Brief Communication

Pseudo-refractory epilepsy

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Drug resistant epilepsy is defined as failure of adequate trials of 2 tolerated, appropriately chosen, and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained freedom from seizure.[1] Early recognition of drug resistant epilepsy is significant for trying alternative therapeutic approaches in the patient including surgery, ketogenic diet, and vagal nerve stimulation. Therefore, the diagnosis of drug resistant epilepsy is very important, but pseudo-resistant epilepsy is not uncommon. Pseudo-refractory epilepsy is usually due to incorrect diagnosis, use of incorrect and/or low dose AED, and poor compliance of patients. Non-epileptic paroxysmal events, including psychogenic non-epileptic seizure (PNES) especially syncope, certain sleep and movement disorders, can be mistaken for epilepsy. An incorrect seizure classification may cause the wrong drug choice. On the other hand, inadequate dosing of an AED may be another reason for pseudo-refraction. Poor compliance with AEDs is also seen frequently.[2,3] The aim of this study was to investigate causes of seizures and subsequent effective management approaches in patients with pseudo-refractory epilepsy.

In the present study, patients who were followed up in our epilepsy department were investigated retrospectively. The files of 2920 patients seen between June 2002 and December 2011 were retrospectively reviewed by the same neurologist in the Department of Epilepsy in Ankara Research and Educational Hospital, Ankara, Turkey. Patients with pseudo-refractory epilepsy were determined according to the following criteria: 1. Patients who did not have enough control of seizures despite at least 2 different AED regimens before being admitted to our department. 2. Patients had no seizure at least one year after the revision of the diagnosis and/or treatment of epilepsy in our epilepsy department. Information on demographic data, medical and epilepsy history, seizure types and frequency, routine EEG, and neuroimaging findings were collected for all patients. An EEG with or without seizure induction, home video recording, and cardiology consultation were also investigated in patients whose diagnosis of epilepsy was doubtful. One hundred and twenty-two patients were examined, but 17 patients were excluded as they had seizures after the adjustment of treatment (12 of them had PNES, but their seizures continued despite the adjustment of treatment). They may have only PNES that was resistant to treatment and/or they had drug resistant epileptic seizures. Five patients had poor compliance; their seizures again did not stop after good compliance. Therefore, 105 were included in this study. All patients who did not respond to treatment in spite of at least 2 different AED regimens were accepted as refractory.

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The mean age was 29±11.53 years (age range 16-70). Seventy-four patients (70.5%) were female and the remaining 31 patients male. No risk factors were determined in 65 (61.9%) patients. There was head trauma in 12 (11.4%) patients, positive family history for epilepsy in 10 (9.5%) patients, febrile convulsion in 9 (8.6%) patients, anoxic birth in 5 patients, and history of CNS infection in 4 patients. Six patients had hypertension, and 2 patients had diabetes mellitus as a comorbid condition. Sixty-three patients were administered polytherapy, with 10 using 3 or more AEDs. Monotherapy was given to 42 patients. However, patients treated with monotherapy used at least one other AED regimen in their previous history.

When routine electroencephalograms were examined, there was no EEG abnormality in 55 (52.4%) patients. Forty-eight patients had generalized/focal epileptiform abnormality (20 of them had generalized epileptiform abnormality and 28 focal epileptiform abnormality). Generalized mild slowing in the EEG was observed in 2 patients. Among 105 patients, 101 underwent cranial MRI. The cranial MRI was normal in 97 patients while, hippocampal sclerosis was present in 3 patients, and diffuse atrophy was seen in one patient.

The reasons for pseudo-refractory epilepsy are summarized in **Table 1**. Incorrect diagnosis of epilepsy was observed in 57 patients, and PNES was considered as a diagnosis in 47. Thirty-two (68%) of them were female. After a review of the files, 37 patients with PNES had a seizure with induction during the EEG recording, and the diagnosis of PNES was made according to the induction of those typical seizures with normal EEG except artifacts. Permission of patients was taken before the induction. First of all, we tried to stimulate seizure with self-induction, normal saline was given to the patient intravenously and seizure semiology and EEG findings before, during, and after seizure were examined. All patients knew that it was not a real drug. The diagnosis of the remaining 7 patients with PNES

Table 1 - Reason for pseudo-refractory epilepsy.

