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FULL-LENGTH ORIGINAL RESEARCH

Focal epilepsies in adult patients attending two epilepsy centers: Classification of drug-resistance, assessment of risk factors, and usefulness of "new" antiepileptic drugs

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Summary

Purpose: To classify the grade of antiepileptic drug (AED) resistance in a cohort of patients with focal epilepsies, to recognize the risk factors for AED resistance, and to estimate the helpfulness of ''new-generation'' AEDs.

Methods: We included 1,155 adults with focal epilepsies who were observed consecutively after 1990 and followed regularly at two epilepsy centers. We systematically collected the clinical, diagnostic, and therapeutic data using a custom-written database. We classified the patients as seizure-free or AED resistant according to the International League Against Epilepsy (ILAE) criteria, and we evaluated the risk factors associated with AED resistance using logistic regression analysis. We further grouped AED-resistant patients in different grades (I, II, and III) according to the number of AEDs already tried as proposed by Perucca.

Key Findings: AED resistance occurred in 57.8% of the 729 patients with symptomatic focal epilepsies and was positively associated with electroencephalography (EEG) abnormalities, seizure type, and the presence of mesial temporal sclerosis. Among 426 patients without detectable causes, the percentage of AED resistance was significantly lower (39.2%) and correlated with EEG abnormalities and psychiatric symptoms. Among AED-resistant patients, the majority (64.6%) had tried three or more AEDs, which fit the more severe grade III proposed by Perucca. Among seizure-free patients, more than one-half (57%) needed to try two or more AEDs before reaching seizure control (14.9% needed three or more AEDs). Furthermore, among seizure-free patients who could be previously classified as resistant to two or more AEDs, 52.2% reached seizure freedom while receiving treatment with ''new generation'' AEDs.

Significance: The ILAE classification of AED resistance, as well the graded classification proposed by Perucca, was easily exploitable in our patients, although these classifications systems appear to have a limited value in predicting seizure outcome. Actually, a small but not negligible percentage of patients reached seizure freedom after trying several AEDs (including "new" AEDs), suggesting repeated trials may be necessary for seizure control.

KEY WORDS: Focal epilepsy, Antiepileptic drug resistance, Antiepileptic drugs.

Focal epilepsies are the most common forms of epilepsy in adults and have heterogeneous etiologies and outcomes. Most of the data relating to the prognosis of focal epilepsies come from studies of patients who are selected on the basis of specific inclusion criteria, such as newly diagnosed patients (Kwan & Brodie, 2000; Mohanraj & Brodie, 2005, 2006; Hitiris et al., 2007), or pathologic conditions (Pittau et al., 2009; Varoglu et al., 2009). The lack of large case series means that the published meta-analyses are based on a limited number of studies of rather small patient populations.

The outcome of epilepsy depends on various factors, including the severity of ictal phenomena, the time of occurrence, and the possible progression of neuropsychological defects. A major prognostic factor is the response to antiepileptic drugs (AEDs) (Mohanraj & Brodie, 2005; Schiller & Najjar, 2008; Schiller, 2009), which in principle seems to be easily measurable, although the criteria used by different authors to identify and define AED resistance are heterogeneous. The International League Against Epilepsy (ILAE)

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recently activated a task force to study the issue of AED-resistance and published a Consensus Proposal (Kwan et al., 2009). This proposal defined ''seizure freedom'' as ''freedom from seizures for a minimum of 12 months or for a period lasting three times the longest pre-intervention inter-seizure interval,'' and AED resistance as ''the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules.'' However, the Consensus Proposal also underlined the limits of the classification due to the limited information available concerning long-term prognosis and the limited information about the risk factors associated with a poor outcome.

Because the ILAE classification (Kwan et al., 2009) did not allow specific evaluation of the seizure resistance with regard to the number of tried AEDs, we also applied the graded classification proposed by Perucca (1998), in which the degrees were based on the number of drugs to which a patient had previously not responded.

We aimed this study to verify the applicability of the AED-resistance classification and to evaluate the risk factors for AED resistance in a large cohort of patients with focal seizures, who were consecutively enrolled and followed. Moreover, we evaluated the effectiveness of the new-generation AEDs that have become available over the last 20 years and we assessed the contribution of these new molecules to reducing the proportion of AED-resistant patients.

