The ILAE definition of drug resistant epilepsy and its clinical applicability compared with "older" established definitions

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Received January 25, 2015
Accepted for publication on-line March 19, 2015
Published on-line April 2, 2015

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SUMMARY

Background. Early identification of potential epilepsy surgery candidates is essential to the treatment process.

Aim. To evaluate the clinical applicability of the ILAE definition of drug resistant epilepsy and its potential in identifying surgical candidates earlier compared to three established "older" definitions of drug resistant epilepsy.

Material and Methods. Retrospective analysis of 174 patients who underwent epilepsy surgery between 1998 and 2009. Clinical factors and course of disease were extracted from patients' charts. Drug resistant epilepsy was classified according to four definitions and the time until fulfillment of criteria compared.

Results. Mean time to fulfillment of criteria of drug resistant epilepsy ranged from 11.8 (standard deviation (SD) 9.8) to 15.6 years (SD 11.3). Time to drug resistance was significantly longer applying the only definition, requiring failure of three antiepileptic drugs (AEDs) (Canada definition), whereas time to fulfillment of all other definitions did not differ. Fifty percent of all patients experienced a seizure free period of ≥1 year prior to being classified as drug resistant, 13% entered another 1-year remission after fulfilling any criteria for drug resistance.

Conclusion. We conclude that the ILAE definition identifies drug resistant epilepsy, with similar latency like two of three formerly used definitions. It is an easy applicable tool to minimize the delay of referral to a specialized center. Intermittent remissions delay assessment of drug resistance for all definitions and 13% of patients enter a remission despite established drug resistance.

Keywords: definitions of drug resistant epilepsy • epilepsy surgery

BACKGROUND

Epilepsy surgery is an effective treatment for patients with drug resistant epilepsy leading to seizure freedom in up to 70% (Sperling et al., 1996; Wiebe et al., 2001; Engel et al., 2003; Neligan et al., 2012). Early identification of appropriate candidates for surgery is essential (José et al., 2012) as surgical intervention early in the course of the disease is superior to further medical trials (ERSET) (Engel et al., 2012). Various definitions of drug resistance have been used in previous studies (Berg et al., 2001; Berg et al., 2003; Camfield and Cam-

field, 2003; Berg and Kelly, 2006). This makes it difficult to compare findings and establish practice recommendations as definitions differ according to the intended use and purpose, and may lead to significant differences in the decision for epilepsy surgery (Berg and Kelly, 2006). To facilitate research and identification of patients with drug resistant epilepsy at an earlier time point, an ILAE Task force was appointed and proposed a consensus definition of drug resistant epilepsy in 2010 (Kwan et al., 2010).

AIM

In this study we aimed to compare three formerly used definitions of drug resistant epilepsy with the ILAE criteria to assess their validity and see whether the new definition would have lead to earlier identification of patients with drug resistant epilepsy. We retrospectively compared three existing definitions for drug resistant epilepsy with the new ILAE definition regarding time to fulfillment in a cohort of surgically treated patients.

MATERIAL AND METHODS

Patients

All patients who underwent epilepsy surgery between March 1998 and June 2009 in the Innsbruck Epilepsy Surgery Program (INES) at the Department of Neurology and the Department of Neurosurgery, Medical University Innsbruck, Austria were evaluated. The centre provides the only epilepsy service in the region and serves a population of about one million. All patients, who were admitted to our center since 1968, were followed regularly at the seizure clinic by an epileptologist. The patients were followed for more than three decades by Prof. Dr. G. Bauer and since 2003 by ET. Data on patient`s medical history including seizure onset, seizure types, seizure frequency, seizure free periods and treatment history were collected by the treating epileptologist at the first visit and entered into a database. At each visit, treatment changes, seizure frequency and seizure free periods were entered into the database as well. Only those patients who were followed long enough to enter the presurgical evaluation were included, and some patients might have been lost at follow up prior to presurgical evaluation and are therefore not represented in our study. Presurgical evaluation included neurological examination, neuropsychological testing, interictal routine EEG, cerebral MRI scan (1.5 Tesla) and prolonged video-EEG monitoring. In case of discordant seizure semiology to lesional MRI findings, ictal SPECT and PET scans, as well as implantation of intracranial subdural and depth electrodes were considered.

Exclusion criteria were surgery due to progressive neoplastic lesions, elective surgery to prevent bleeding complications of cavernoma or arteriovenous malformation (AVM), and insufficient data on clinical course and outcome.

