew steadily: (all new female patients) 153–47.7%, 497–45.7%, 877–53.2%, and 1,112–55%), in the time period of <1992, 1992–2001, 2002–2011, and 2012–2020, respectively.

In group I, 44.5 and 25.7% of the pregnant women presented in the first and second trimesters, respectively. Over time, more PWWE arrived at an earlier stage of pregnancy; a strong, increasing trend in their number could be detected. Patients referred by gynecologists, those treated at other hospitals, or those without regular follow-ups were evenly distributed across different trimesters. Patients in group II, 61.5% (N = 8), appeared mainly in the second and third trimesters since toxemia or cerebrovascular complications develop more frequently in these trimesters.

4.2.2. Seizure types

More than half of the patients (N = 104, 57.4%) experienced generalized seizures, with tonic-clonic being the most common (a total of 56.9%). The remaining women had other types of seizures, such as absence, myoclonic, or atonic seizures. An additional 28.2% (N = 51) of the subjects had focal to bilateral tonic-clonic seizures. In the studied population, 41.9% (28.2% focal to bilateral tonic-clonic seizure, 13.7%) had a focal seizure. No significant difference was observed concerning the seizure types between the observed periods. Of all pregnancies in our study (N = 181), EEG recordings were made in 69% (N = 125), and 11.2% (N = 14) of them showed interictal epileptiform abnormalities. The distribution of EEG tests in the different care groups was as follows: group I, 75.2% (N = 76); group II, 46.2% (N =6); and group III, 64.2% (N =43). Comparing the time interval periods, the distribution of EEG recordings was the following: 100% (N = 10) in G1, 57.1% (N = 16) in G2, 66.2% (N = 43) in G3, and 71.8% (N = 56) in G4. There were no seizures during pregnancy in two-thirds of the patients (65.2%, N = 118). If different time intervals were examined, the ratio was even better: G1, 54.5%; G2, 53.6%; G3, 61.15%; and G4, 86%. Hence, seizure freedom has become more common over the past decades. If the follow-ups (I) were carried out in our tertiary center, the ratio of seizure freedom during pregnancy was 73.1%, while in the consultation group (III), it was 55.2%. An increase was most often noted in the second trimester (50% of known cases), followed by the third (37.5%) and first trimesters (12.5%).

Due to maternal non-compliance, seizures in the peripartum period were detected in all pregnancies as follows: G2, four cases (14%); G3, four cases (6.2%); and G4, five cases (6.4%). In G2 and G3, three out of four (75%) and four out of five (80%) pregnancies, respectively, were carried out with a previous seizure free period of more than 12 months. In G4, all five pregnancies (100%) were seizure-free. In the case of care group I, 10 cases (9.9%) were detected. Seizure freedom could be observed in 73.3% of the pregnancies. No change in frequency was observed in 11.9% of the cases, while in 13.8% of the cases, the frequency of

seizures decreased, and seizure frequency increased in one patient (0.9%) only. During pregnancy, in a total of 37 cases (20.4%), a tonic-clonic seizure was recorded. The percentage of cases with one seizure kept decreasing in the studied periods: G1, 50% (N = 5); G2, 17.8% (N = 5); G3, 21.5% (N = 14); and G4, 16.6% (N = 13). Examining the groups categorized according to the type of care, we found the lowest seizure frequency in pregnancies where regular care was provided in a tertiary center (I. 12.8% (N = 13), II. 46.1% (N = 6), III. 26.8 % (N = 18) ($p = 0.005$). A PWWE had a higher chance of having seizure freedom in the regular-care group I: OR = 2.9 (2.15–3.65) $p < 0.0001$.

