ORIGINAL ARTICLE

Is pseudo-intractability in population of patients with epilepsy still alive in 21 century? Audit of 100 seizure free patients, referred with the diagnosis of pharmacoresistant epilepsy

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Whoever saves a life, it is considered as if he saved an entire world.
(*Babylonian Talmud*, Sanhedrin 4:8 (37a)).

Abstract

OBJECTIVE: There is no universally accepted definition of pseudo-intractable epilepsy. Pseudo-intractability means that the resistance to treatment is, in fact, caused by clinical errors.
The purpose of our study was to identify the reasons for intractability and subsequent effective therapeutic management approaches in a group of patients with established pseudo-intractable epilepsy.
METHODS: The study was designed as a retrospective audit of 100 adult patients who, in their past medical history, were diagnosed as having intractable epilepsy but, following adjustments to their medical management, were seizure free for at least 2 years. Patients underwent standard clinical evaluation, including EEG and/or video-EEG monitoring. We re-evaluated past medical, family, seizure and pharmacological history and morphological findings. Epilepsy was re-classified according to the ILAE classification.
RESULTS: We identified possible errors including incorrect diagnosis and/or inappropriate previous epilepsy management in all 100 patients. Incorrect diagnosis (seizure type and/or syndrome) was observed in 47 patients (47%). Thirty two patients (32%) with idiopathic generalized epilepsy were treated for complex focal seizures with inappropriate choice of medication. Therapeutic errors were identified in 48 patients (48%). Issues with medication compliance were found in 20 patients (20%). Potential seizure precipitating factors were detected in 23 patients (23%).
CONCLUSIONS: Our study of 100 patients confirmed that the problem of pseudo-intractability still exists. Every case of pharmacoresistance in epilepsy could potentially be caused by one or more clinical errors.

Abbreviations:

ILAE - International League Against Epilepsy
IGE - idiopatic generalized epilepsy
CBZ - carbamazepine
PHE - phenytoin
GBP - gabapentin
TGB - tiagabine

INTRODUCTION

Epilepsy affects approximately 0.5–1% of the population (Forsgren *et al.* 2005). It needs to be acknowledged as a serious problem that 20 to 30% of patients with epilepsy are medically intractable (Kwan *et al.* 2000). Typical clinical features of medically intractable patients include intractable seizures, excessive drug burden, cognitive decline, psychosocial dysfunction, depression, anxiety, dependent behaviour, restricted lifestyle, unsatisfactory quality of life and increased morbidity and mortality (Brodie & Kwan 2002). Therapeutic options for this group of patients are limited.

Published literature suggests that only 5–10% of all patients with epilepsy are potential candidates for epilepsy surgery (Chapman *et al.* 2005). In the study of Benbadis *et al.* (2004), only 18% of all referred patients with refractory epilepsy were potential candidates for epilepsy surgery (Benbadis 2005). Outcome of epilepsy surgery is variable, between 40–80% of patients become seizure free, depending on the type of epilepsy (Chapman *et al.* 2005; Hadač & Marusič 2004).

Reassessment of video-EEG records in some referral monitoring centres described in literature revealed that 20–30% of patients whose seizures were intractable to medication had a completely different, epilepsy-unrelated, medical complaint. Most of them had psychogenic non-epileptic seizures (Benbadis *et al.* 2004). Our own clinical experience is similar (Hovorka *et al.* 2007). Patients with psychogenic non-epileptic seizures are relatively well-described in the literature (Benbadis & Hauser 2000; Hovorka *et al.* 2007).

It is known that not all patients with intractable epilepsy are truly pharmacoresistant (Komárek & Hovorka 2004). Resistance to treatment in these patients, 'pseudo-intractability', results from clinical errors with serious long-term consequences. Pseudo-intractability is a significant problem. On one side, it is relatively easy to treat but on the other, it is often underestimated and unrecognized in clinical practice. This group of patients is not getting enough attention in the literature. In one of the rare publications, Viteva & Zahariev (2009) described pseudo-resistance in 39 patients with epilepsy.

The purpose of our study was to identify the reasons for intractability and to detect effective management approaches that led to seizure control in this group of patients with established pseudo-intractable epilepsy.

METHODS

The present study was designed as a retrospective audit of 100 adult patients who, in their past medical history, were diagnosed as having intractable epilepsy but, following adjustments to their medical management, were seizure free for at least 2 years. These patients were originally referred to our epilepsy centre for further management due to 'intractability' of their epilepsy. As part of routine clinical practice at our epilepsy centre following their referral, all patients underwent standard clinical evaluations, including EEG and/or video-EEG monitoring. We re-evaluated past medical and family history, seizure history, pharmacological history and morphological findings. Epilepsy was re-classified, according to the International League Against Epilepsy (ILAE) classification, as localization-related epilepsy, idiopathic generalized epilepsy, and symptomatic/cryptogenic generalized epilepsy.

