

The General and Social Health Long-Term Outcome of Adult Epilepsy Patients at the Kork Epilepsy Center



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ABSTRACT

Objectives The majority of epidemiological studies show that there is an increased burden of somatic comorbidities among people with epilepsy (PWE) compared with the general population. We sought that in the subgroup of patients with satis-

factory and stable seizure situation and healthy style of living, the general health and quality of life might be similar to people without epilepsy and investigated the long-term outcome and the prevalence of comorbidities and the social outcome of adult patients who had been continuously treated at our center for at least 25 years.

Material and methods We consecutively collected our adult out-patients for 10 months and identified those patients who had been treated at our center for at least 25 years. Among this group we assessed demographic data, epilepsy syndrome, seizure situation, antiepileptic therapy, the number of previous AEDs, the socioeconomic situation and co-morbidities.

Results Out of a total of 1672 patients, 14.4 % (n = 241) patients fulfilled our inclusion criterion. In 200 the files allowed an appropriate analysis of the data. Mean treatment duration in Kork was 36 years (25 – 52). 60% of patients were seizure-free for more than one year. 80% of the seizure-free patients did not complain of adverse events. Adverse events were more often among patients with ongoing seizures. Somnolence, gait disturbances and tremor were the leading symptoms. Better seizure outcome correlated with higher education, better professional education and lower unemployment rates. Diseases such as cardiovascular diseases or diabetes mellitus were not more frequent than in the general population. PWE do not have necessarily an impaired prognosis of their general health.

Introduction

The burden of drug-resistant epilepsy including impaired quality of life and increased morbidity and mortality has been extensively addressed in the literature [1–3]. Despite the introduction of numerous new antiepileptic drugs (AEDs) since the early 1990s and the complimentary options of epilepsy surgery, neurostimulation or dietary treatments, the therapeutic prognosis of epilepsies has not convincingly changed. Around one third of epilepsy patients appear to be at least partially AED-resistant prior [4], during [5] and still after the introduction of numerous new AEDs [6, 7].

The majority of numerous epidemiological studies among people with epilepsy (PWE) reported an increased burden of somatic comorbidities [8]. Most studies were interested in the impact of active epilepsies in the patients with a bad long-term prognosis.

However, the other two thirds of epilepsy patients, i. e. those with a rather good prognosis have not been in the focus of scientific interest to the same extent. Not very much is known about their long-term outcome in general although a risk of premature mortality has also been reported in PWE with seizures in remission and off medication [9].

Still, we got the impression that many of our patients with a satisfying course of their epilepsy also have a satisfying general condition and social life which might have a major impact on very practical drawbacks all PWE still have to face: At least in Germany, it is almost impossible for any patient with epilepsy to get accepted as client by insurance companies due to the assumed elevated long-term health risk of epilepsy patients irrespective of the underlying epilepsy syndrome. Undoubtedly there is an elevated morbidity and mortality in patients with ongoing seizures [1–3]. In principle,

acute and especially chronic tolerability issues may arise even in seizure-free patients if they continue AED treatment, and many people with epilepsy will face a long-term or often lifelong drug therapy [10]. Enzyme-inducing AEDs mean an elevated risk of developing vitamin or hormone deficiencies with an impact on the general health [11–14], although many seizure-free patients are probably only under monotherapies and/or low dosage AED treatments [15] so that the drug load is less hazardous.

In the Kork Epilepsy Center we have the chance to follow out- and in-patients for long periods of time. Many patients have been referred for decades. This gave us the opportunity to have a closer look at the seizure, drug tolerance and general health situation of adults that have been seen at our hospital for a long time, i. e. at least for 25 years. We sought to show that patients with sustained seizure freedom most probably do not have significant long-term health issues whereas patients with active and AED-resistant epilepsy are at a higher risk of developing additional health problems due to a higher drug load and thus of chronic adverse events under AEDs.

Material and Methods

From May of 2014 until February of 2015 we consecutively collected all adult in- and out-patients who had been referred to the department of adults at the Kork Epilepsy Center. This department comprises an out-patient service as well as three in-patient wards. Since additional adult patients were treated at our Séguin-Clinic for persons with epilepsy and severe intellectual disabilities, we did not gather every adult epilepsy patient of our center completely in the time period mentioned above. In addition, our study population certainly shows an under-representation of PWE and intellectual deficits.