4.2.3. Treatment

Data collection started in 1992 when newer types of ASMs were not yet commercialized: e.g., LTG was first launched in 1994 and allowed to be used during pregnancy only after 2002. Its use became widespread in the 2010s. In each time interval, different populations were treatment free: G1, 30% (N = 3); G2, 21.6% (N = 6); G3, 16.9% (N = 11); G4, 23% (N = 18). Monotherapy was most common in every time interval (G1-G4) and treatment group (I–III). If bitherapy was necessary, the typical approach involved combining an older-type ASM with the newer LTG. When we examined the types of medications, we found a shift toward newer types of ASMs as time passed. Between 1992 and 2001, only older types of ASMs were in use. After 2002 and, especially after 2012, the use of newer-type ASMs became increasingly common, mainly favoring LTG and, later, LEV. Having become available, ASMs such as lacosamide (LAC), zonisamide (ZNS), and topiramate (TPM) were also prescribed occasionally after 2012. The reduction in the use of CBZ and the rise in the use of LTG were both statistically significant, $p < 0.0001$. If the treatment groups were compared, more ASM types and newer ASM types were used. In group II, the number of patients was too low to draw conclusions. LEV and LTG were more commonly used in the regular care group I compared to patients who were sent to our center for consultation but not treatment (OR
= 3.18 (2.49–3.87) $p < 0.0001$. As for dosage change, treatment group I could be followed clearly. Altogether, the dosage was changed in 39 cases (38.6%). This often meant an increase in the dose taken (94%).

4.2.4. Outcome of pregnancies

The majority of pregnancies ended with live births (91.7% N =166), which increased over time in each treatment group. Spontaneous abortion did not differ significantly among the

time interval groups (5%, N = 10), and induced abortion was also low (2.7%, N = 5). Over time, the need for consultation by gynecologists increased after 2002. In most cases, the cause of spontaneous abortion could not be determined. The obstetric examination and, if there were any genetic examinations, the findings were negative. There was one case where the twins had no heart sign on regular examinations in the first trimester. In cases of induced abortion (N = 5), two pregnancies occurred in the regular follow-up group (I.), and three pregnancies happened in group III (consultation). The first patient in group I was 43 years old and was undergoing psychiatric treatment with multiple medications. She took her own life during her pregnancy, unaware of her condition. Although it is unclear whether she was consistently taking antiseizure medication, the foetus exhibited polyhydramnios. However, subsequent genetic and pathological examinations did not reveal any abnormalities. The second woman was 40 years old. She did not take ASM and had no seizures during her pregnancy. In group III, two women received treatment for psychiatric diseases, and another one was included because of tuberous sclerosis. Besides the foetopathies mentioned earlier, one pregnancy exhibited complex foetopathies (multicystic kidney, pyelectasis, macrosomia, and polyhydramnios). The patient who experienced epilepsy but was not taking antiseizure medication during her pregnancy was initially referred to us for consultation and remained under our care thereafter. Thus, no direct association could be established with epilepsy.
A more detailed neonatological examination would have revealed additional abnormalities. Altogether, some kind of foetopathy was mentioned in six pregnancies (3.3%). In one case, the patient was on CBZ; in another, she used LTG; and in the third case, it is uncertain whether the mother took any antiseizure medication (ASM) (as previously mentioned). The remaining pregnancies proceeded without the use of ASM. Most pregnancies were unplanned without problems (86.7% N = 157). Six of the pregnancies (3.3%) had complications during delivery, mostly of gynecological origin (e.g., placental abruption, meconium, or preterm delivery). One of the patients suspended from taking ASM in the third trimester had a seizure; consequently, her gynecologist had to perform a cesarean section. Five of the patients had toxemia, eclampsia, and some had seizures after delivery and stayed in our care. One patient developed herpes encephalitis and had a middle cerebral artery occlusion with symptomatic seizures. These patients were not in our care (groups II., III.).

