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Characteristics and predictive biomarkers of drug resistant epilepsy -- study in Georgia

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ABSTRACT

Aim: The authors conducted a case-control study to estimate predictive factors for timely identification of patients at higher risk for developing drug resistant epilepsy. **Methods:** The retrospective case-control study was conducted among people diagnosed as having drug resistant epilepsy (cases) and their controls, identified as having drug-responsive seizures. All participants were admitted to the tertiary Epilepsy Center at the Institute of Neurology and Neuropsychology (Tbilisi, Georgia) during 2011. The data on demographic features and disease characteristics were analyzed. Multiple logistic regression analysis was used to identify independent risk factors for development of intractable epilepsy. **Results:** A total 334 patients were identified; 84 (34%) met the criteria for drug resistant epilepsy. One hundred and sixty-four age- and gender-matched controls with drug-responsive epilepsy were identified. Relative to the control group, the drug resistant seizure group had increased frequency of perinatal pathology (24% *vs*. 12%), febrile seizures (22% *vs*. 12%), seizure frequency at disease manifestation (62% *vs*. 19%), occurrence of convulsive seizures (84% *vs*. 70%), electroencephalo-graph (EEG) epileptiform discharges (94% *vs*. 77%), polytherapy (90% *vs*. 12%), multilobar lesions (30% *vs*. 16%), hippocampal sclerosis (18% *vs*. 5%), and malformations of cortical development (8% *vs*. 2%). Multivariate analysis indicated four factors with independent predictive value for development of intractable epilepsy: frequency of seizure, polymorphism of seizure, polytherapy, and epileptiform EEG abnormalities.

Quick Response Code:

The presence of all four factors in combination resulted in a 98% of probability of developing drug resistant epilepsy. **Conclusion:** Several factors appear to have prognostic value in identifying the risk for drug resistant epilepsy. These factors may prove useful in non-specialized health care settings for timely identification of individuals with elevated risk for drug resistant epilepsy. However, retrospective design and possible recall bias must be considered when interpreting or extrapolating these results.

INTRODUCTION

Epilepsy is one of the most common chronic neurological disease, and affects up to 60 million people worldwide; with no age, racial, social class, national or geographic boundaries[1,2]. Epilepsy causes increased physical and psychosocial morbidity and it imposes a large economic burden on health care systems.

Approximately 2/3 of patients with epilepsy become seizure-free following correct diagnosis and on appropriate treatment with antiepileptic drugs automated external defibrillator (AED). However, about 30% of patients with epilepsy continue having seizures despite adequate treatment and tare considered to have drug resistant epilepsy (DRE). Patients with uncontrolled seizures experience high rates of injury, psychosocial disabilities, (e.g. undereducation, unemployment, and impaired socialization), and psychiatric disturbances[3]. Seizure control is particularly important for prevention of the disability, morbidity, and mortality in people with drug resistant epilepsy.

According to the International League Against Epilepsy (ILAE) DRE has been defined as the "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom"[4].

DRE usually requires treatment with higher doses of antiepileptic drugs and/or polytherapy, often resulting in adverse effects and leading to poorer quality of life (QOL)[5]. Some patients appear to have drug resistance, but have not tolerated several AEDs due to multiple allergic reactions or other adverse effects. Weight gain caused by antiepileptic drugs (AEDs) constitutes a serious problem in the management of patients with epilepsy[6]. Also, there is the increased risk for development of reproductive- endocrine disorders and infertility in women with epilepsy on long-term AED therapy[7]. Fetal exposure to AEDs increases the risk of congenital malformations[8] and neurodevelopmental impairment[9,10] in offspring of women with epilepsy.

Many patients, particularly the elderly, are more sensitive to central nervous system related adverse effects of AEDs, such as somnolence and cognitive impairment[11], further compromising effective seizure control.

In cases of DRE as defined by the ILAE[4], neurosurgical intervention needs to be considered, however, surgical intervention is not indicated in all patients[12,13]. In some cases, a ketogenic diet or vagus nerve stimulation should be discussed[14].