Methods

Starting from 1990, we included in a custom written database the information related to all patients who were observed consecutively at the Epilepsy Centers of the Carlo Besta Foundation Neurological Institute and San Paolo University Hospital. Among these patients, we included in the present study all patients with focal epilepsies who were older than 18 years, observed at least twice between 2006 and 2009. We excluded patients who were noncompliant, patients with incomplete seizure control whose treatment was left unchanged for particular reasons, and patients who underwent epilepsy surgery.

The database was created in Microsoft Access (Microsoft, Redmond, WA, U.S.A.) and included information about family history of epilepsy; previous neonatal, febrile, or acute seizures; age at seizure onset; the presence of neurologic, psychiatric, and cognitive defects (arbitrarily classified as mild, moderate, or severe); seizure type; and pathologic electroencephalography (EEG) and neuroimaging findings.

In accordance with the terminology proposed by the ILAE (Engel, 2001), the epilepsies due to specific etiologies consistent with the presentation of seizure/epilepsy were defined as ''symptomatic,'' as were those associated with unequivocal signs of brain damage (including mesial temporal sclerosis [MTS]). All of the other epilepsies were defined as ''probably symptomatic'' except those associated with a family history indicating autosomal transmission that were defined as ''genetic.'' Based on these diagnostic criteria, the patients with probably symptomatic epilepsy could have mild (but not moderate or severe) nonfocal neurologic signs or mild cognitive impairment, and normal or nonspecific neuroimaging findings.

Seizure types were defined based on the classification proposed by Engel (2001), and we included patients with generalized seizures without any obvious focal onset if they were associated with unambiguous evidence indicating a focal origin (clinical and imaging or EEG findings).

We collected information about current AED treatment and all of the AEDs received in the past. We did not include AEDs that were withdrawn because of possible side effects or given at an uncertain dosage. In line with the ILAE proposal (Kwan et al., 2009), we grouped the patients as being seizure-free or AED resistant. Moreover, because the ILAE classification did not allow for evaluation of the seizure resistance with regard to the number of tried AEDs, we applied the graded classification proposed by Perucca (1998), in which the degree was based on the number of drugs to which a patient had previously not responded (Table 1). To evaluate the history of AED resistance, the same classification was also used to describe the immediately preceding condition of the patients who were seizure-free at the time of data analysis.

We labeled as ''new AEDs'' all of the molecules introduced over the last 20 years that have been available for at least 3 years: lamotrigine, levetiracetam, felbamate, gabapentin, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide.

Statistical analysis

We analyzed the data relating to the population as a whole by means of univariate analysis using the chi-square test with Bonferroni correction for multiple comparisons. All of the risk factors capable of predicting AED resistance that showed a significant association ($p < 0.05$) in univariate analysis were investigated by means of multivariate logistic regression, which was applied separately to the

Table 1. Applied classifications of the response to AED

Seizure freedom[a]	Seizure-free period longer than 12 months or, in the case of rare seizures, for a period lasting at least three times the longest interseizure interval
AED resistance[a,b]	
Grade I	Resistance to one primary AED
Grade II	Resistance to two primary AEDs used sequentially (grade IIA) or in combination (grade IIB)
Grade III	Resistance to three or more primary AEDs used sequentially (grade IIIA) or in combination (grade IIIB)

[a]In line with the criteria of ILAE classification.
[b]In line with grades proposed by Perucca (1998).

patients with symptomatic and "probably symptomatic" epilepsy.

All of the statistical analyses were carried out using SPSS statistical software, version 14 (SPSS Inc., Chicago, IL, U.S.A.), and p-values of <0.05 were considered statistically significant.

Results

Of the 1,155 enrolled patients (584 female), 824 had been followed for more than 3 years. According to the criteria of ILAE classification, 567 (49.1%) were seizure-free and 588 (50.9%) were considered AED resistant. At the time of our observation, seizure-free and AED-resistant patients had similar age (45.1 ± 16.2 vs. 45.1 ± 14.7 years) and sex distributions (women 50.3% vs. 50.8%). The follow-up duration was also similar (6.7 ± 5.0 and 6.4 ± 5.1 years). As expected, the number of previously tried AEDs was lower in the seizure-free group (1.5 ± 1.8 and 3.7 ± 3.4, p < 0.001).