5. DISCUSSION

I. Status epilepticus

5.1.1. Basic Characteristics

SE is an important and lifethreatening form of epilepsy. This study is the first in our region to summarize SE cases and evaluate the treatment and outcome. Just as in other SE studies, the gender ratio was nearly equal and more than half of the patients were elderly. Our research is of special importance since almost half of the patients were still active, i.e., they belonged to the working-age population. Among middle-aged patients, the most common etiologies included alcohol consumption, non-compliance and stroke. Meanwhile, infection and stroke most often affected elderly patients. The onset of stroke was typical at an older age but in our cohort - similarly to alcoholism - the incidence of stroke was high in younger patients. No strict seasonality was observed but data aggregation by month showed peaks in January and December during the winter, and in August during the summer. There was no close relation between SE and holidays either. Although this is an interesting finding, we could not find unequivocal clarification for it. However, it must be noted, that stable and unstable atmospheric pressure and temperature go from one extreme to the other in Hungary in the aforementioned months. Motta et al. also reported increased seizure frequency in unstable weather conditions. A quarter of the patients had NOSE. They were older than those with previously diagnosed epilepsy, moreover, they usually suffered from severe co-morbidities. Their history of epilepsy started with SE and mortality among them was higher. Despite the adequate therapy of SE, their prognosis was poor. Based on our results, previous epilepsy was 74.4%, quite similar to those of a Norwegian study (73%), but lower (43%) than in a large prospective cohort study. It should be noted that the latter publication only examined refractory or super refractory SE cases. On the basis of our findings, one third of the patients diagnosed with epilepsy did not visit their epileptologist on a regular basis. This is regarded to be as an example of non-compliance/adherence behaviour because, in this country, yearly follow-up by an epileptologist is necessary to subsidize ASM prescriptions. So, we think that this type of non-adherence may contribute to the evaluation of SE. This emphasizes the importance of care in preventing SE. Regular care is of similar importance as, for example, preventing SUDEP (sudden unexpected death in epilepsy).

5.1.2. Etiology

Infection was the leading cause of SE in our cohort. Among the patients with pre-existing epilepsy, non-compliance, alcoholism and stroke followed infections by frequency,

while alcoholism, stroke and tumor were the most common aetiologies among NOSE patients. In a Norwegian SE cohort, cerebrovascular diseases, intracranial tumors, low ASM levels, and neurodegenerative disorders were listed as the most common cause for SE. Alcohol- and stroke-related cases of SE were less common in our study than in an article by Leppik. He found stroke to have caused 52.3% of the cases of SE among the elderly adults and 17.7% in middle-aged adults, while, in our study, the figures were 16.3 and 7.4%, respectively. It is worth mentioning that stroke was remarkable in younger age groups and among the 65–80 year-old patients. As far as stroke patients are regarded, ischaemic stroke occurred more frequently in all age groups, except for the patients aged between 65 and 80 years; the latter group was more often hit by haemorrhagic stroke. The high occurrence of haemorrhagic stroke in SE is interesting, because ischaemic stroke is more frequent in the elderly. All SE patients had a history of hypertension, which is one of the most important risk factors of stroke. In a recently published study, Ulvin et al. found the level of generalized convulsive SE at 67% in the non-refractory SE group, and at 47% in refractory SE. In contrast with Ulvin et al. in our study, the focal form of SE was most common, just as in the publications by Sutter et al. and Novy et al. Possible contradictions among these findings may be due to disparities in etiology.

5.1.3. Treatment

The number of ASMs prior to status epilepticus did not influence the number of ASMs used to control SE. Compared to other SE studies, fewer patients needed general anesthesia (17 vs. 41% by Ulvin; and 9.8% by Delaj). The choice of the ASM did not influence the need for general anesthesia. Some medications (e.g., benzodiazepines) used in SE may have severe adverse drug reactions like respiratory depression, so for NCSE patients (e.g., stroke) a good alternative therapy might be newer type of ASM. Most of the patients needed only one or two ASMs at discharge, and newer types of ASMs were in favour: we assumed that the role of drug interactions among multimorbid patients was an important argument. Seizure freedom was significantly longer among patients taking levetiracetam, carbamazepine, and valproate.