RESULTS

Study group consisted of 100 patients (46 men, 54 women) with age range of 19 to 82 years (mean 37.9 years). Age at the onset of epilepsy ranged from 4 to 76 years (mean 23.0 years), duration of epilepsy at the time of evaluation ranged from 3 to 37 years (mean 12.3 years). Reported seizure frequency at the time of initial clinical evaluation is presented in Table 1.

Possible epilepsy management errors, including incorrect diagnosis and/or inappropriate previous pharmacotherapy were identified in all 100 patients. The main causes of pseudo-intractability observed in our patient group are presented in Table 2. A combination of more than one cause was identified in some patients.

Incorrect diagnosis of seizure type and/or epilepsy syndrome was found in 47 patients (47%). Thirty two patients (32%) with IGE were treated as having a focal epilepsy. Intractability in these patients resulted from inappropriate choice of medication, i.e. use of antiepileptics that are potentially ill-advised in IGE (Hovorka 2009). Lack of efficacy was observed in 28 patients (28%) with IGE treated with carbamazepine (CBZ, 12 patients, 12%), phenytoin (PHE, 8 patients, 8%), gabapentin (GBP, 6 patients, 6%) and tiagabine (TGB, 2 patients, 2%). On contrary, 15 patients (15%) with focal epilepsies were treated as having an IGE with inappropriate pharmacotherapy, mainly a broad-spectrum AED. AEDs effective in the treatment of focal epilepsies were not used in these patients.

Therapeutic errors in patients with correct diagnosis of seizure type/syndrome were identified in 48 patients (48%) and were the most frequent reason for pseudo-intractability in our group of patients. Patients with diagnostic errors leading to inappropriate choice of medication were not included in this group.

Tab. 1. Reported seizure frequency at the time of initial clinical evaluation (n=100).

Frequency of seizures	n (%)
One seizure a year	18 (18)
Several seizures a year	50 (50)
Several seizures a month	10 (10)
Several seizures a week	11 (11)
Several seizures a day	3 (3)
Not clearly defined	8 (8)

Tab. 2. The main causes of pseudo-intractability (n=100).

Factor	n (%)*
Therapeutic errors with correct diagnosis	48 (48%)
Incorrect diagnosis (seizure type/syndrome) with inadequate therapy	47 (47%)
Seizure precipitating factors	23 (23%)
Medication non-compliance	20 (20%)

* More than one cause was identified in some patients

Tab. 3. Compliance problems detected (n=100).

Compliance problem	n (%)
Inconvenience of treatment	4 (4%)
Refusal to take any medication	3 (3%)
Feeling stigmatised by the epilepsy	3 (3%)
Uncertainty about the need for drugs	3 (3%)
Fear of addiction	2 (2%)
Forgetfulness due to impaired memory	2 (2%)
Long intervals between visits to the physician	2 (2%)
Misunderstanding how to take the AED	1 (1%)

The most frequent therapeutic error, identified in 24 patients (24%), was the use of sub-therapeutic doses of AEDs. Transitory adverse events occurring during treatment initiation or up-titration discouraged physicians from prescribing higher doses of the selected AED in 14 patients (14%) treated with older AEDs including carbamazepine, phenytoin and valproate. Failure to prescribe the maximum tolerated dose without a clear reason was identified in 10 patients (10%) who were prescribed newer AEDs, especially lamotrigine, topiramate and levetiracetam.

Use of a combination of two AEDs with clinically significant pharmacokinetic interactions resulting in decreased concentrations of the affected drug was identified in 12 patients (12%). Combinations of lamotrigine with enzyme-inducing AEDs (carbamazepine, phenytoin or primidone) were ineffective in 10 patients (10%).

Clinically important (pharmacokinetic) interactions between AEDs and other drugs resulting in clinically important decrease in AED serum concentrations were observed in 6 patients (6%); this was between lamotrigine and hormonal contraceptives in 4 cases (4%) (Sabers *et al.* 2003) and between AED and other drugs with enzyme-inducing potential in 2 patients (2%).

In 6 patients (6%), treatment with initial or alternative monotherapy was insufficient in controlling seizures but, despite this, was not followed by further pharmacotherapy options such as combination treatment with two or, alternatively, more AEDs.

A combination of carbamazepine and lamotrigine was found ineffective in 2 patients (2%), possibly due to similar mechanism of action – pharmacodynamic interaction.

Possible paradoxical increase in seizure frequency as a manifestation of phenytoin toxicity was identified in 2 patients (2%).

Problems with **medication compliance** of some kind were identified in 14 patients (14%). The majority of patients with compliance problems in our study fell into the 'partial compliance' category with inadequate treatment management (Cramer 2002), meaning that only 4% were found not to take any medication at all. The particular forms of compliance problems detected in our study are presented in Table 3.

Presence of potential **seizure precipitating factors** was detected in 23 patients (23%), as presented in Table 4.

