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The Effect Of Immunotherapy on Seizure Frequency in Drug Resistant Focal Seizures

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Abstract

Objective: *Epilepsy is an important neurological disorder with serious consequences for both patients and society. Even though most cases of epilepsy can be controlled with antiseizure drugs, some types are resistant to medication.The present study,aims to investigate the effect of methylprednisolone treatment on seizure frequency in patients with drug resistant focal impaired awareness seizures.*

Materials and Methods:*This study involved 20 patients with focal impaired awareness seizures who had used multiple antiseizure drugs but had not experienced a seizure-free period longer than six months. The clinical and demographic characteristics of the patients were assessed. Each patient received 1000 mg intravenous (IV) pulse methylprednisolone therapy for 5 consecutive days. Patients were followed up for three months before and after the treatment. Seizure frequencies and electroencephalogram (EEG) findings,during the three months pre-treatment and post-treatment periods were compared. Patients experiencing a decrease in seizure frequency of more than 50% three months after treatment, in comparison to the pre-treatment period,were considered responders to the therapy.*

Results: *As a result of the study,4 patients responded positively to the treatment.One of these 4 patients became completely seizure-free.However,no statistically significant difference was found between pre-treatment and post-treatment seizure frequencies.Among nine patients with epileptiform findings on their pre-treatment EEG, these findings disappeared in four patients post-treatment.Nevertheless, the differences in EEG findings before and after treatment were also not statistically significant.*

Conclusion: *In our study, a single course of IV methylprednisolone therapy in patients with focal impaired awareness seizures did not yield a significant therapeutic response.It has been surmised that,a more efficient response to treatment would be achieved in case of continuing corticosteroid therapy with repeated doses in patients with treatment refractory focal impaired awareness seizures.*

Key words: *Refractory epilepsy,focal epilepsy,immünotheraphy,antiseizure drugs,epilepsy*

Introduction

Epilepsy affects millions of individuals worldwide[1].While the majority of patients with epilepsy can be controlled with antiseizure drugs, approximately one third of them are resistant to drug treatment. Accordingly, the mortality and morbidity rate of the disease increases. Drug resistant epilepsy is the inability to achieve seizure freedom despite the use of two or more appropriate anti-seizure drugs as monotherapy or combined treatment[2].Although drug-resistant epilepsies are seen in all types of epilepsies, they are more common in focal epilepsies[3,4]. In focal epilepsies, the underlying cause is the most important factor affecting prognosis and seizure recurrence[5].Recent studies indicated that neuroinflammation might play a role in the etiology of these

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refractory epilepsies.When there is any neuronal damage in the central nervous system,a neuroinflammation due to proinflammatory molecules occurs, and this neuroinflammation causes the seizure threshold to decrease[6].Consequently, numerous immunotherapy studies were carried out targeting neuroinflammation in refractory epilepsies; however, a definitive treatment protocol has yet to be established[7,8].This study evaluates the response to high dose corticosteroid therapy in patients with refractory focal impaired awareness seizures.The effects of treatment on seizures and electroencephalogram were examined in these patients.

Materials and Methods

The study was approved by Ministry of Health Ankara Diskapi Yildirim Beyazit Training and Research Ethics Committees (approval number: 28/22, date:04.04.2016).Twenty patients with focal impaired awareness seizures were involved in the present study. Patients who experienced focal impaired awareness seizures,had used more than one antiseizure drug and had not been seizure free for >6 months were classified as refractory epilepsy patients. The demographic characteristics are summarized in Table 1.The disease duration in the patient group ranged between 10 and 59 years, and the mean disease duration was found to be 24 years.The duration of use antiseizure drug ranged between 7 and 48 years,while the mean duration was found 20.5 years.All 20 patients exhibited focal impaired awareness seizures, and three of them had focal to bilateral tonic-clonic seizures.Eleven patients were using more than two antiseizure drugs.Inflammatory findings (Mesial temporal sclerosis) were detected on cranial MRI in 5 patients, while the cranial MRI findings were normal in 15 patients.Epileptiform activity was observed on pre-treatment EEG recordings in 9 patients (Table 2).All patients received intravenous methylprednisolone pulse steroid therapy at a dose of 1000 mg/day for five days.The patients were followed for three months before and after the treatment.Seizure frequencies and EEG findings during the three-month periods before and after treatment were evaluated.Patients who had a >50% decrease in seizure frequency in comparison to the pre-treatment period were classified as having a significant response to treatment.Brain wave activities of the patients were recorded using a Nihon Kohden EEG device, and the EEG tracings were analyzed in a double-blinded manner to assess the presence of epileptiform activity.The results were statistically analyzed using SPSS version 16.0. For the evaluation of treatment response, the Wilcoxon test,a non-parametric analysis method, was used. Fisher’s Exact Test was employed for subgroup analyses.