5.1.4. Outcome

In accordance with the literature, mortality from SE was high and age dependent. In-hospital mortality was 25%, in SE studies showing high variability in different studies (9–37%). However, the mortality in pre-existing epilepsy was less than in NOSE in our study. According to our findings, NOSE could be considered as a high risk factor for mortality emphasizing the importance of NOSE. Etiology also had a considerable impact on the outcome beyond SE. All patients who had cancer died. In focal SE mortality was significantly

higher than in the generalized type. Focal neurological lesions such as stroke and tumors caused mostly focal epileptic seizures, which may explain the outcome. The number and type of older and newer ASMs did not influence the outcome of SE. In terms of seizure remission, there were no significant differences between new and old type ASMs; important was to terminate SE. In his publication, Schmidt came to a similar conclusion concerning refractory epilepsy: newer types of ASMs were not more efficient than the old ones. SE might also be regarded as an extreme refractory type of convulsion. Only one out of nine patients survived NCSE. All of these patients had severe co-morbidities and were of advanced age. In general, the low occurrence of NCSE might be due to being underdiagnosed in non-neurological wards, where the patients were treated for their primary diseases on one hand, on the other hand in lack of long-term EEG on the intensive care unit and Stroke Unit ward less patients are discovered with NCSE. Implementing long-term EEG on these wards in case of predictors (large infarct size, large atherothrombotic etiology, high NIHSS score on admission) would help the diagnosis of NCSE and lead to early treatment and better outcome.

Limitations

We are aware that our study has several limitations. First of all, the current study is an observational study and not a randomized, controlled trial. Therefore, selection bias might have affected the results. Secondly, treatment options and definitions have changed during the investigated period. Unfortunately, because the several aetiological and triggering effects only low case numbers would have been achieved with subgroup analysis. Nevertheless, this study has invaluable assets including prospective data collection and detailed information on all subjects. Further strength of our study may be the real-life data sets leading to the better understanding of real-life clinical settings and the outcome of routine status epilepticus treatment.

In summary, several conditions complicate the picture in everyday practice so real-life data are essential in order to understand real patients in the ward. No strict seasonality of SE cases was observed. The worst outcome of SE was linked to advanced age, aetiology, new onset status epilepticus (NOSE), NCSE and focal status epilepsy. The choice of the ASM did not influence the need for general anesthesia. The administration of newer type ASMs in the SE treatment may have an impact on the prescription pattern after discharge, however older type ASMs are a reasonable choice to achieve seizure freedom after SE. Seizure freedom was

significantly higher among patients taking levetiracetam, carbamazepine and valproate. This study highlights the importance of regular care and follow-up of patients.

II. Women with epilepsy

The treatment and guidance of pregnant epileptic patients involve several considerations in balancing the risks between the mother and her child. Care for pregnant women with epilepsy requires a specialized team, early advice, and coaching to make the best and safest plan possible for both the woman and her child. In the past decades, to provide evidence-based care for them, many countries and different registries have started collecting and analyzing data to fulfil their task. To our knowledge, our study is the first to collect such data and address this issue in Hungary.

5.2.1. Basic characteristics

In the 20th century, WWE often hesitated to risk becoming pregnant due to potentially severe impacts on their quality of life. Even when they did become pregnant, they had to face the possibility of either inadequate seizure control or the devastating risk of fetal complications.

As safer drugs became available, WWE tended to have more and more pregnancies carried out while using ASMs. Besides, the number of new patients also grew gradually, as did the ratio of WWE among them. More factors were responsible for more women turning to our center for care individually or at their gynaecologists' request. Epilepsy became more prominent in our region due to health education, and regular consultations with gynaecologists also facilitated positive changes. Our study supports this finding: more than 80% of the studied pregnancies happened after 2002. A Danish study found similar results. The proportion of pregnant epileptic patients rose from 0.5% in 1989–1993 to 0.98% in 2009–13, according to their study. Moreover, in a Canadian study, the number of pregnancies increased gradually. It might be assumed that having access to the newer types of ASMs, women were more inclined to undertake pregnancies, even when taking more medications. This could be a contributing factor to the growing number of pregnancies observed. Moreover, better compliance was probably an important cause; as safer ASMs became available, more women took their ASMs and experienced no seizures.