DISCUSSION

Possible errors, including diagnosis and/or previous epilepsy treatment were identified in all 100 audited patients. These errors, we believe, led to the previous intractability in these patients. Following relevant diagnostic adjustments and pertinent therapeutic changes, all these patients became seizure free and, at the time of audit, were seizure free for a minimum of two years. Our study confirmed that the problem of pseudo-intractability in epilepsy still exists, even at the time when sophisticated diagnostic and therapeutic options are available. Our data suggest that any case of 'pharmacoresistance' in epilepsy could, in fact, be a result of one or more clinical errors.

Duration of active epilepsy (Table 5) in the group of patients with incorrect diagnosis was twice that of patients with other causes of pseudo-intractability. Incorrect diagnosis resulting in a selection of potentially ill-advised drugs could be most harmful for the patient. When using antiepileptic drugs, the clinician should be aware of their potential for aggravating specific forms of epilepsy, especially idiopathic generalized epilepsy (Thomas *et al.* 2006). Making the diagnosis of

IGE is a critical step in the management of patients with seizures (Benbadis 2005).

Furthermore, it is of significance that the audited group of patients also included 15 patients (15%) with focal epilepsies treated as having an IGE. Consequently, these patients were treated with broad spectrum AEDs and not the AEDs indicated and more suitable for the management of focal epilepsies (Hovorka 2009).

Sub-therapeutic doses of AEDs were identified in 24 patients (24%) in our cohort. In their prospective study, Tan *et al.* (2005) followed up 40 patients admitted to an emergency unit due to seizures. Of these 40 patients, 22.5% had sub-therapeutic AED levels despite good compliance (Tan *et al.* 2005). AED dose adjustment (supported by AED plasma levels measurement) led to complete seizure control in all 24 patients in our cohort.

With respect to the other therapeutic errors identified in our cohort of patients, our results suggest it is important for the clinicians to be familiar with the principles of pharmacokinetic and pharmacodynamic interactions between different AEDs as well as between AEDs and medicines from other therapeutic groups (Besag *et al.* 1998). The four major enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital and primidone) stimulate the metabolism and reduce the serum concentrations of most other concurrently administered AEDs (Perucca 2002; 2006). A combination of lamotrigine with enzyme-inducing AEDs (carbamazepine, phenytoin or primidone) was ineffective in 10 patients (10%) in our cohort. These patients became seizure-free after these enzyme-inducing AEDs were discontinued or replaced with AEDs with no enzyme-inducing properties.

Noncompliance often results from a failure in communication. Clear communication with the patient provides the basis for an effective patient-physician partnership. But even when the physician has given clear instructions and stressed the importance of following the medication regimen, noncompliance could be common reason for incomplete seizure control or variable side effects (Schachter & Schomer 1997). Low IQ, poor memory, personality disorder, older age and lower education level have been identified in some patients as predictors of possible compliance problems (Cramer *et al.* 1989; Cramer *et al.* 2002; Cramer 2003). Compliance issues led to pseudo-intractability in a significant group of 14 patients in our cohort. Many of the identified problems were potentially avoidable by intensified, ongoing communication with the patients to relieve patient fears and to eliminate uncertainties. Provision of compliance aids could also facilitate compliance.

Another key factor in managing epilepsy is identifying and avoiding potential seizure precipitating factors. These are the factors that are believed to increase the risk of having a seizure. It may or may not be related to the underlying cause of epilepsy. Triggers for seizures vary from person to person, and some people may not have any identifiable precipitating factors (Nakken *et al.* 2005). Precipitating factors were identified as the cause of pseudo-intractability in 23 patients (23%) in our cohort. Determination of potential precipitating factors should be an essential part of diagnostics in epilepsy to avoid miss-management of patients who are not responding to treatment due to persisting contra-effect of precipitating factors.

Tab. 4. Potential seizure precipitating factors detected (n=100).

Factor	n (%)
Sleep deprivation	5 (5%)
Alcohol use	5 (5%)
Catamenial seizures	4 (4%)
Sleep patterns	3 (3%)
Drug abuse	2 (2%)
Exposure to strobe light	2 (2%)
Emotional stress	2 (2%)

Tab. 5. Duration of active epilepsy (years) in relation of diagnostic errors.

All patients with pseudo-intractability	Pseudo-intractable patients with diagnostic error	Pseudo-intractable patients without diagnostic error
n=100	n=47 (47%)	n=53 (53%)
Mean=12.3	Mean=14.8	Mean=6.2
Min–Max=3–37	Min–Max=6–37	Min–Max=3–17

Epilepsy was classified, according to the International League Against Epilepsy (ILAE) classification, as localization-related epilepsy, idiopathic generalized epilepsy, and symptomatic/cryptogenic generalized epilepsy.

CONCLUSIONS

We believe our study contributes to the literature base defining the term of pseudo-intractable epilepsy. The question "Do I really have to have seizures?" was implicated in every patient in our cohort of 100. Reviewing this cohort of patients provided important cues for the clinical management of pharmacoresistant patients as well as, importantly, epilepsy patients in general.

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