Reason	No. of patients
Non-epileptic event	57
PNES	47
Other non-epileptic event	10
Incorrect classification leading to incorrect treatment	7
Inadequate dosing of AED	11
Poor compliance and inappropriate life style	42

PNES - psychogenic non-epileptic seizure, AED - antiepileptic drugs

was made after the psychological evaluation. The other 2 patients were diagnosed as PNES after the examination of home video camera recording. Antidepressant drugs and/or psychotherapy were administered to all patients with PNES. The AED treatment was discontinued in 38 patients. These patients had normal EEG except one, and that patient had mild slowing background activity in his EEG. The cranial MRI was also normal in all of them. Nevertheless, the remaining 9 patients with PNES had interictal epileptiform discharges in their routine EEG, and cranial MRI revealed hippocampal sclerosis in 2 patients, so AEDs were also maintained in addition to psychiatric therapy. All of these patients were seizure free during the follow period (follow up period: 13-55 months)

The remaining 10 patients with the incorrect diagnosis had a non-epileptic paroxysmal event. Seven of them had syncope. All patients with syncope underwent cardiology consultation and 4 of them underwent surgery due to cardiac problems. The cardiologist regulated treatment of the other 3 patients. Two patients had obstructive sleep apnea, and one patient had severe hypoglycemia. The EEG was normal in all patients. Cranial MRI was normal in 9 of them, but one cranial MRI revealed diffuse atrophy in a patient. The AEDs of patients with non-epileptic paroxysmal event were discontinued after correct diagnosis. They had no seizure after the regulation of treatment (follow up time: 15-68 months)

An incorrect diagnosis of seizure classification that led to incorrect drug choice was observed in 7 patients. Idiopathic generalized epilepsy syndromes, especially juvenile myoclonic epilepsy and juvenile absence epilepsy were unrecognized and inappropriately treated with narrow spectrum AEDs (for example, carbamazepine) in these patients. These patients were seizure free after the employment of a suitable AED (follow up period: 12-81 months). Inadequate dosing of AED was seen in 11 patients. All of them were under polytherapy. Complete seizure control was achieved after the regulation of AEDs (follow up period: 16-72 months)

Noncompliance with AED and inappropriate life style was established in 42 patients. Family members and friends in addition to a good doctor-patient relationship supported these patients. Precipitating factors for seizures were explained to the patients. Nineteen patients also underwent psychiatric consultation. Compliance did not correlate with age and education.

Twelve patients with poor compliance also had a wrong diagnosis of seizure classification that led to the choice of wrong drug. All patients were seizure free after good compliance, regulation of life style, and AED treatment (follow up period: 14-94 months).

Errors in diagnosis are usually due to non-epileptic seizures (PNES, syncope and so forth), incorrect seizure classification, and failure to identify causative factors, or seizure syndromes. Induction of PNES is sometimes necessary in the outpatient EEG laboratory. Home video camera recording is usually helpful to differentiate PNES and true epileptic seizures. However, long-term video EEG monitoring may be used in many cases to identify exactly what is happening with the patient.[2,3]

Incorrect classification of seizures may lead to choosing an incorrect AED. A classic example is the misdiagnosis of juvenile myoclonic epilepsy (JME) and treatment with narrow spectrum antiepileptic drugs such as carbamazepine. Another error in the management of epilepsy is inadequate dosing of medication. Patients may be treated with the correct AED, but the dosage is inadequate. Physicians should be sure that the AED dosage is at the maximum tolerated level before adding a second medication.[2,4,5] The other factor causing inadequate seizure control is poor patient compliance. Patient education and a good relationship between family members, patients, and doctors is necessary to obtain good compliance. It is also important to inquire about possible triggering factors such as alcohol, stimulants, and sleep deficiencies.[3]

Bajacek et al[4] investigated 100 patients who were diagnosed with intractable epilepsy before admission. All these patients were seizure free at least 2 years after adjustments to their treatment. The reasons for pseudo-refractory epilepsy in this study were incorrect diagnosis, inappropriate previous epilepsy management, and/or poor compliance, and inappropriate life style.

Viteva and Zahariev[5] also investigated factors causing development of pseudo-resistance epilepsy. One hundred and ninety-one patients were evaluated retrospectively. The main groups of factors that caused pseudo-resistance were diagnostic (46.15%) and

therapeutic errors (69.2%), poor compliance (33.3%), external factors (5.1%), as well as a combination of these (53.8%). They also found that compliance correlated weakly with age and education; however, they also observed that high and moderate correlation was present in male patients younger than 20 years old.

Although the size of the sample is large, some limitations in this study were present: The diagnosis of PNES was not easy; PNES and epileptic seizures sometimes cannot be differentiated especially in patients with both.

In conclusion, pseudo-refractory epileptic patients are still a major problem in our clinical practice. The differentiation between pseudo-refractory and true refractory epilepsy is very important in avoiding unnecessary treatment, and future management of true refractory epilepsy. The main causes of pseudo-refraction epilepsy are incorrect diagnosis, incorrect treatment, poor compliance, and inappropriate life style of patients.

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