AED resistance and risk factors

The presence of previous acute seizures; familial epilepsy; neurologic, psychiatric, and cognitive defects; pathologic EEG and neuroimaging findings; identified causative factor; seizures with initial consciousness impairment; multiple seizure types; and akinetic seizures, all correlated with AED resistance (Table 2).

Because of our previously defined diagnostic criteria, there was sufficient information to classify the epilepsy as symptomatic of an identified cause in 645 patients; a further 84 cases showing overt signs of brain damage in the absence of an identified etiology, were also classified as symptomatic. Five patients had a family history indicating an autosomal dominant form of genetic epilepsy, which was associated with a positive molecular diagnosis in two cases.

A factor that closely correlated with AED resistance was the presence of an identified etiology (p < 0.001). Indeed, AED resistance occurred in 57.8% of the symptomatic patients and 39.2% of the others. Because of this finding, and taking into account that many of the associated pathologic findings indicating unequivocal brain damage of specific etiology (e.g., previous acute seizures, severe neurologic defects, and specific neuroimaging findings), we separately evaluated these two groups using logistic regression analysis.

Among the patients with symptomatic epilepsies, the multivariate analysis indicated that AED resistance was associated with the presence of pathologic EEG findings (odds ratio [OR] 2.20, p = 0.011), seizures with initial and prominent consciousness impairment (OR 1.61, p = 0.006), multiple seizure types (OR 1.48, p = 0.034), and tonic–akinetic seizures (OR 2.44, p = 0.031). Among the patients with probably symptomatic epilepsies, the risk of AED resistance was significantly lower in those with a family history of epilepsy (OR 0.51, p = 0.019), whereas it increased with the presence of epileptiform EEG anomalies (OR 2.36, p = 0.008) and psychiatric symptoms (OR 1.97, p = 0.025) (Table 3).

Table 2. Main characteristics of the case series and results of univariate analysis

	AED responsive (567) N (%)	AED resistant (588) N (%)	Univariate analysis χ^2 (p-value)
Neonatal seizures			
Yes	13 (2.2)	19 (3.2)	0.183
Febrile seizures			
Yes	37 (6.5)	52 (8.8)	0.140
Acute symptomatic seizures			
Yes	14 (2.5)	33 (5.6)	**0.016**
Family history of epilepsy			
Yes	88 (15.5)	65 (11.1)	**0.039**
Age at seizure onset			
>15 years	374 (66.0)	356 (60.5)	0.093
Seizure type[a]			
Early consciousness impairment	207 (36.5)	264 (44.9)	**0.002**
Sensory	376 (66.3)	386 (65.6)	0.626
Motor	130 (22.9)	148 (25.2)	0.243
More than one type	144 (25.4)	190 (32.3)	**0.010**
Tonic–clonic	99 (17.5)	80 (13.6)	0.100
Tonic–akinetic	18 (3.2)	38 (6.5)	**0.009**
Neurologic defects	139 (24.5)	190 (32.3)	**0.001**
Psychiatric defects	121 (21.3)	199 (33.8)	**<0.001**
Cognitive impairment	125 (22.0)	210 (35.7)	**<0.001**
Pathologic EEG	482 (85.0)	554 (94.2)	**<0.001**
Positive neuroimaging (CT or MRI)[b]	262 (46.2)	334 (56.8)	**<0.001**
Identified causes	308 (54.3)	421 (71.6)	**<0.001**

Significant values are in bold.
[a]Six hundred sixty-eight patients had more than one seizure type.
[b]Neuroimaging consisted mainly of one or more MRI (1,002 patients) or CT scan (130 patients), which revealed clear focal, diffuse or multifocal cerebral damage in 52.6%, and uncertain findings in 8.3%.

