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Reasons for uncontrolled seizures in children: The impact of pseudointractability

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ABSTRACT

Purpose: We investigated the various possible reasons for uncontrolled seizures in patients under 18 years of age to determine the impact of pseudointractability. We also investigated the various forms of pseudointractability in children with uncontrolled seizures.
Methods: In this cross-sectional retrospective chart review study, all patients under 18 years of age with their first seizure occurring at least 6 months prior to the referral date, taking at least one antiepileptic drug (AED), and having at least one seizure in the past 3 months were studied. The presumed reason for uncontrolled seizures was arbitrarily considered to be one of these five categories: poor adherence; wrong medication; wrong dose of the correct medication; diagnosis other than epilepsy; and finally, medically refractory epilepsy. Statistical analyses were performed using Chi-square and Fisher's Exact tests to determine potentially significant differences, and a P value less than 0.05 was considered significant.
Results: During the study period, 198 patients were referred to us due to uncontrolled seizures. Ninety patients (45%) were taking one AED, 55 (28%) were taking two AEDs, and 53 (27%) patients were taking more than two AEDs at the time of referral. Four percent of these patients did not have epilepsy. Forty-seven percent of the children with uncontrolled seizures had medically refractory epilepsy; 37% were taking the wrong AEDs; 10% were taking suboptimal doses of AEDs; and 2% had poor drug adherence.
Conclusion: Uncontrolled seizures in children are a commonly encountered problem, particularly at epilepsy clinics. One should consider all possible reasons for these uncontrolled seizures, including non-epileptic seizures, pseudointractability, and medically refractory epilepsy. The mainstay for making a correct diagnosis is a detailed clinical history.

1. Introduction

Epilepsy is defined as a condition characterized by chronic recurrent epileptic seizures due to a primary disturbance of brain function [1]. Epilepsy is a common chronic neurological disorder in children [2]. The mainstay of treatment in children with epilepsy is antiepileptic drug (AED) therapy. In the past two decades, many new AEDs have been introduced to the market, so that there are now more than 20 medications available to treat epilepsy. The physician, therefore, has many choices and can tailor therapy. However, having many alternatives also allows for the possibility of choosing an inappropriate or suboptimal agent that may result in uncontrolled seizures (pseudointractability) [3,4]. On the other hand, more than one-third of individuals with epilepsy have persistent seizures despite taking appropriate AEDs: these are considered as refractory [5,6].

In this study, we investigated the various possible reasons for uncontrolled seizures in patients under 18 years of age to determine the impact of pseudointractability. We also tried to determine the various forms of pseudointractability in these patients.

2. Methods and material

In this cross-sectional retrospective chart review study, all patients under 18 years of age who were referred (either as self-referral or referred by another physician) to the outpatient epilepsy clinic at Shiraz University of Medical Sciences from January 2009 through October 2009 due to presumably uncontrolled seizures were studied. Inclusion criteria were as follows: age below 18 years at the time of referral; with the first seizure occurring at least six months prior to the referral date; taking at least one AED since the presumed diagnosis; and finally, having at least one seizure in the past three months. A clinical diagnosis of the child's disorder was made based on clinical grounds, and all patients had to be under the care of the epileptologist at our institution. Outpatient electroencephalography (EEG) was performed in all patients at the time of referral. Study time for EEG was 10 min, and we performed intermittent photic stimulation in all patients. Hyperventilation was typically performed in children above five years of age if they were cooperative. Inpatient video-EEG monitoring study was performed when considered necessary for the diagnosis. The study time for the

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Table 1
Final diagnosis of patients who were referred with uncontrolled seizures.

Final diagnosis	Number (%)	Syndromic classification	Number (% from total)
Symptomatic generalized epilepsy	98 (49.5)	Lennox–Gastaut syndrome	62 (31)
		Infantile spasm	13 (6.5)
		Others	23 (12)
Focal epilepsy (other than temporal lobe epilepsy)	48 (24)		
Idiopathic generalized epilepsy	28 (14)	Juvenile myoclonic epilepsy	10 (5)
		Childhood absence epilepsy	7 (3.5)
		Juvenile absence epilepsy	5 (2.5)
		Others	6 (3)
Temporal lobe epilepsy	11 (5.5)		
Unclassified epileptic seizures	5 (2.5)		
Diagnosis other than epilepsy	8 (4)	Psychogenic non-epileptic seizures	3 (1.5)
		Syncope	2 (1)
		Breath-holding spells	1 (0.5)
		Sleep myoclonus	1 (0.5)
		Tramadol-induced seizures	1 (0.5)

video-EEG monitoring was 120 min, and it was required to record both wakefulness and sleep (either normal or drug induced) in all patients. Other tests (i.e., blood tests, imaging studies, etc.) were requested based upon the clinical judgment.