About 60-80% of the patients with drug resistant focal epilepsy become seizure free after epilepsy surgery[15] and up to 30% do not require continued AED treatment if DRE is identified on its early stage. It is well accepted, that early surgical intervention in most cases of drug resistant epilepsy leads to favorable medium to long term outcomes[16]. However, surgical treatment of epilepsy is often underutilized because of delayed referral of patients to the tertiary epilepsy centers[17]. As a result, patients do not receive potentially curable surgical treatment, which leads to increased medical and economical burden of medically economic burden[16,18]. Beyond misconceptions about surgical risks and poor communication between epileptologists and community physicians[17], the lack of clear criteria for early identification of potential drug resistant cases among primary or secondary health care practitioners is problematic. In such settings, having the clinically meaningful diagnostic and prognostic criteria for early recognition of patients with increased risk of development of drug resistant epilepsy would facilitate timely implementation of non-medicamentous interventions[19].

This is the study in Georgia designed to identify factors associated with DRE; the results from which may aid health care practitioners in the classification of patients at a high risk of developing medically intractable seizures.

METHODS

We carried out a case-control study at the tertiary Epilepsy Center of the Institute of Neurology and Neuropsychology (ECINN), Tbilisi, Georgia, which is referral center for the patients suspected to have epileptic seizures. All participants having drug resistant epilepsy (cases) and their controls were selected from the Epilepsy Registry of INN.

The medical records of the patients with epilepsy who were seen in ECINN (Tbilisi, Georgia) and were entered into the "Epilepsy Registry" from January 1 to December 31, 2011, were reviewed retrospectively. The diagnostic work-up besides included medical history as well as neurological examination, standard electroencephalography (EEG), and magnetic resonance imaging (MRI). Beside of this, inclusion in the study required an epilepsy diagnosed by a multidisciplinary team and good compliance to AED treatment.

The seizures and epilepsies were classified based on of ILAE criteria[20]. The DRE was defined according to the ILAE consensus criteria for definition of drug resistant epilepsy[4].

Detailed methodology of selection participants with drug resistant epilepsy (cases) has been described elsewhere[10].

Age and gender matched individuals, registered in the INN at the same time interval were selected for control group (164 individuals). Controls had fully controlled seizures (drug-responsive epilepsy-controls) for at least one year prior to inclusion in the study or a three times longer seizure-free period compared to the period prior to the start of antiepileptic drug treatment, whichever was longer. All patients were previously diagnosed epilepsy with using a similar multidisciplinary approach (standard EEG, neuropsychological assessment, MRI, epileptological consultation, final decision-making council). Demographic features and disease characteristics were obtained from medical records of INN retrospectively.

The study protocol was approved by the National Council of Bioethics. In all cases, informed consent was obtained prior to inclusion in the study.

EEG

At least one standard 30 min 21 channel EEG capturing wakefulness or sleep was recorded. Hyperventilation and photic stimulation was performed during all EEG recordings.

Focal and generalized interictal epileptiform discharges (IEDs) and focal slowing were registered. Focal IEDs were defined as sharp waves, focal and generalized spikes, spike and wave discharges in single or rhythmic runs, focal polyspikes, and generalized polyspikes with secondary bilateral synchrony.

Due to the paucity of ictal events during standard EEG recordings ictal EEG findings were not included in the analysis.

MRI

MRI was performed with 1.5T or 3T high field scanners (Magnetom Avanto and Magnetom Verio, SIEMENS, Germany). The epilepsy MRI protocol included T1 (tse) -weighted 3D axial magnetization prepared rapid gradient echo images with and without intravenous contrast application, with axial and sub-millimetric slicing coronal T2 (tse)-weighted turbo spin-echo, coronal T2-weighted fast fluid attenuated inversion recovery, T2*-weighted axial and diffusion weighted pulse sequences, slices thickness-2.0 mm. Coronal scans were oriented in the perpendicular plane to the long axis of the hippocampus.

