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CAUSES OF INTRACTABLE SEIZURES IN A SURVEY OF 10,000 EPILEPTIC CHILDREN

A. NASIRIAN, M.D.

From the Dept. of Pediatric Neurology, Tehran University of Medical Sciences, Tehran, I.R. Iran.

ABSTRACT

Although treated properly for epilepsy, a number of epileptic children have intractable seizures and about 5-10 per cent of them do not respond to anti-epileptic drugs. In the years 1986-1996 about 10,000 epileptic patients were treated in the Children's Medical Center in Tehran. A retrospective study of their medical records revealed that 41 of them had intractable seizures.[1]

Of these 41 patients, 56.9% had partial epilepsy, 12.2% grand mal epilepsy, 14 % atypical petit-mal, 7.3% Lennox syndrome, 7.3% infantile spasm and 2.4% myoclonic epilepsy. All of them had received at least two anti-epileptic drugs. 34.1% were not treated regularly. 31.7% had organic brain dysfunction and 51.6% had behavior disorder (hyperactivity-aggressiveness, etc.).

These figures show a lower rate of intractable seizures than that of international statistics. The most important cause of intractable seizures seems to be irregular treatment of the epilepsy.

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INTRODUCTION

Epilepsy is a widespread entity involving 5 per thousand of the world population. More than 60% of the involved can be treated completely, nearly 60 to 80% of them are treatable, and about 5-10% do not respond to any medication[1] and are intractable seizures.

A clear definition for the term "intractable" does not exist yet.[2] Generally an intractable seizure is accepted when the patient does not respond to the treatment. But when is a treatment seen as adequate?[3] According to Othtsuka et al. the term intractable is justified when the patient has not responded to all kinds of treatment that are available at the present time. Gilman et al. use the word intractable for those cases that do not respond to first line anti-epileptics such as carbamazepine, phenytoin and valproate, when used in full doses with suitable drug levels or proper combination of them.[5]

The known causes of intractable seizures are a. misdiagnosed epilepsy, b. mistreatment with unsuitable drugs, c. drug interaction, d. irregular treatment (noncompliant patient), e. metabolic disorders, and f. epileptic disorders that are intractable per se (Lennox syndrome, infantile spasm, myoclonic epilepsy).

Misdiagnosis can lead to choice of unsuitable drugs.[4] To avoid this, an exact observation of the patient, clinical examination and evaluation of the EEG is necessary. The choice of suitable medication, administration in sufficient doses and avoidance of improper drug interaction is important.[5] Drug levels in blood should be determined regularly. Determination of blood levels of phenytoin, phenobarbital, carbamazepine, primidone, and ethosuximide is practical and useful. This is not the case in other drugs such as lamotrigine, valproate and benzodiazepines. Irregular administration of anti-epileptics may result in seizure intractability. Therefore, patient and parent compliance is of great importance.[1,6]

Eventually existing underlying diseases should be detected and treated. Clinical signs of metabolic disorders resemble mental retardation, motor disorders and seizures, as well as other diseases of the central nervous system.[5]

Infantile spasm, Lennox-Gastaut syndrome and myoclonic epilepsy belong to the category of naturally in-

tractable seizures. The rate of successful treatment in these entities is low.[6,7]

MATERIAL AND METHODS

During the years 1986 through 1996 ten thousand epileptic patients were treated in the Children's Medical Center in Tehran. The diagnosis was based on history, physical examination and EEG. The type of epilepsy was recognized by history, observation, EEG and CT.

For this retrospective study the following information was extracted from the records of the patients: Age of onset, sex, family history, neurologic signs and symptoms, type of epilepsy, drugs taken, how long treated, response to treatment, kind of seizure control (complete, relative, intractability), EEG findings, CT or MRI findings, background disease, etiology and outcome in status epilepticus.

The patients were clinically examined 3 times in a period of 4 months with repeated EEG and the data recorded in a table. When no response to the medication was noticed the case was registered as intractable.

Table I. Frequency of the type of epilepsy in 41 cases of intractable seizure.

Type	Percent
Partial and partial complex epilepsy	56.9%
Grand mal epilepsy	12.2%
Atypical petit mal	14%
Lennox syndrome	7.3%
Infantile spasms	7.3%
Myoclonic epilepsy	2.4%

Table II. Frequency of drugs used in intractable epilepsy for more than 3 months.

Drug	Percent
Primidone	85.4%
Carbamazepine	80.5%
Clonazepam	65.9%
Valproic acid	61.0%
Acetazolamide	31.7%
Phenytoin	29.3%
Prednisolone	4.9%
Phenobarbital	2.4%

Table III. Frequency of underlying disorders in intractable epilepsy.