We identified patients who had been treated at our center for at least 25 years. Data on these patients were systematically investigated. We recorded the epilepsy syndrome and seizures, seizure frequency, current and previous AED therapies, current and previous adverse events, social and familial status and co-morbidities, as well as additional drug treatments based on the individual history taken at the examination during the period defined above.

The study was approved by the local Ethical Committee at the University of Freiburg, Germany.

For data analysis only descriptive statistics were used.

Results

Among a total of 1672 patients we identified 240 (14.4%) who had been treated continuously at our center for at least 25 years. 200 patients were finally included due to complete datasets. Gender distribution was almost equal (50.5% female). Mean age was 54 years (27–87 years). Mean duration of treatment at our center was 36 years (25–52 years). Mean age at onset of epilepsy was 9 years with 12% starting during the first year and 28% between age one and five years. The highest age at onset of seizures was 55 years.

The most common ICD-10 classifications were G40.2 (68%) and G40.3 (22.5%). The most common seizures were generalized tonic-clonic seizures. 87.5% of our 200 patients had at least one during the course of their disease. The second and third most common seizure types were focal impaired awareness seizures with autom-

► **Table 1** Seizure outcome.

| | n | % |
|--|-----|----|
| Freedom of seizures * | 120 | 60 |
| One seizure to several seizures per year | 35 | 18 |
| At least one seizure per month, less than one seizure per week | 27 | 14 |
| At least one seizure per week, less than one seizure per day | 14 | 7 |
| Daily seizures | 4 | 2 |
| Total | 200 | |

Freedom of seizures = freedom of seizures for at least one year prior to the last observation carried forward

atisms (55.5%) and other focal seizures including aware seizures with various leading symptoms (37%). Absence and myoclonic seizures were reported in 13% and 8%, respectively.

We defined seizure freedom as a seizure-free period of at least one year. According to this definition, 120 patients (60%) were seizure-free. Few seizures per year were reported in 18%. 14% had monthly, 7% weekly and 2% daily seizures.

Seizure freedom was often sustained (► **Table 1**). In 53% of all patients the longest seizure-free interval lasted longer than 10 years (maximum 40 years). Seizure freedom lasted 1 to 9 years in 29%, 1 to 11 months in 14% and less than one month in 4%.

53% of the seizure-free patients were on one antiepileptic drug (AED), 38% on 2 AEDs and 4% on three AEDs. Another 3% of the seizure-free patients had undergone successful epilepsy surgery and were off drugs. Figures were different in patients who were not seizure-free: AED monotherapy was performed in 13%, two AEDs were given in 44%, three in 31%, 4 in 10% and 5 or more in 2%. All patients in this group were under AED treatment.

The most commonly used AEDs were levetiracetam (21.5%), valproic acid (20.5%), lamotrigine (19.5%), carbamazepine (14.5%), phenobarbital (14.5%) and phenytoin (10.5%). Other AEDs with less frequent use comprised oxcarbazepine, zonisamide, topiramate, benzodiazepines, lacosamide, eslicarbazepine acetate, perampamil, bromides, sulthiame, gabapentin, ethosuximide, mesuximide and pregabalin.

70% of the seizure-free patients became seizure-free after the use of a maximum of 5 AEDs. 13% became seizure-free with the first AED, 15% each with the second or third and 17.5% with the fourth AED. On the other hand, one patient became seizure-free after and under the 14th AED which was add-on lacosamide in this case. Mean number of AEDs in the seizure-free group was 4.4 (range 1–14). Among the non-seizure-free patients in 81% more than 5 AEDs had been tried. The mean number of AEDs was 10 (range 3–23).

Adverse events were not systematically or actively assessed. They were reported in the files. Under these conditions 26% complained of adverse events. Adverse events were reported by 20% of the seizure-free patients and in 36% of patients with ongoing seizures. In 29% of patients with at least monthly seizures and in 61% of patients with more frequent seizures, adverse events were

reported. Over all patients somnolence (28.3%), ataxia and tremor (9.4% each) were most common. Less common adverse events comprised sleep disturbances, impaired coordination, cognitive deficits, dizziness, visual field problems and other visual symptoms, sensory or motor deficits, polyneuropathies, altered blood counts, abnormal electrolyte levels, osteoporosis or impaired bone density, Dupuytren's disease, shoulder pain, hoarseness and acne.