Statistical analyses were performed with SPSS version 20. Armonk, NY: IBM Corp. Descriptive statistics with 95% confidence intervals (CI) were obtained for demographic and clinical variables. Mean and standard deviation were calculated for characterization of central tendencies. Pearson's Chi squared test was used to determine association between categorical variables (Fisher's exact test was used where appropriate). Multiple logistic regressions with forward stepwise selection were used to identify independent risk factors for drug resistant epilepsy. Variables that showed significant results or were close to significance threshold in univariate analysis (antiepileptic drug polytherapy, amount of seizures two years prior to antiepileptic drug initiation, multilobar MRI abnormalities, epileptiform discharges on EEG, seizure polymorphism, perinatal abnormalities, convulsive seizures, hippocampal sclerosis or malformation of cortical development on MRI, history of febrile seizures) were entered into the multivariate model. The entry criterion was a $P = 0.05$ and the exit criterion was a $P = 0.1$. Hosmer-Lemeshow goodness-of-fit and -2 Log likelihood tests were used to examine the final model. Odds ratio with 95% CI[21] and B coefficients were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical data of 334 patients was evaluated and 208 individuals (62%) were seizure-free. For 126 (38%) patients, at least one seizure was observed within previous 6 months' period. Among these subjects, 38 cases (30%) were noncompliance to prescribed treatment and nonepileptic paroxysmal events were identified in another 4 individuals (3%). Finally 84 persons (66%) met the criteria of drug resistant epilepsy.

Demographic features and disease characteristics

The mean age of patients with drug resistant epilepsy was 26.2 ± 12.2 years (range: 4 to 57 years); 56 patients (67%) were female, whereas, 28 (33%) were male. The mean age for initial seizure was 8.9 ± 7.8 years (range: 1.2 month to 33 years) and the mean duration of epilepsy was 17.2 ± 10.4 years (range: 2 to 43.3 years). Seventy-six patients (90%) with drug resistant epilepsy cases were receiving more than one antiepileptic drug at the time of evaluation and this association was statistically significant ($P < 0.001$) [Table 1]. A median of five different antiepileptic drug trials, either with a single drug or in combination, were conducted in individuals with drug resistant epilepsy before inclusion into the study. In most patients with drug resistant epilepsy and on monotherapy carbamazepine (CBZ), valproic acid (VPA) or phenobarbital (PB) was used. Conversely, relatively few patients used lamotrigine or levetiracetam (LEV). The most popular polytherapy combination was CBZ + VPA (18%) and CBZ + LEV (16%).

Among individuals with drug responsive seizures CBZ, VPA and PB were the most frequently used as monotherapy regiments.

Overall 52 patients (62%) from cases and 31 (19%) from controls had frequent seizures (i.e. ≥ 1-3/week) during the first two years of disease manifestation ($P < 0.001$) [Table 2].

Seizure types

The majority of patients with drug resistant epilepsy (80 patients, 95%) had focal seizures with or without generalized tonic-clonic seizures; one patient with drug resistant epilepsy had only focal seizure without loss of consciousness that did not substantially disrupt QOL. Convulsive seizures were more frequently associated with drug-resistant epilepsy compared to individuals with drug responsive epilepsy. Seizure polymorphism was more frequently observed among drug-resistant epilepsy cases (68; 82%) compared to individuals with drug responsive epilepsy (99; 60%) ($P = 0.002$) [Table 3].