We studied the demographic and clinical findings. Age, gender, seizure type(s), seizure frequency, medication(s), other clinical findings (i.e., EEG, imaging studies, blood tests, etc.), and final diagnosis of all patients were registered routinely. Relevant clinical variables were summarized descriptively to characterize the study population. The presumed reason for uncontrolled seizures was arbitrarily considered to be one of these five categories: 1. Poor adherence, defined as more than one missed dose per week; 2. Wrong (suboptimal) medication, defined as inappropriate AED for the syndromic diagnosis (e.g., carbamazepine for childhood absence epilepsy or ethosuximide for frontal lobe seizures [3]); 3. Wrong (suboptimal) dose of the correct medication; 4. Diagnosis other than epilepsy (e.g., psychogenic non-epileptic seizures, syncope, movement disorder, or breath-holding spells); and finally, 5. Medically refractory epilepsy, defined as failure of adequate trials of two tolerated, appropriately chosen, and used AED schedules to achieve sustained seizure freedom [6]. For example, if a patient with childhood absence epilepsy had received reasonable doses of both valproate and ethosuximide (whether as monotherapies or in combination) in his drug history, he was considered to have medically refractory epilepsy.

Statistical analyses were performed using Chi-square and Fisher's exact tests to determine potentially significant differences, and a P value less than 0.05 was considered significant. This study was conducted with the approval of the Shiraz University of Medical Sciences Review Board.

3. Results

During the study period, 198 patients under 18 years of age were referred to us due to uncontrolled seizures. One hundred twenty-seven (64%) were males and 71 (36%) were females. The mean age (± standard deviation) at the time of referral was 9 years (±5). The minimum age was 8 months and the maximum age was 17.5 years. Seizure frequency in the past three months (up to the referral time) was reported to be daily in 93 patients (47%), weekly in 28 (14%), and monthly or occasionally in 77 patients (39%). Final diagnoses of these patients are summarized in Table 1. Ninety patients (45%) were taking one AED, 55 (28%) were taking two AEDs, and 53 (27%) patients were taking more than two AEDs at the time of referral. The patterns of taking AED(s) among different diagnoses are summarized in Table 2. Sex distribution among various diagnoses was not different statistically, in two-by-two comparisons. Electroencephalogram findings in patients with uncontrolled seizures are summarized in Table 3. Normal routine EEGs were sometimes observed in patients with idiopathic generalized epilepsy or focal epilepsy, but EEG was almost always abnormal in patients with symptomatic generalized epilepsy ($P = 0.0001$). Long-term video-EEG monitoring was often abnormal in patients with epilepsy. Brain MRI findings in patients with uncontrolled seizures are summarized in Table 4. Brain MRI was more often abnormal in patients with focal epilepsy or symptomatic generalized epilepsy compared with that in patients with idiopathic generalized epilepsy ($P < 0.02$). However, the results were similar in patients with idiopathic generalized epilepsy compared with that in patients with non-epileptic paroxysmal seizure-like attacks ($P = 0.5$); non-specific findings such as atrophy or cyst (among other possibilities) could be seen in both conditions. Blood tests were not performed in most patients, and they were not conclusive in others who had them done (irrespective of the final diagnosis). Presumed reasons for having uncontrolled seizures among all patients are summarized in Table 5. Presumed reasons for having uncontrolled seizures among patients with a confirmed epilepsy syndrome are summarized in Table 6. The most common reason for having uncontrolled seizures in patients with idiopathic generalized epilepsy was considered

Table 2
Pattern of AED usage among patients with uncontrolled seizures.

Diagnosis	One AED	Two AEDs	3 or more AEDs
SGE	37 (38%)	31 (32%)	30 (30%)
Focal other than TLE	28 (58%)	8 (17%)	12 (25%)
IGE	15 (54%)	9 (32%)	4 (14%)
TLE	4 (36%)	2 (18%)	5 (46%)
UE	3 (60%)	2 (40%)	0
Diagnosis other than epilepsy	3 (37.5%)	3 (37.5%)	2 (25%)

AED: antiepileptic drug; SGE: symptomatic generalized epilepsy; TLE: temporal lobe epilepsy; IGE: idiopathic generalized epilepsy; UE: unclassified epilepsy.

Table 3
Results of EEG studies in patients referred with uncontrolled seizures.

Diagnosis	Routine EEG			Video-EEG monitoring		
	Normal	Abnormal	Not done[a]	Normal	Abnormal	Not done
SGE	2 (2%)	93 (98%)	3	0	24 (100%)	74
Focal other than TLE	8 (17%)	38 (83%)	2	1 (6%)	15 (94%)	32
IGE	6 (21%)	22 (79%)	0	2 (33%)	4 (67%)	22
TLE	4 (36%)	7 (64%)	0	2 (33%)	4 (67%)	5
UE	5 (100%)	0	0	1	0	4
Diagnosis other than epilepsy	8 (100%)	0	0	0	0	0

SGE: symptomatic generalized epilepsy; TLE: temporal lobe epilepsy; IGE: idiopathic generalized epilepsy; UE: unclassified epilepsy.
[a] In some patients routine EEG was not done due to financial reasons.