Over time, women were older at the time of becoming pregnant. This might be because more WWEs had more than one child, so they were older when they became pregnant again. In addition, women's ages during pregnancy also increased in the population. Similar results were found in a study by Shihman et al. Our results align with the general age trends for

women becoming pregnant in the Hungarian population. Over the years, many more patients have had regular checkups (I) earlier in the first trimester, emphasizing the importance of care, which was also recognized by patients. Sometimes, the first epileptic seizures may be experienced during pregnancy, especially due to toxaemia or diseases of the central nervous system. These cases also require attention since these patients are unfamiliar with epilepsy, so their examination and follow-up are important. The result of care group III highlights the importance of tertiary epilepsy centers where gynaecologists can consult with specialists having experience with PWWE.

5.2.2. Seizures

Among the seizure types, tonic-clonic seizures pose the greatest risk to the fetus the most, regardless of whether they are generalized or focal-to-bilateral tonic-clonic seizures. In our study, these were present in more than three-quarters of the pregnancies (85.6%) and were significantly less common in the regular care group I. This emphasizes the importance of regular checkups and good cooperation with the patient. Peripartum seizures occurred in our follow-up group I due to poor maternal compliance. This was often driven by fears of fetal abnormalities and, in some cases, was due to alcoholism. Monotherapy was the most common choice for treatment, chosen for its effectiveness and safety. We found different patterns in the different treatment groups. Only a few patients received more than two ASMs. Bitherapy was especially useful when LTG or LEV alone was not enough. As part of bitherapy, ASMs (e.g., CBZ and VPA) could be administered at lower doses. When discontinuing VPA was not an option, the dosage of VPA was kept as low as possible (mostly under 600 mg) in all-time groups. Although seizures still occurred in some cases, the frequency increased only in a few cases.

5.2.3. Treatment

Major changes in the favoured drugs of choice for use in pregnant epileptic patients have been observed over the years. While carbamazepine was the number-one choice in the 1990s, its use showed a huge decline after the 2000s. Simultaneously, lamotrigine had a steep rise, followed by levetiracetam in the 2010s. Similar findings were also found after the analysis of the EURAP registry. The use of LTG and LEV gradually increased over the years, especially in the regular care group I, where the choice of ASM favoured medications with fewer or no side effects for pregnancies. Unfortunately, there were some patients, even in the regular care group I, in whom VPA could not be discontinued, but the dosage could be reduced (<600 mg). Although the effects of VPA on the fetus have been discussed only in a recent publication, a study from 1999 reported that VPA might have a negative impact on

pregnancy in a dose-dependent manner. Therefore, we decreased the dose of VPA as much as we could to reduce the risk of side effects already in the early treatment groups (even in G2). According to the literature, exposure of the fetus to the new ASMs is less likely to increase the risk of major congenital malformations compared to older drugs. Therefore, the importance of regular care with the use of LEV and LTG can be emphasized, which is more common in this group, showing that in this case, the epileptologist will consider a safer ASM in fertile women in due time. Among our patients, few had to take psychiatric medications during pregnancy or had severe psychiatric problems, which might increase the risk of abortions and foetopathies. According to Bangar et al., these women have to cope with two clinically relevant and important issues simultaneously, besides possible drug interactions and non-adherence, emphasizing the importance of care.

Dosage changes usually mean an increase in a quarter of all patients. The factors associated with dosage change were a low serum ASM level or interictal epileptiform discharges on EEG. Our data indicate that most of our patients underwent EEGs, which – had it revealed epileptiform activity – could lead to adjustments in treatment. As a result of our findings, we offered every pregnant woman to do an EEG in the second trimester and, if necessary, to repeat it for over a decade. Low serum ASM levels were most often observed with the use of LTG. The rest were associated with LEV or CBZ. It is well-known that some ASDs are likely to have a decreased serum level due to physiological changes during pregnancy. Our results are comparable to those based on data from the EURAP registry. In this study, doses had to be increased in 26% of the cases. We also found that lamotrigine needed to be increased most often, followed by levetiracetam and valproate.