With regard to etiology, symptomatic epilepsy (i.e. structural including hippocampal sclerosis, focal cortical dysplasia, dysplastic tumors, gliosis, arteriovenous malformation (AVM), cavernoma, cerebral atrophy, postoperative, postinfectious, posttraumatic and perinatal lesions) was distinguished from cryptogenic (i.e. of unknown cause) epilepsy.

Clinical factors

By retrospective chart review, age at seizure onset, age at surgery, seizure frequency during the last presurgical year, number of antiepileptic drugs (AEDs) prior to surgery, time to AED failure and number and duration of remissions (table 1) were determined. A remission was defined as one year or more of complete seizure freedom. AED failure was defined as recurrent seizures despite therapy with an appropriately chosen and dosed AED. Seizure frequency was assessed and documented at every visit by the treating physician either through extraction from the seizure diary or seizure frequency claimed by the patient and entered into the database. Data on the entire course of disease prior to referral to hospital including seizure frequency, occurrence of seizure free periods and time and reason for AED changes were retrospectively assessed by the treating physician at first visit to the seizure clinic by collection of medical records from general practitioners or referring pediatric units. In case of incomplete documentation of seizure frequency and duration of seizure free periods, seizure frequency as recollected by the patients were taken as reference and an average seizure frequency was estimated by the available data. Time point of intractability was established in retrospective according to three existing definitions of drug resistant epilepsy (Berg et al., 2001; Berg et al., 2003; Camfield and Camfield, 2003; Berg and Kelly, 2006) as well as the new ILAE definition (Kwan et al., 2010). The three “older” definitions of drug resistant epilepsy used in this study were taken from a prospective cohort study in children by A. Berg and M. Kelly

Table 1. Clinical data

Patients' demographics	**n = 174 (%)**
Sex	
female	86 (49%)
male	88 (51%)
Localization of seizure onset zone	
temporal	148 (85%)
extratemporal	26 (15%)
Etiology	
cryptogenic (i.e. unknown cause)	22 (13%)
symptomatic (i.e. structural)	152 (87%)
Symptomatic etiology	**(n = 152)**
hippocampal sclerosis (HS)	47 (31%)
dual pathology with HS	40 (26%)
gliosis	1 (1%)
focal cortical dysplasia	25 (16%)
AVM	3 (2%)
cavernoma	7 (5%)
posttraumatic	6 (4%)
perinatal	2 (1%)
postinfectious	5 (3%)
tumour	7 (5%)
postoperative	1 (1%)
other	8 (5%)
Seizure frequency per month	Mean 13.3 (SD 44.5) Median 3.5 (range 0.0 to 500.0)
Seizure frequency year before surgery per month	Mean 11.5 (SD 27.5) Median 5.0 (range 0.0 to 300.0)
Age at seizure onset (years)	Mean 15.1 (SD 12.7) Median 12.6 (range 0.1 to 52.2)
Age at surgery (years)	Mean 38.5 (SD 11.9) Median 39.0 (range 14.0 to 70.1)
Time to surgery (years)	Mean 23.5 (SD 14.7) Median 21.7 (range 1.0 to 47.8)
Number of AEDs before surgery	
1–3 AEDs	34 (20%)
4–7 AEDs	101 (58%)
>7 AEDs	39 (22%)

(Berg and Kelly, 2006) and are in the following referred to as " Canada definition", "Connecticut definition" and "surgery definition" according to the way they were referred to in this paper. They required a) failure of a minimum of three AEDs and the occurrence of an average of one seizure every two months within the last year of follow up (Canada definition) (Camfield and Camfield, 2003), b) failure of two appropriate AEDs and the occurrence of an average of one seizure per month for ≥ 18 months and no more than 3 months seizure freedom during that time (Connecticut definition) (Berg and Kelly, 2006) and c) failure of two AEDs (Surgery definition) (Berg and Kelly, 2006). Those three were compared with the consensus definition of the ILAE which requires failure of two tolerated and appropriately chosen and used treatment schedules as monotherapy or in combination (ILAE definition) (Kwan et al., 2010). Drug resistant epilepsy was grouped into three patterns: 1) primary refractory with no occurrence of remission during the entire course of disease, 2) secondary refractory with one period of remission defined as seizure freedom ≥ 1 year and 3) relapsing remitting with more than one remission before meeting the criteria of drug resistant epilepsy.

