Refractory epilepsy: treatment by immunoglobulin
Epilepsia refratária: tratamento com imunoglobulina

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ABSTRACT

Objective: To evaluate the therapeutic effect of the use of immunoglobulin in patients with refractory epilepsy. Methods: Twenty patients with refractory epilepsy were treated with immunoglobulin therapy. Results: Five patients became free from seizures. Thirteen patients improved 50-80% and two patients had no reduction in number of seizures. Conclusions: All patients benefited significantly and cognitive and motor performance improvements were quite clear. We considered immunoglobulin as a valuable alternative to treat refractory epilepsy, even though it is an expensive treatment.

Keywords: Epilepsy/therapy; Immunoglobulin/therapeutic use

INTRODUCTION

Refractory or difficult to control epilepsy are characterized by persistent and varied epileptic seizures, despite the appropriate use of specific medications. These seizures do not present positive result to anticonvulsants, even when prescribed at maximum acceptable doses, under monotherapy or combination therapy. Considering the prevalence of epilepsy of 3 per one thousand in childhood, it is estimated that 20-25% of children with epilepsy are part of the group that has refractory affections\(^{(1)}\).

It is worth mentioning that about 50 million people have epilepsy and, out of them, 40 million are in developing countries.

The determining causes of refractory epilepsy are related to the structural impairment caused by cerebrovascular malformations, metabolic disorders, infectious diseases or traumas related to pre-, peri- and postnatal periods. Early onset and frequency of seizures are indicative factors of refractory response to treatment. It is, therefore, a severe clinical picture, relatively frequent, in which variability of the seizures is high, considering their number, intensity and type. Moreover, we should consider that refractory epilepsy is followed by blockage or regression of cognitive and behavioral functions. As a determining cause, we assume that there is a dysfunction of the system responsible for cerebral immunity, a fact that makes anticonvulsants ineffective to control seizures\(^{(2)}\).

OBJECTIVE

To assess the therapeutic benefits obtained with the use of immunoglobulin in epileptic seizures refractory to conventional drugs.

METHODS

We assessed 20 patients (10 male and 10 female), age range of 13 months to 14 years (mean of 5 years) who presented epileptic seizures of varied pattern, which...
started in the second year of life. Ten patients presented history of West syndrome and were treated at the time of the diagnosis with ACTH.

Three patients had tuberous sclerosis and one had Sturge-Weber syndrome; five patients had cerebral damage owing to neonatal hypoxia. All patients were submitted to clinical neurological assessment, imaging exams of the head - skull computed tomography, magnetic resonance imaging, and cerebral scintigraphy (SPECT), and electroencephalogram. All patients presented delay in neural-psycho-motor development. They had been treated with anticonvulsants either by monotherapy or combination therapy. The drugs used were phenobarbital, phenytoin, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, topiramate, felbamate, valproic acid, clonazepan, clobazan and nitrazepan.

Treatment was performed with intravenous immunoglobulin 400 mg/kg/day for five consecutive days, repeated monthly for 9 months.

Categorical variables were presented in descriptive format using absolute and relative frequencies. Quantitative variables were descriptively presented. Family members were instructed concerning the clinical picture and the proposed therapeutic regimen.

RESULTS

Three patients (15%) presented total remission of seizures. Two patients (10%) remained seizure-free for 9 and 10 months, respectively. Concerning the number of seizures, five patients (25%) presented improvement with reduction of seizures by 80%, two patients (10%) improved 70%, six patients (30%) improved 50%, and two patients (10%) did not respond to treatment (table 1). Adverse events were irrelevant, except in two patients: one had skin allergic reaction that was resolved by replacing immunoglobulin by another with lower IgA content; the other also developed skin allergic reaction, but since there would be only one more cycle, we decided to complete the treatment because the response had been good till then. In addition to seizure control, family members and therapists observed clear improvement in motor and cognitive performance.

<table>
<thead>
<tr>
<th>Seizures</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Total remission</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Up to 10-month remission</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Reduction by up to 80%</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Reduction by up to 70%</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Reduction by up to 50%</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Unaltered</td>
<td>2 (10)</td>
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<tr>
<td>Total</td>
<td>20 (100)</td>
</tr>
</tbody>
</table>

DISCUSSION

Refractory epileptic seizures have many consequences to patients and family members because they interfere in the neuromotor and neurobehavioral development, in addition to causing major impact in family and social structure. The existence of frequent and persistent seizures maintains family members under constant tension.

The use of anticonvulsants becomes a complex operation, because even with the combination of many different drugs, the results fall short of expectations. Undesirable drug effects are sometimes manifested before control of epileptic seizures, which interfere in patients life. The association of immunoglobulin in treatment of refractory epileptic seizures presented satisfactory responses, according to some authors, given that reduction in number of seizures varied from 30% to 80%.

Three patients treated did not present any more convulsive seizures and two were seizure-free for 9 and 10 months, respectively. Refractory seizures should be related with probable immune mechanisms, intrinsic to the central nervous system, which might interfere and lead to no positive response to anticonvulsants. The mode of action of immunoglobulin is still unknown, but some authors wonder that there may be a neuromodulatory mechanism as a support to prevent local immunodeficiency or as a regulator of occasional immune cerebral dysfunction.

In a previous study, performed with patients with West syndrome, cerebrospinal fluid (CSF) test showed immunoglobulin G content below normal levels before treatment; this type of alteration was not found in blood. After treatment, we found IgG CSF content higher than initially, confirming the results found by Van Engelen. These data may be a consistent justification for positive response to treatment of refractory seizures with immunoglobulin, because it crosses the blood-brain barrier.

The electroencephalogram records present improvement during treatment with partial or total reduction of epileptic discharges. The literature reports partial reduction of discharges by 49%, in average, as well as motor and cognitive improvement found in our patients.

The first signs of improvement were detected in our patients as of the first and second cycles of immunoglobulin, even before reducing the number of seizures. Subsequently, improvement was due to adding effects determined by reduced frequency and intensity of seizures, partial reduction of anticonvulsants and probable local action of immunoglobulin. Despite the fact that the number of treated patients to present is still small, results have proven to be satisfactory and promising. Finally, we should also report the comment included in the Guidelines for the Use of Intravenous Immunoglobulin in Neurological Diseases.
by the Association of British Neurologists, in 2002, emphasizing that intravenous use of immunoglobulins should be preferably confined to controlled randomized studies. The severe and progressive nature of epilepsy makes it reasonable to consider the use in cases in which other treatment approaches have failed\(^{(13)}\).

Other studies, including more cases, should be performed to better assess this therapeutic option.

CONCLUSION

The present study shows a quite gratifying perspective for the treatment of refractory epileptic seizures, even though the publications about the topic are still scarce, the number of patients treated is limited, and the mechanism of action is not well defined.

This is an approach that deserves to be followed up, because the use of intravenous immunoglobulin has revealed satisfactory results in cases of refractory epilepsy. The reduction in number of seizures and the cognitive motor improvement seen in our patients contributed to more appropriate quality of life both for patients and family members. These facts strongly justify this type of therapeutic procedure, even though it is quite expensive.

REFERENCES