Seizure semiology

Based on seizure semiology possible seizure focus among persons with drug resistant epilepsy was consistent with frontal, temporal, parietal or other origins in 23 (27%), 26 (31%), 5 (6%) and 10 (12%) cases respectively. In 19 individuals (23%) seizure semiology was inconclusive and one patient had

Table 1: Clinical and demographic characteristics of patients with DRE and controls, *n* (%)

Demographic/disease characteristics	DRE (*n* = 84)	Controls (*n* = 164)	*P*-value
Age (years), mean (SD); [min; max]	26.2 (12.2); [4; 57]	28.5 (12.5); [6; 59]	-
Gender (male)	28 (33)	74 (45)	-
Febrile seizures	18 (22)	20 (12)	0.052
Perinatal pathology	19 (24)	22 (12)	0.043
Head trauma as an etiology	3 (4)	12 (7)	-
Family anamnesis of epilepsy	5 (6)	17 (10)	-
Polytherapy	76 (90)	20 (12)	< 0.001

DRE: drug resistant epilepsy; SD: standard deviation

Table 2: Seizure frequency at disease manifestation, *n* (%)

Seizure frequency	DRE (*n* = 84)	Controls (*n* = 164)	*P*-value
1-3/year or less	5 (6)	79 (48)	-
1-3/month	27 (32)	15 (9)	-
1-3/week	29 (35)	54 (33)	-
Everyday	23 (27)	16 (10)	-
Frequent (≥ 1-3/week)	52 (62)	31 (19)	< 0.001
Infrequent (≤ 1-3/month)	30 (37)	133 (81)	-

DRE: drug resistant epilepsy

Table 3: Distribution of types of seizure across study groups, *n* (%)

Seizure types	DRE (*n* = 84)	Controls (*n* = 164)	*P*-value
Convulsive seizures	69 (84)	107 (70)	0.014
Convulsive seizures only	2	8 (5)	
Convulsive seizures with non-convulsive attacks (focal/generalized)	67 (80)	99 (60)	
Non-convulsive seizures only	14(17)	51(31)	-
Absence and/or myoclonia	1	4	
Focal seizures only (simple and/or complex)	13 (16)	47 (29)	
Unclassified	1	6 (4)	-
More than one type of seizures	68 (82)	99 (60)	0.002

DRE: drug resistant epilepsy

generalized seizures. Nearly the same distribution of seizure semiology was observed in the control group (frontal 22%; temporal 39%), without a statistically significant association.

Etiology of epilepsy

Of the 84 drug resistant epilepsy patients, the etiology of epilepsy was established to be structuralin 83 (99%). In 1 case genetic etiology was considered. In the control group focal epilepsy was observed in 146 (89%) individuals, in 12 cases (7%) generalized epilepsy was established and 6 cases (4%) were unclassified. In most cases, (101; 62%) structural etiology was diagnosed. In 12 (7%) patients, genetic etiology was considered and in 51 (31%) etiology remained unknown. There was no statistically significant association observed between drug responsiveness and etiology of epilepsy.

Standard EEG data

Epileptiform activity presented as focal spikes, polyspikes, sharp waves, spike-wave, sharp-wave discharges, was observed in 79 (94%) of patients with drug resistant epilepsy and in 126 patients (77%) with drug responsive epilepsy (P = 0.001) [Table 4].

MRI findings

MRI investigations were performed in all cases (with the 1.5 or 3 tesla devices). In 26 (31%) patients with drug resistant epilepsy and in 63 (38%) with drug responsive epilepsy no pathology was revealed. Among them, all cases of generalized epilepsy (1 person in drug resistant epilepsy group and 12 individuals in control group) were found no lesion by MRI. Multilobar lesions were identified in 25 (30%) patients with drug resistant epilepsy and in 26 (16%) patients in the control group. In both groups, lesions were mostly located within the frontal or temporal lobes [12 (13%) and 22 (14%); 15 (18%) and 18 (11%), respectively].

The most frequent MRI pathologies such as mesial temporal sclerosis, malformation of cortical development and focal cortical dysplasia occurred significantly were significantly more often occurred among drug resistant epilepsy patients. In the control group major findings were brain tumor and post-stroke encephalomalacia [Table 5].

Multivariate analysis

Variables that showed significant association with drug resistant epilepsy were entered into the multivariate model. Factors included: frequent seizures during the first two years since diagnosis of the disease (B = 2.599; P < 0.001), more than one seizure type (B = 1.366; P < 0.014), polytherapy (B = 4.766; P < 0.001) and epileptiform discharges on EEG (B = 1.836; P < 0.017) were retained in final model as independent predictors of DRE. Probability analysis showed that with all four factors presented, there is a 98% of chance, that case will further become drug resistant. The Table 6 shows probability of DRE development for various combinations of independent predictors.