Relationship between AED resistance and specific etiologies/brain lesions

An evaluation of the relationship between AED resistance and the most frequent etiologies (n > 50, including mesial temporal sclerosis; MTS) using chi-square analysis followed by Bonferroni correction showed that only MTS had a significant association (77%, p < 0.001). The patients who had experienced a previous vascular accident were at a significantly lower risk of AED resistance (43.4%, p = 0.008) than patients with other etiologies for seizures. Many patients with cortical malformations were AED resistant (67.7%), but the association did not survive Bonferroni correction (p = 0.089). Figure 1 shows the relationship between all etiologies and AED resistance. Even the more malignant causes were associated with a relatively high percentage of seizure-free patients (23.0% of the patients

Table 3. Risk factors for AED resistance in symptomatic and "probably symptomatic" patients

	Symptomatic (N = 729)		Probably symptomatic (N = 426)	
	Multivariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Anamnesis				
Acute seizures	1.92 (0.95–3.91)	0.071	n.e.	n.e.
Familial epilepsy	0.92 (0.57–1.50)	0.740	0.51 (0.29–0.89)[a]	**0.019**
Clinical findings				
Neurologic defects[b]	0.70 (0.48–1.02)	0.067	1.23 (0.48–3.10)	0.668
Cognitive defects[b]	1.19 (0.77–1.83)	0.438	1.85 (0.85–4.01)	0.114
Psychiatric symptoms	1.23 (0.82–1.84)	0.315	1.97 (1.09–3.56)	**0.025**
Diagnostic examinations				
Pathologic EEG	2.20 (1.20–4.04)	**0.011**	2.36 (1.24–4.38)	**0.008**
Positive neuroimaging	1.03 (0.69–1.53)	0.897	n.e.	n.e.
Seizure types				
Early consciousness impairment	1.61 (1.15–2.25)	**0.006**	0.80 (0.51–1.24)	0.308
More than one type	1.48 (1.03–2.12)	**0.034**	1.16 (0.72–1.87)	0.541
Tonic–akinetic	2.44 (1.07–4.36)	**0.031**	0.60 (0.10–3.69)	0.585

OR, odds ratio; CI, confidence interval; n.e., not evaluated. Significant values are in bold.
[a]Negative association.
[b]Mild neurologic defect or cognitive impairment.

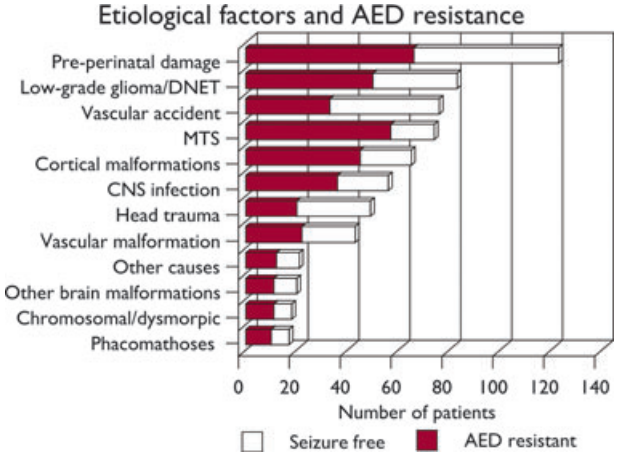

Figure 1.
Proportion of AED-resistant patients associated with different etiologies (DNET, dysembryoplastic neuroepithelial tumors).
Epilepsia © ILAE

with MTS, and 32.3% of those with cortical malformations).

In addition to the patients with identified etiologies, we included 84 patients without an identified etiology but with overt signs of brain damage among the patients with symptomatic epilepsy. In this small group, 32.1% had moderate/severe neurologic defects, 55.9% had moderate/severe cognitive impairment, and 54.8% had nonspecific neuroradiologic findings. Like the other group of symptomatic patients, this group included a high percentage of AED-resistant patients (63.1%).

AED treatment in seizure-free patients and those in the different subclasses of AED resistance

Figure 2 shows the number of AEDs used at the time of the last observation in the seizure-free and in AED-resistant patients indicating the difference in the complexity of the AED regimens in the two groups. Almost two thirds of the seizure-free patients but only one-third of the AED-resistant patients were treated with a single drug; furthermore, about one-third of the AED-resistant patients received three or more AEDs.

Classification of the response to AEDs

Of the 588 patients who were considered AED resistant, 22.9% were grade I, 27.0% were grade IIB, and 50.1% were grade IIIB. None of the patient were grades IIA or IIIA, probably because of the widespread and consistent approach of tapering one drug only after assessing the sufficient tolerability (and efficacy) of the new drug.