5.2.4. Outcome

In our study, most pregnancies in WWE were uneventful and could be carried out without major problems. For most women, if they had seizures at all, they remained focal, and even if they had tonic-clonic seizures, generally associated with worse outcomes, the actual burden was small. All these findings concord with the findings from several different registries, like the EURAP and Danish registries, to mention but a few. WWE's live births were 91.7%. As a matter of fact, 91.7% of the WWE in this study delivered live babies; this finding is similar to that from a Turkish study. Remarkably, more pregnancies ended with live births over time. The rate of spontaneous and induced abortions was relatively constant. Similar to data from the Hungarian Central Statistical Office, the rate of spontaneous bortions remained between 7 and 8/1,000 women from the 1990s until now in the general population. Abortions were mainly miscarriages. Some studies link older-type ASM use with higher rates

of miscarriages, but these findings could not be confirmed by many larger cohorts. A study observed almost a million pregnancies where the spontaneous abortion rate did not increase among WWE-taking ASDs compared to those who did not. Unfortunately, fetal death happened in a twin pregnancy, which means 0.5%, whereas, in a meta-analysis, stillbirth and fetal death represented 1%. The study based on the EURAP registry found no differences in the intrauterine death rates between old and new monotherapies. An increased risk was only found with polytherapy. In our study, we did not find a relationship between spontaneous abortions and different drugs, nor did we see a higher abortion rate with polytherapy, but we should remark that we had only a few patients on polytherapy. However, some studies assume that polytherapy alone might not be associated with an increased risk, only when the combination contains valproate. It is also well-known that fetal complications are dose-related. We found no adverse associations with valproate, but the dosage remained low even in the early periods. Although valproate was officially advised against only in 2018, its adverse effects had been published much earlier. For this reason, it has been common practice at our center to avoid prescribing valproate to fertile women since as early as the first few years of the examined period, and ever since, valproate has been used only when necessary. This is represented in our study, as only a handful of the studied WWE were on valproate therapy, most of them at lower doses (<600 mg/day). We also registered very few cases of foetopathies (2.7%), which falls in the range of 2–3% found in the normal population. We could not detect any relationship between foetopathies and ASM either. However, we found that patients who received psychiatric treatment, or those who would need it, were at a higher risk for induced abortions.

Limitations

Of course, our study also has limitations. First, this was an observational study. Secondly, treatment options and definitions have changed within the examined period. In our study, we processed the data of 191 pregnancies, the low number of cases may have influenced the number of detected malformations. At the same time, a similar population can be expected in a real-life situation depending on the catchment area. The advantages of our study are the prospective data collection and the available detailed information about the cases. Another strength is the collection of real-life data, which can be beneficial in understanding real clinical cases. Thirty years of data collection in a single center is also a strength.

In summary, with reliable, flexible care and the use of safer ASMs, the number of pregnancies increased over time. We hope that attitudes towards epilepsy will also change.

Based on our data, better care can be provided in specialized centers, but cooperation with obstetricians can also be emphasized. Despite the fact that their number decreased during our study, there are still women who do not receive the necessary care and information. Our data prove that pregnant women with epilepsy can have an uneventful pregnancy similar to the normal population, if professional care is available.

6. Summary

Epilepsy is chronic disease, in many cases needs life-long treatment, modifies different aspects of life and and might have life-threatening consequences. In this work two aspects of epilepsy were examined that have been altered by biological events. Firstly, we focused on the outcome of SE in view of anticonvulsant therapy during SE and in the follow-up period, risk factors such as age, co-morbidity, pre-existing epilepsy, as well as the underlying pathology, in the East-Hungarian region. Secondly, we investigated a special scenario: pregnancy among women with epilepsy (PWWE).