Comorbidities, which were also not actively addressed, were not apparent in 32.5% of the seizure-free and in 12.5% of the non-seizure-free patients. In the seizure-free cases 35.8% had one comorbidity, 16.7% two comorbidities, 10.8% three, 2.5% four, 0.8% five and 0.8% seven. The corresponding figures in the group of non-seizure-free patients were 26.3%, 32.5%, 16.3%, 6.3%, 1.3%, 2.5%, and 2.5%, respectively.

Common comorbidities included psychiatric symptoms (49.5%) followed by nervous system (31%), circulation, (14.5%), muscle and skeleton (12%), and endocrinological symptoms (9%). The leading additional diseases were intellectual deficits (20.5%), organic psychiatric disorders (14.5%, 3.5% personality disorders) and hypertension (12.5%). These co-morbidities were distributed almost equally in the group of seizure-free patients (10.8%, 12.5%, 11.7%) but not if seizure freedom had not been achieved (35%, 18.8%, 13.8%).

Common internal diseases such as disorders of the circulation, diabetes mellitus and hypertension had a prevalence of 5%, 2% and 13%, respectively.

51% of the seizure-free patients but only 26% of the not seizure-free patients were married, had been married, were widowed or lived or had lived in a cohabitational relationship.

10% of the seizure-free patients had a high school degree, 59% had a qualified professional education, 54% were or had been employed at the first market, 9% were unemployed at the time of our survey, and 11% were receiving disability benefits. The corresponding figures in the group of patients with ongoing seizures were 3%, 44%, 15%, 15%, and 24%, respectively. ► **Table 2** summarizes our findings.

Discussion

Although the long-term results presented here are relatively reassuring, one should not forget that the structure of our epilepsy center probably suggests a positive selection bias: We do see a lot of adults with additional comorbidities and also with intellectual deficits in our department but usually adult patients with epilepsy and severe intellectual deficits are appointed to and treated in the department of patients with severe intellectual disabilities at our center, so that our results may tend to reflect false positive results.

Furthermore, patients not satisfied with our treatment due to ongoing seizures, adverse events or both and deaths during the past period of at least 25 years were not covered by this cross-sectional study. Mortality is clearly increased in adult patients with difficult-to-treat epilepsy syndromes [16, 17] and even in patients with seizures in remission and without antiepileptic drug treatment [9].

Our results confirm that the long-term prognosis of epilepsy in adulthood is not too bad. 60% of our patients were seizure-free for more than one year. A majority of patients achieve seizure freedom quite early in the course of the disease and mainly after few differ-

► **Table 2** Comparison between seizure-free patients and patients with ongoing seizures.

| | Seizure-free | Ongoing seizures |
|---|--------------|------------------|
| 1 AED | 53% | 13% |
| 2 AEDs | 38% | 44% |
| 3 AEDs | 3% | 31% |
| History of 1 AED | 13% | 0 |
| History of 2 AEDs | 15% | 0 |
| History of 5 or less AEDs | 70% | 19% |
| Mean number of AEDs in the history | 4.4 | 10 |
| Adverse events | 20% | 64% |
| Comorbidities not present | 32.5% | 12.5% |
| Intellectual deficits | 10.8% | 35% |
| Organic psychiatric disorders | 12.5% | 18.8% |
| Hypertension | 11.7% | 13.8% |
| Married, widowed or cohabitational relationship | 51% | 26% |
| Qualified professional education | 59% | 44% |
| At least once employed on first market job | 54% | 15% |
| Unemployed | 9% | 15% |

ing AED regimens. These results confirm the extensive literature dealing with the topic [16–24].

Higher education and social level corresponded with a better seizure situation. However, it is difficult to say whether this is one of the determinants or a result of a satisfactory seizure frequency. In another huge epilepsy cohort the income of families did not correspond with the clinical course or long-term seizure outcome of childhood epilepsy. However, in this study the parental income and not of the patients themselves was addressed [25]. In general it has been shown earlier that epilepsy correlates with psychosocial and socioeconomic difficulties, lower academic levels, higher unemployment rates and less frequent marriages than in the General population [8, 26–38].