Among the 567 patients who were seizure-free, an evaluation of the treatments used before they became seizure-free, showed that 43.0% achieved seizure control on their first AED, 24.9% on their second AED (AED resistance grade I), and 17.2% and 14.9% on their third (grade II) or subsequent AED (grade III), respectively (Fig. 3).

Considering the population as a whole, 21% became seizure-free on their first AED, 12.2% on the second, 8.4% on the third, and 7.3% on their fourth or subsequent AED.

Usefulness of "new" antiepileptic AEDs

The 1,155 patients tried 4,895 AEDs during the study period; 1,717 were "new" AEDs. At the time of data analysis, 685 patients had tried at least one new AED and 513 (44.4%

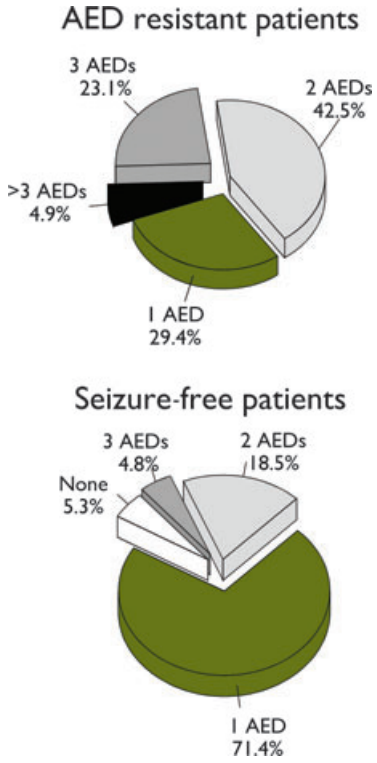

Figure 2.
Current AED schedules of seizure-free and AED-resistant patients.
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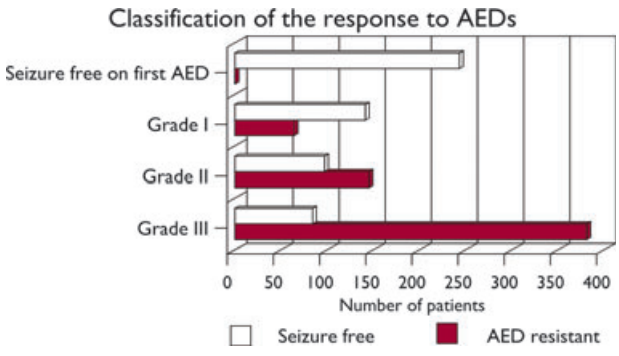

Figure 3.
Different grades of current and previous AED resistance in patients who were still AED resistant and those who were seizure-free at the time of data analysis.
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of the entire series) were still being treated with at least one new AED (116 on monotherapy and 397 in combined treatment).

Of these 513 patients, 367 continued to experience seizures and 146 (28.5%) were seizure-free (Fig. 4); this group included 29 patients treated with a new AED as first choice,

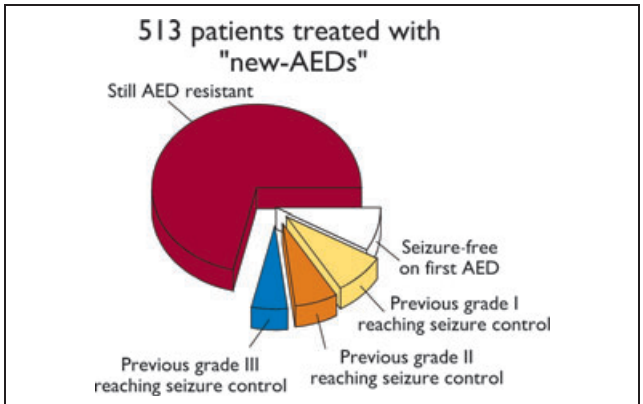

Figure 4.
Response to treatment schedules including new AEDs.
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33 with previous grade I, 42 with previous grade IIB, and 42 with previous grade IIIB of drug resistance.