Underlying Event	Percent
Normal	56.1%
Difficult delivery	9.8%
Head trauma	4.9%
Metabolic disorders	7.3%
Encephalitis	4.9%
Tuberous sclerosis	4.9%
History of convulsion	4.9%
Neonatal diseases (seizure, sepsis, hemorrhage, etc.)	9.8%

RESULTS

41 patients out of 10,000 epileptic children had intractable seizures (4.1 %). Types of epilepsy causing intractable seizures had the following frequency: focal epilepsy 56.9%, grand mal epilepsy (major motor epilepsy) 12.2%, Lennox syndrome 7.3%, atypical petit mal (14 %), infantile spasm 7.3%, and myoclonic epilepsy 2.4%.

Age of onset was 3 days to 15 years (mean age 33 months, medium age 4 years).

The incidence of the disease in patients 1-4 years old was as high as in those 4-16 years old.

The sex ratio was 51.2% male to 48.8% female. 34.1% of the patients have had irregular treatments. 29% showed developmental delay. 31.7% had signs and symptoms of brain dysfunction such as microcephaly, hemiparesis, hypotonia (each 7.3%), strabismus (9.9%), muscle spasm and hyperreflexia (7.3%), and behavior disorders (56.1%) (aggressiveness 41.47%, hyperactivity 14.4% (because of drug reaction or brain damage), depression 4.9%, anxiety 2.4%). 3 cases had a history of status epilepticus. 43% had a background disease (difficult delivery 9.8%, neonatal asphyxia, sepsis, jaundice or metabolic disorders consisting of organic acidemia, phenylketonuria, hypoparathyroidism (7.3%), head injury, encephalitis, tuberculosis (each 4.9%). 24 cases had brain CT scans showing, in 29.3%, disorders like cortical atrophy, hypodensity, and hyperdensity. 31% were mentally retarded or had cerebral palsy. 43.9% had taken more than 2 drugs.

The main drugs taken by the patients consisted of primidone 85.4%, carbamazepine 80.5%, clonazepam 65.9%, and sodium valproate 61%.

Age of onset for partial epilepsy showed two peaks, the first being between 0-1 year and the second between 4-16 years. Other types showed a peak between 1-4 years.

DISCUSSION

In the present study, intractable seizure is encountered mostly in partial epilepsy.

Studies in other countries reported Lennox syndrome,

West syndrome, complex partial epilepsy and partial epilepsy to be more prevalent.[8] The cause for this difference seems to be the small number of cases (Japan 135, Brazil 80, and the present study 41).[9] A remarkable point in this study of intractable seizures is its relatively low incidence in comparison to world statistics.[10] Irregular treatment (patient poor compliance) is not only our difficulty. 50% of patients in Brazil had irregular treatment.[11]

Table IV. Frequency of other complaints in intractable epilepsy.

Complaint	Percent
Normal	43.9%
Aggressive	41.4%
Hyperactivity	14.4%
Obsessive-compulsive	4.9%
Depression	4.9%
Anxiety	2.4%

Table V. Frequency of abnormal physical examination in intractable epilepsy.

Result of physical examination	Percent
Normal	68.3%
Microcephaly	7.3%
Spastic hemiparesis	7.3%
Ataxia	7.3%
Spastic quadriparesis	7.3%
Strabismus	4.9%

Table VI. Frequency of CP or MR in intractable epilepsy.

CP or MR	Percent
Normal	68.3%
Cp and MR	9.7%
Mental retardation	22%
Spastic CP	7.3%
Athetoid CP	2.4%

Table VII. Number of drugs used in intractable epilepsy.

Number of drugs	Percent
Two drugs	5%
Three drugs	45%
Four drugs	25%
Five drugs	20%
Six drugs	5%

We assume that we were more successful in the control of epilepsy regarding the fact that only 47.5% of our patients were symptomatic, whereas other sources report symptomatic patients between 50 to 85%.[12] As an example, a symptomatic incidence of 35.5% is reported from Brazil.[13] The age of our patients and those from Japan was under 1 year, whereas 66% of those from Brazil were over 5 years old.[8]

Lack of underlying disease either remote or of acute onset in epileptic patients increases the chance that the seizure be controlled more easily.[14]

Regarding the results of this study one can conclude that the earlier the epilepsy is diagnosed and appropriate therapy started, the better intractable seizures can be prevented.[15] A remarkable number of our patients had irregular treatment.[16] This problem is due to some factors, the most important being the unavailability or poor availability of some necessary drugs in this country.[17] Other factors are the very busy and exhausted doctors and nurses, who do not find enough time to explain for parents the nature of the epilepsy and its long-term treatment, so that they discontinue it at the first signs of recovery.[18] Poor availability of special laboratories for drug level determination is another problem that makes appropriate treatment difficult.[19,20] Some of our patients had many of these predisposing factors.

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