Still, occasionally one succeeds despite unfavourable circumstances. The good news for one patient in our series was that in spite of all experience that freedom of seizures is extremely unlikely after several appropriate AED trials [39] this patient became seizure-free with the 14th AED. Thus, while any irrational polytherapy and actionism in epilepsy treatment should certainly be avoided, one should never give up.

It is not surprising that comorbidities were more frequent in the group of PWE who were not seizure-free which was already described by others [40]. Psychiatric symptoms were leading. One has to consider that their frequency was certainly influenced both by a causal and a resultant bias, i. e., their role as an underlying cause of the epilepsy and as a result of the epilepsy, respectively [8]. Numerous studies addressed the question of comorbidities in epilepsy [4–7, 10–20, 35, 39–45] and were nicely reviewed in a very recent article by Serkedaki and Novy [8]. Novy and co-workers recently reported higher rates of comorbidities than in the general

population [40] which was not a finding in our study, at least if we consider hypertension, vascular diseases and diabetes.

One further question of this study was to assess whether epilepsy patients with good seizure outcome do have additional clinically relevant impairments of their health. Apparently general health was not necessarily impaired markedly, especially not in case of a satisfying seizure situation. It is therefore not justified that, for instance, insurance companies do not accept patients only because of an epilepsy diagnosis. It would be wise to differentiate between good and bad seizure outcome prognosis. It was tempting to investigate whether in our patient group common diseases and conditions that frequently occur in Western industrialized countries were reported more or less frequently than in the general population. The prevalence of disorders of the circulation, diabetes mellitus and hypertension was 5%, 2% and 13%, respectively and thus lower than in the general German population according to structured interviews among 26.000 persons in 2012, which reported a prevalence of 8.3%, 7.7% and 28.4%, respectively [41].

It is somewhat surprising that the prevalence was clearly lower in our group of persons with epilepsy even in people with ongoing seizures. Seizure-free patients reported such diseases very occasionally. There is no evidence that people with epilepsy are at a higher risk of developing these enormously costly diseases (for both society and insurance plans) compared to the general population. We suggest that the regular health check appointments including physical and laboratory investigations and a healthier lifestyle due to the underlying chronic disease might have led to these results, and this should help in reconsidering the lifetime health risk of people with epilepsy, especially in the case of a good prognosis of the epilepsy itself. For studies that revealed higher comorbidity risks in epilepsy patients it has been suggested that in patients with regular appointments with physicians might have a higher trend to report comorbidities [8, 46]. In our study the consideration of this effect would have led to even better real outcomes concerning hypertension or diabetes rates.

In the future, the health prognosis of PWE should be even better. The good tolerability profile of some of the newer AEDs [42] might improve the health prognosis even further.

Patients with drug-resistant epilepsies are double disadvantaged: Not only do they still have active epilepsies with hereby resulting higher morbidity and mortality; but they are also often subject to more complex AED regimens with a higher risk of additional drug-induced adverse events.

A more accurate approach to the problem of co-morbidity would have been using standardized questionnaires to assess sleep disorders [43] or intellectual deficits [44] or applying objective methods like x-ray densitometry to measure bone density [45] or measurements of nerve conduction velocities etc. We believe that the incidence of comorbid symptoms would have been higher that way although the general distribution of the single co-morbidities among the patients should have not been influenced critically. We finally have to admit that the method to assess general health data in our group and in the survey cited [41] was certainly different so that the comparability is reduced.

The general message of this paper is that in accordance with the literature more than 50% of adult epilepsy patients have a favora-

ble long-term prognosis and that in our patient group especially seizure-free patients did not have a restricted health prognosis.

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Conflict of Interest

Bernhard J. Steinhoff has received speaker's honoraria from Desitin, Eisai, GW pharmaceuticals, MedScape, Novartis, Shire and UCB. He was a paid consultant of Actelion, B. Braun, Eisai, and UCB. Christoph Kurth and Anke M. Staack have received speaker's honoraria from Desitin, Eisai and UCB. They were paid consultants for Eisai and UCB. Matthias Bacher has received speaker's honoraria from Desitin. Reinhold Kornmeier and Maxi Burkhardt have no conflict of interest to disclose.

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