DISCUSSION

The main goal of antiepileptic treatment is complete control of seizures without the side effects of anticonvulsants; however, in 30-35% of cases an effective outcome is not achieved because seizures are resistant to anticonvulsant treatment.

Identifying patients at higher risk of drug resistance as soon as possible is particularly important in epilepsy management. Various predictors of drug resistance have been identified; however, accurate prediction is still a problem. In our previous study on the cohort in Georgia, 26% of the individuals with epilepsy experienced drug-resistance according to international criteria[22,23]. The results of the current study provide insights regarding possible risk factors associated with drug-resistant epilepsy.

Recent studies have identified several factors that

Table 4: Standard EEG findings in DRE and control group, *n* (%)

EEG findings	DRE (n = 84)	Controls (n = 164)	P-value
Normal EEG	2 (2)	7 (4)	-
Abnormal EEG	82 (98)	157 (96)	-
Slow waves	3 (4)	31 (19)	-
Epileptiform discharges	79 (94)	126 (77)	0.001
Sharp waves	35 (42)	91 (55)	-
Spikes	6 (7)	6 (4)	-
Spike-waves (SW)	13 (16)	14 (9)	-
SW < 3 Hz	1	-	-
SW 3-4 Hz	-	2	-
SW 4-6 Hz	1	-	-
Polyspikes	2	-	-
Sharp-slow waves	21 (25)	13 (8)	-

EEG: electroencephalography; DRE: drug resistant epilepsy

Table 5: MRI findings in individuals with DRE and controls, *n* (%)

MRI finding	DRE (*n* = 84)	Controls (*n* = 164)	*P*-value
Normal	26 (31)	63 (38)	-
Abnormal	58 (69)	101 (62)	-
Lobar lesion	29 (35)	68 (42)	-
Multilobar lesion	25 (30)	26 (16)	0.023
Midline lesion	4 (5)	1	-
Infratentorial	-	6 (4)	-
MTS	15 (18) With lacunar lesion-1 With encephalomalacia-1 Bilateral-1	8 (5)	0.002
Cortical atrophy	7 (8) With leukoencephalopathy-1	19 (23)	-
MCD	7 (8) FCD-6 Heterotopy-1	3 FCD - 2 heterotopy -1	0.03 0.02
Leukoencephalopathy	5 (6)	8 (10)	-
Gliosis	5 (6) With arachnoid cist-1	10 (12)	-
Glioneural tumor	4 (5)	1	-
Other brain tumors	-	11 (13)	-
Dysgenesias of the corpus callosum	2	-	-
Hypothalamic hamartoma	2	-	-
Polimicrogyria	2 With bilateral schizencephaly-1	1	-
Lacunar lesion	2	3	-
TSC	2	1	-
Ulegyria	1	-	-
Postoperative cyst	1	-	-
Multiple cystic lesions	1	-	-
Encephalomalacia	1	20 (23)	-
Cerebral hemiatrophy	1	-	-
Arachnoid cyst	-	7 (8)	-
Cavernous angioma	-	5 (6)	-
Schizencephaly	-	2	-
Dandy-Walker anomaly	-	1	-

MRI: magnetic resonance imaging; DRE: drug resistant epilepsy; MTS: mesial temporal sclerosis; MCD: malformation of cortical development; FCD: focal cortical dysplasia; TSC: tuberous sclerosis complex

Table 6: Estimated probability of development DRE according various presentations of predictor variables

Variation of factors presented	Probability of development of DRE
All four factors	0.979
Frequent seizures*, politherapy, epileptiform discharges	0.922
Frequent seizures, politherapy, seizure polymorphism	0.880
Politherapy, seizure polymorphism, epileptiform discharges	0.774
Frequent seizures, politherapy	0.652

*At least one seizure per week during the first two years of disease manifestation. DRE: drug resistant epilepsy

may have prognostic significance for the development of drug resistance; in particular, focal epilepsy and frequent seizures before antiepileptic drug treatment initiation are more often associated with drug resistant epilepsy. The similar results were revealed in our study, where the vast majority of patients with drug resistant epilepsy had focal seizures and high frequency of seizures during the first two years of disease manifestation.