Statistics

Statistical analysis was performed using the statistical software SPSS. All statistical assessments were two-sid-

Table 2. Comparison of time to fulfillment of criteria for drug resistant epilepsy

	Surgery	Canada	Connecticut	ILAE
Surgery	**Median 8.9 years Range 0.5–53.0 years Mean 11.8 years**	P < 0.001*	P = 0.157	P = 0.02
Canada	P < 0.001*	**Median 14.8 Range 0.7–53.4 years Mean 15.6 years**	P < 0.001*	P < 0.001*
Connecticut	P = 0.157	P < 0.001*	**Median 9.1 years Range 0.5–53.0 years Mean 12.0 years**	P = 0.06
ILAE	P = 0.02	P < 0.001*	P = 0.06	**Median 10.0 years Range 0.4–53.0 years Mean 13.3 years**

Wilcoxon Rank Test: * significance level after Bonferroni correction p < 0.008

ed. Univariate analysis was performed using the Wilcoxon signed rank test for assessment of differences between two definitions. Significance levels were set at p < 0.008 after Bonferroni correction for controlling the family wise error rate. The Friedman Test was used for overall comparison of all four definitions.

Standard protocol approvals, registrations, and patient consents

This is a retrospective non-invasive study, which does not require ethics committee approval according to the Austrian Law on Research.

RESULTS

A total of 200 patients underwent epilepsy surgery between 1998 and 2009. Patients were excluded due to elective surgery to prevent bleeding of cavernoma (n = 12) and AVM (n = 2) as well as in case of resection of tumor with oncological indication (n = 8). Four patients were excluded due to insufficient data on clinical course and outcome. 174 patients (86 women) met inclusion criteria, and were further analyzed. Mean age at surgery was 38.5 years (standard deviation (SD) 11.9; median 39.0 years; range 14.0 to 70.1), mean age at seizure onset was 15.1 years (SD 12.7; median 12.6 years; range 0.1 to 52.2). Mean time from seizure onset to surgery was 23.5 years (SD 14.7; median 21.7 years; range 1.0 to 47.8) (table 1). Eighty-seven percent of the patients (n = 151) received initial monotherapy (CBZ 35%, PHT 13%, PB 6%). A combination therapy of two AEDs was established in 13% (n = 23) as the primary treatment regimen, in 45% (n = 79) after failure of an initial monotherapy, and in 59% (n = 103) after failure of two AEDs in monotherapy. Thirteen patients did not receive three or more AEDs and could not therefore meet the Canada definition. Twenty two percent (n = 39) received more than seven AEDs prior to surgery.

Criteria of drug resistance were met on average after 11.8 years (SD 9.8; median 8.9 years; range 0.5 to 53.0) following diagnoses according to the surgery definition, 12.0 years (SD 10.0, median 9.1 years, range 0.5 to 53.0) according to the Connecticut definition, 15.6 years (SD 11.3; median 14.8 years; range 0.7 to 53.4) according to the Canada definition and 13.3 years (SD 10.8; median 10.0 years, range 0.4 to 53.0) according to the ILAE definition. Time to drug resistance was significantly longer using the Canada definition compared to the others (p < 0.001). Neither the Connecticut (p = 0.06) and the surgery definition (p = 0.02) differed from the current ILAE definition (table 2), nor from each other.

Thirty-five percent of the patients (n = 61) experienced one remission (secondary drug resistant) prior to drug resistance with a mean duration of 7.1 years (SD 8.2; median 3.3 years; range 1.0 to 43.0), 15% (n = 25) displayed a relapsing remitting course with more than one remission, of whom 56% (n = 14) experienced two, 36% (n = 9) experienced three and eight percent (n = 2) experienced four remissions. Mean duration of the longest remission was 6.1 years (SD 3.8; median 6.0 years; range 1.0 to 15.0). The remaining 50% (n = 88) never experienced one year or more seizure-freedom before surgery (primary drug resistant group). In 13% (n = 22) of patients a 1-year seizure remission could be achieved after initial fulfillment of ILAE criteria for drug resistance. Mean time from diagnosis of drug resistance to actual surgery ranged from 25.5 (Canada definition) to 29.5 years (Connecticut definition) depending on the definition applied.

DISCUSSION

In this retrospective comparison of different definitions of drug resistance, which were applied in the past to determine the time point of referral to a specialized center for presurgical evaluation, the ILAE criteria would not have led to earlier identification of patients with drug resistant epilepsy. Two of three formerly used definitions resulted in similar durations to establishment of drug resistance, giving validity to the "older" definitions. Even with the stringent criteria of the ILAE definition it took on average 13 years until a patient's epilepsy could be considered drug resistant, which was comparable to two of three former definitions. Prior to this, half of the patients experienced at least one year of seizure freedom and thirteen percent entered another 1-year remission after they had already met any criteria for drug resistance. The major difference among the definitions resulting in later establishment of drug resistance was the number of failed AEDs required by each definition. While three AEDs must have failed applying the Canada definition, only two are required for fulfillment of all others, which resulted in a significantly longer time to drug resistance when applying the Canada definition compared to any of the other definitions. Other factors taken into account by former definitions like seizure frequency and absence of seizure free periods for a defined time (Berg et al., 2001; Camfield and Camfield, 2003; Berg and Kelly, 2006) would not delay assessment of drug resistant epilepsy further, as there was no significant difference between the other two definitions and the current ILAE definition.