Two databases were created for our purposes. In case of SE, the outcome was studied among patients with the ICD code for SE. For investigating PWWE we analysed 30 years' data acquired from the Debrecen Epilepsy Database regarding their treatment and outcomes in our region.

We concluded that etiologic factors of SE varies among different age groups, and also among patients with and without previously known epilepsy. The most frequent etiological factors were infections (systemic and CNS), stroke, alcoholism and non-compliance. In comparison with international data significant regional differences emerged. Higher mortality was associated with older age, cancer as comorbidity, focal and non-convulsive forms of SE, and new-onset status epilepticus, these were in line with international trends. Whether new or old ASM was used did not affect mortality. In-hospital mortality was followed by a six month' peak after discharge. Older patients tended to die during hospitalisation, younger patients more likely died after discharge, mostly due to their comorbidities. Among survivals those taking levetiracetam, valproate or carbamazepine had the highest chance to achieve seizure freedom. According to our data most PWWE had a normal, complication free pregnancy similarly to their healthy peers. With a reliable flexible care and safer ASMs, the number of pregnancies grew over time. The rate of live births also increased, while the rate of abortions remained constant. Among PWWE not receiving regular care the use of older drugs and polytherapy were more frequent and epileptic seizures occurred more, supporting the need for regular care. Overall, regular care is safer for a PWWE, but it is equally important that gynaecologists and epileptologists consult about the cases even if the PWWE is treated in another centre. Based on the interim analysation of our data we could optimise our treatment protocol for these patients.

Our data highlight the importance of regular care and a multidisciplinary approach in the treatment of epilepsy patients, the education and involvement of the patients in the decision.

7. New establishments

1. We created a database to study patients treated for status epilepticus in our regionin order to evaluate the etiological factors, treatment and outcome (long term mortality, seizure freedom) of SE. The importance of this is highlighted by the fact that real life data is necessary for such a severe disorder as status epilepticus.
2. The most common etiologies were infections, stroke, alcoholism and non-compliance/non-adherence. The factors differed between age groups and based on whether the patient did or did not have previous epilepsy. Important fact regarding this study that almost half of the studied population belonged in the active age-group. Poor outcomes in SE were associated with older age, aetiology, new-onset status epilepticus, NCSE and focal SE. The choice of ASM did not affect the need for general anaesthesia.
3. Many patients with status epilepticus needed treatment due to non-compliance. Our study emphasises the importance of regular epileptological care.
4. Introducing newer type ASM into the treatment of SE might influence maintenance therapy later, however, older type drugs are also reasonable choices for achieving and maintaining seizure freedom after SE. Seizure freedom was significantly more common among patients taking levetiracetam, carbamazepine and valproate.
5. We collected thirty years' worth of data about pregnant women with epilepsy, regarding the outcome and treatment during pregnancy, first in our region. Based on our data, most PWWE is uneventful, and has a comparable rate of complications as their healthy peers. Decade after decade more women undertake becoming pregnant, even if more medications were needed. The ratio of live births increased, while the number of spontaneous and induced abortions remained constant. These positive changes might have been influenced by the availability of newer type ASMs and better care.
6. Women not getting regular care the use of older drugs and polytherapy was more common, they were more likely to experience a seizure during their pregnancy. Based on our data, the number of these women has been decreasing year by year.
7. All in all, regular care is the most appropriate, safest choice for PWWE. Our data also showed, however, that it is also important for epileptologists and obstetricians to consult about these patients, even if the woman is treated in a different centre.

8. As a result of our data's interim monitoring, the following model was used to take care of PWWE in our centre: therapeutic drug monitoring of ASM serum levels in the first and second trimesters and EEG recording in the second trimester. The epileptologist declares the safety of childbirth and lactation from a neurological point of view. Mothers are requested to come for checkups at the end of the postpartum period and regularly during the first year after labour. The child(ren)'s documents during that time are also required. We initiate discussions about pregnancy with women of childbearing age before the pregnancy actually occurs. Over time, fathers come more and more often to our care to support their partners.

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