The seizure-free patients treated with a new AED accounted for 25.5% of all seizure-free patients. In particular, the use of a new AED seemed to be determinant in achieving freedom from seizures in 43.2% of the 97 patients previously included in grade IIB and in 50.0% of the 84 previously included in grade IIIB. Adding together the patients previously considered resistant to two or more AEDs, 52.5% became seizure-free while receiving a new AED.

Discussion

Classification of AED resistance

The classification proposed by Kwan et al. (2009) proved to be easily practicable in providing information about seizure freedom and AED resistance in a relatively large population of adult subjects with focal epilepsies. Therefore, it seems to be a useful means of identifying ''potentially'' AED-resistant subjects (Alexandre et al., 2010).

The total percentage of our seizure-free subjects (47.1%) is considerably lower than that reported in other case series (Mohanraj & Brodie, 2005; Bauer et al., 2007; Schiller & Najjar, 2008).

Considering the grades of AED resistance proposed by Perucca (1998), the percentage of patients with the most severe grade IIIB (32.9%) is in line with those reported by others using various definitions of AED resistance (Regesta & Tanganelli, 1999; Genton, 2004; Beleza, 2009) and with that previously observed by us in a larger series of adults with focal epilepsies attending tertiary centers (OREp Lombardy, 1996). Therefore, this percentage probably corresponds to the percentage of actually difficult to treat patients, whereas lower grades (I and II) of AED resistance can be useful to group the patients with still undefined response to medical treatment.

Almost half of the seizure-free patients achieved seizure freedom with their first AED, which suggests that there is a large subpopulation of patients with naturally ''benign'' and easy-to-treat focal seizures. This percentage is lower than that reported by others (Shorvon et al., 1978; Richens et al., 1994; Heller et al., 1995; Mohanraj & Brodie, 2005), who found that more than two thirds of the patients become seizure-free on their first AED. However, most of these included patients with generalized epilepsies (which are probably more susceptible to being controlled), whereas we included only patients with focal epilepsies. The low percentage of patients achieving seizure freedom on their first AED may also be due to the considerable proportion of patients with severe epilepsies referred to epilepsy centers.

Of interest, a relatively large number of patients achieved seizure freedom after trying more than two AEDs; indeed, 14.8% of the patients in grade IIIB became seizure-free, a percentage that is definitely higher than the <5% reported by Perucca (1998) but similar to that reported by Schiller and Najjar (2008) in patients with different forms of epilepsy, most of whom had focal epilepsy. This nonnegligible percentage suggests that even the grade III proposed by Perucca (1998) could be not sufficient to consider a patient putatively unresponsive to any medical treatment. This finding is in line with the observation of Luciano & Shorvon (2007) and Callaghan et al. (2007), who reported a similar percentage of seizure remission in a population of adult patients with various seizures types, previously considered as AED resistant. A more complex algorithm, including not only the number of tried AEDs, but also other risk factors, might be a more effective approach to evaluate AED resistance. Indeed, it seems that the failure of one or two AEDs can be considered a predictor of AED resistance only in the presence of associated risk factors (such as MTS or cortical malformations), whereas in other patients it is worth considering further AED trials.

Risk factors for AED resistance

Because the presence of a specific etiology correlated closely with AED resistance, we evaluated symptomatic and probably symptomatic focal epilepsies separately. Our definition of ''probably symptomatic'' agrees with that proposed by Engel (2001) for epilepsies without any detectable anatomic or dysfunctional factor, and generally overlaps the concept of cryptogenic epilepsy. The latest proposals of the ILAE task force (Berg et al., 2010) recommend defining symptomatic epilepsy based on its specific etiology because epilepsy inevitably has a causative factor, an approach that avoids equivocal definitions. However, in our experience, this leaves more than one-third of patients with focal seizures (probably with still undetectable structural lesions or genetic determinants) in a sort of penumbra if even the detailed diagnostic workup used in dedicated centers is unable to identify a specific etiology. However, this ''penumbra'' seems to have a provisional value, as it allows the identification of a subpopulation with a more benign prognosis (at least in terms of AED resistance) than those with identified etiologies. Moreover, it can be expected that at least some of these patients will be identified as having a new genetic disorder, possibly inherited by means of non-autosomal (or nonmonogenic) transmission.