The most important reason for the delay to surgery may be seen in dynamic disease patterns with seizure free periods of one year or longer, which were observed in half of our patients. Even after a patient's epilepsy is considered drug resistant there is a considerable chance that seizures might stop or improve significantly with trial of a new AED (Trinka et al., 2001; Callaghan et al., 2007; Mohanraj et al., 2007; Langfitt et al., 2008; Liimatainen et al., 2008), which could also be observed in our cohort. These findings underline the dynamic process of drug responsiveness and the necessity to continuously reevaluate drug response during treatment. As these dynamic disease patterns characterize certain types of epilepsies and no classification system for drug resistance takes this into consideration, it will remain difficult to determine the best time point to proceed to surgical intervention in a given patient. Biomarkers might help in detecting those at risk for drug resistance at an earlier stage and prevent them from disappointing and fruitless medical trials and their potential side effects.

Apart from this a maybe even more important factor causing the delay to surgery is the late referral of patients to a specialized center by the treating physician even after drug resistance has been established. This is also reflected by the long interval between diagnosis of drug resistance and surgery of up to 30 years in our patient cohort. Reasons for this might on one hand again be seen in intermittent remissions, on the other hand in the lack of easy applicable criteria of drug resistance in the past. Therefore this might be one of the major achievements of the ILAE criteria of drug resistant epilepsy, as they represent a clearly delineated, easy to apply standardized tool that facilitates research and establishing practice recommendations when referral to a specialized center or allocation for presurgical evaluation should be considered. Though it does not necessarily mean, that a patient will never have a chance to become seizure free by another drug trial after meeting these criteria. Applied in retrospective two of three formerly used definitions were not fundamentally different from the ILAE definition with regard to duration until fulfillment, but simply more extensive and complicated for use in practice.

When it comes to decide upon surgery in an individual patient other factors like etiology, seizure severity and disability created by the seizures are of course taken into account.

The main weakness of our study is the retrospective study design and selection of those patients only, who were followed long enough to enter presurgical evaluation and whose epilepsy was determined to be applicable for surgery. Thus the study population does not represent the whole spectrum of drug resistant epilepsies, but only those suitable for surgery. Therefore certain epilepsy syndromes and etiologies are overrepresented and findings are not applicable for all drug resistant epilepsies. Furthermore a part of the latency to surgery in this study population can be explained by lack of availability, as there was no epilepsy surgery program in Innsbruck prior to 1999. A factor that has to be taken into account as well is the huge delay of referral to a center in previous years mainly due to lack of information and treatment guidelines for general practitioners. The introduction of criteria for drug resistant epilepsy like the ILAE definition is an important tool to minimize this delay.

CONCLUSION

In retrospect, time to drug resistance according to the ILAE definition did not differ from two of three formerly used definitions of drug resistant epilepsy. We do not anticipate the ILAE definition to result in earlier detection of drug resistance compared to other definitions demanding failure of two AEDs but to give easy applicable criteria when referral to a specialized center must be considered and minimize the delay between establishment of drug resistance and surgery. Dynamic disease patterns delay assessment of drug resistance according to each definition similarly and a substantial proportion of patients may enter a remission on medical treatment despite previously fulfilling the definition of drug resistant epilepsy.

DISCLOSURES

Alexandra Rohracher received travel support from Eisai.

Claudia A. Granbichler received travel support from UCB, Eisai, Cyberonics and Gerot-Lannacher.

Giorgi Kuchukhidze received research support from FWF (Fonds zur Förderung der wissenschaftlichen Forschung), Austrian Science Fund, Project number P 21636-B18 and speaker honoraria from UCB.

Eugen Trinka has acted as a paid consultant to UCB, Eisai, Bial, Medtronics, Ever Neuropharma, Biogen-idec, and Sunovion. He, or his institution, has received research funding from GSK, biogen-idec, Novartis, Red Bull and UCB and speakers honoraria from GSK, Böhringer Ingelheim, Eisai, Bial, Cyberonics, and Sanofi-aventis as well as the Austrian Science Fund, Jubiläumsfond der Österreichischen Nationalbank and from the EU.

Judith Dobesberger, Julia Höfler, Martin Ortler, Iris Unterberger, Gerald Walser and Aljoscha Thomschewski do not report any disclosures.

All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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