Disease manifestation an early age, long duration of epilepsy, structural/metabolic and unknown etiology, as well as particular brain abnormalities (mesial temporal sclerosis, malformations of cortical development) are most commonly associated with drug resistant epilepsy. There is close concordance between these findings and our study results: multilobar brain lesions were significantly more often identified in people with drug resistant epilepsy than in patients with drug-responsive epilepsy; similarly, mesial temporal sclerosis and focal cortical dysplasia were more prevalent brain abnormalities in patients with drug resistant epilepsy compared to controls. Those data are consistent with other studies that have shown higher occurrence of DRE with cortical dysplasia, mesial temporal sclerosis, and dual pathology[24,25].

Remote head trauma or brain infection, perinatal pathology, febrile seizures, family history of epilepsy[26], abnormal neurological status and mental retardation[27] lead to elevated risk for development of drug resistance in individuals with drug resistant

epilepsy. Also, in our study a history of perinatal pathology was found in patients with intractable epilepsy.

Stable abnormalities on EEG (e.g. persistent focal slowing or frequent focal epileptiform EEG patterns) are also considered as prognostic markers of poor seizure control. Likewise, in our study, EEG epileptiform abnormalities were observed more often in drug resistant epilepsy patients compared to controls.

Also, consistent with other studies (references), poor seizure control was significantly associated with seizure polymorphism.

We found polytherapy to be associated with higher probability to development of drug resistant epilepsy. Similarly, polipharmacy and the number of failed AED (more than four) trials were significant predictors for drug resistant epilepsy[28].

Age, gender, history of trauma as epilepsy etiology and family anamnesis of epilepsy were not difference between the two groups.

Multivariate analysis

Multivariate analysis showed that frequent seizures during the first two years of disease manifestation, polytherapy, seizure polymorphism and epileptiform discharges on EEG are four independent factors associated with drug resistant epilepsy, and in combination, there is up to 98% certainty that case will be in the rug resistant epilepsy group. Various combinations of these four variables also increase probability of developing drug resistant epilepsy [Table 6]. This estimation could be used at primary or secondary neurological settings for timely identification of patients with raised probability of development of drug resistant epilepsy.

This study has some limitations that should be mentioned. Because of retrospective design of the study data are collected from medical records and study participants that could be less accurate and prone to recall biases. The study is hospital based thus may be influenced by selection bias, and extrapolation to the general population may be limited. Small sample size should be considered as well. Polytherapy was shown to be independent risk factor for development of drug resistant epilepsy, however, polytherapy also could be considered as a result of epilepsy cases where seizures are difficult to control. So, this finding should be interpreted carefully and predictive value of polypharmacy should be considered as an additional value in context of other predictive variables.

We identified predictive biomarkers associated with development of drug resistant epilepsy. This can be used as a tool for timely identification of individuals with elevated risk of intractable seizures for further referral for pre-surgical evaluation. This may enhance cost-effective and potentially curative treatment of patients with DRE, leading to improved QOL and mitigation of social and economic burden on health care system.

DECLARATIONS

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Authors' contributions

Designed and executed the study, and assisted the writing and editing of the final manuscript: M. Alkhidze, S. Kasradze

Assisted with the data analyses, and writing of the paper: G. Lomidze

Designed the study and collaborated in the writing and editing of the final manuscript: A. Tsiskaridze

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Conflicts of interest

No specific funding source is associated with the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication. The remaining authors have no conflicts of interest.

Patient consent

In all cases, informed consent was obtained prior to inclusion in the study.

Ethics approval

The study protocol was approved by the National Council of Bioethics.

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