In our ''symptomatic'' patients, AED resistance correlated positively with the presence of multiple seizure types and types that seldom occur in focal epilepsies, such as tonic or atonic seizures that are known to be often refractory to medical treatment (So, 1995; Tassinari et al., 2008). This association likely also indicates that complex or multiple epileptic neuronal networks are highly refractory to AEDs. Moreover, AED resistance correlated with the presence of `seizures with early or prominent consciousness impairment, thus suggesting an origin in cortical regions that are more likely to generate ictal discharges that are difficult to control.

Among the epilepsy-associated brain lesions, MTS significantly correlated with AED-resistance as reported previously in other case series (Semah et al., 1998; Stephen et al., 2001; Pittau et al., 2009; Varoglu et al., 2009). However, our findings also indicated the presence of a minority of patients with a ''benign'' prognosis, as reported by Labate et al. (2006). As suggested by the finding of Semah et al. (1988) and Varoglu et al. (2009), associated risk factors may influence the risk of a bad prognosis.

A considerable proportion of our patients with cortical malformations, another etiology that often sustains severe epilepsies (Bartolomei et al., 1999; Semah & Ryvlin, 2005) were seizure-free. Our inclusion criteria (adult patients with clear focal seizures) probably influenced the percentage of patients achieving seizure freedom.

Among the ''probably symptomatic'' subjects, the positive relationship between AED resistance and psychiatric pathologies can be interpreted as a reactive condition in patients whose seizures are constraining in the absence of any significant neurologic or cognitive defects (Beghi et al., 2002; Modrego et al., 2002).

Of interest, the inverse relationship between a family history of epilepsy and AED resistance suggests that, even in the absence of a clear ''genetic'' picture (found in only five of our patients), the ''probably symptomatic'' group includes a percentage of patients with relatively benign genetically determined epileptic syndromes.

Pathologic EEG findings correlated significantly with AED resistance in both the symptomatic and probably symptomatic patients, as has been found in most case series in which the relationship was evaluated, mainly patients with newly diagnosed epilepsies (see review by Sander & Sillanpaa, 2008), whereas pathologic imaging findings did not. This underlies the importance of ''dysfunctional'' cortices, which can be detected clearly using neurophysiologic methods but are less consistently detectable by means of ''anatomic'' techniques.

AED treatments

Treatment approach

The evaluation of previous and current medical treatments revealed a high number of treatment changes involving ''old'' and ''new'' AEDs, which suggests that the neurologists treating our patients had a dynamic therapeutic approach. Nevertheless, the treatment schedules were simple, as the current pharmacologic therapies included only one AED for most seizure-free patients and almost one third of the AED-resistant patients. This suggest that the centers treating our population consider a treatment regimen based on the lowest possible number of AEDs to be optimal for reducing side effects and drug interactions.

The usefulness of ''new'' AEDs

We included the antiepileptic molecules that have become available over the last 20 years, including those that are tapered mainly because of the risk of idiosyncratic or long-term side effects, such as felbamate and gabapentin (Leppik, 1995; Krauss et al., 1998; Perucca, 2002). We also included AEDs the pharmacologic spectra of which are similar to those of the ''old'' AEDs, but which have pharmacokinetic advantages or are better tolerated, such as oxcarbazepine (Schmidt & Elger, 2004). Our data are therefore unsuitable for comparatively evaluating the effectiveness of different AEDs, which is in any case beyond the scope of the study. Moreover, given that data collection stopped 2 years ago, we probably underestimated the use of more recently introduced AEDs.

While bearing these limitations in mind, the new AEDs seem to be extensively used, as more than half of our patients had tried one or more new AEDs, and one-third of them were still being treated with these drugs at the time of our last observation.

The percentage of patients becoming seizure-free on a ''new'' AED was small but worthy of note. Those with a history of grade II or grade III AED resistance accounted for 46.4% of all the patients achieving complete seizure control. This suggests that, together with the development of the more rational use of all AEDs over the last few decades that the discovery of new molecules provides a real opportunity for patients with still-resistant focal epilepsies, particularly given the multiple limitations of a surgical approach.

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Disclosure

The authors have no conflicts of interest to disclose. We confirm that we 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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