Table1. Demographic characteristics of patients

	Number (Median)
Age	38 (21-71)
	Number (%)
Sex	
Female	10(50)
Male	10 (50)
Education	
Illiterate	3(15)
Elementary	8(40)
Middle	4(20)
High School	3(15)
University	2 (10)
Employment	
Employed	5(25)
Unemployed	15(75)

Table 2. Medical assessment of patients

	Number (%)
Type of seizure	
Focal impaired awareness seizures	20 (100)
Focal to bilateral tonic-clonic seizures	3 (15)
Those with abnormal MRI findings	5 (25)
Number of antiseizure drugs > 2	11 (55)
Those with epileptiform findings in pretreatment EEG	9 (45)
Those with epileptiform findings in posttreatment EEG	6 (30)
	Number (Median)
Disease duration (Years)	24 (10-59)
Treatment duration (Years)	20.5 (7-48)

Results

Four patients (20%) responded to treatment (≥50% decrease in seizure frequency), whereas 16 patients (80%) did not respond. Among the patients who responded to treatment, 1 patient was completely seizure-free after treatment. However, there was no significant difference between the number of seizures before and after treatment ($p = 0.18$). All patients who responded to treatment were female. Among the non-responders, 6 (37%) were female, and 10 (63%) were male. No significant difference was found between responders and non-responders regarding sex ($p = 0.9$). One patient (25%) among the responders and 2 patients (12.5%) among the non-responders experienced focal to bilateral tonic-clonic seizures. No significant difference in seizure types was observed between the groups ($p = 0.51$). All patients who responded to treatment had normal cranial MRI findings, whereas 5 (31.3%) of the non-responders exhibited abnormal cranial MRI findings. There was

no statistically significant difference in cranial MRI findings between the groups (p = 0.53). All treatment responders were using more than two antiseizure drugs, while 7 non-responders were also using more than two antiseizure drugs. No significant difference was observed in the number of antiseizure drugs used between responders and non-responders (p = 0.9). (Table 3)

Table 3. Clinical Characteristics of Patients Who Benefited from Treatment (≥50% Reduction in Seizure Frequency) vs. Those Who Did Not

	Responders (n:4)	Non-responders (n:16)	p-value
Sex Female Male	 4 (100) 0 (0)	 6 (37) 10 (63)	 0.90
Seizure type Focal to bilateral tonic-clonic seizures	 1 (25)	 2 (12.5)	 0.51
Number drugs before treatment >2 <2	 4 (100) 0 (0)	 0 (0) 9 (56.3)	 0.90
Those with inflammatory change in MRI	0 (0)	5 (31.3)	0.53

Epileptiform findings on EEG disappeared in 4 patients (20%) after the treatment, while no changes were detected in 16 patients (80%). There was no significant difference between pre-treatment and post-treatment EEG findings (p = 0.18). Among the patients whose epileptiform findings resolved on EEG, 2 (50%) were female and 2 (50%) were male. In the group with unchanged EEG findings, 8 (50%) were female and 8 (50%) were male. No significant gender difference was observed between the two groups (p = 1.0). One patient (25%) whose epileptiform findings resolved on EEG and 2 patients (12.5%) with unchanged EEG findings had secondary generalized seizures. No significant difference was observed in seizure types between these groups (p = 0.51). Inflammatory cranial MRI findings were present in 2 patients (50%) whose epileptiform findings resolved on EEG and in 3 patients (18.8%) with unchanged EEG findings. This difference was not statistically significant (p = 0.25). Three patients (75%) whose epileptiform findings resolved on EEG and 8 patients (50%) with unchanged EEG findings were using more than two antiseizure drugs. No significant difference was observed in the number of antiseizure drugs used between these groups (p = 0.59). (Table 4)

Table 4. Characteristics of those having EEG findings resolved after treatment and those having EEG findings not resolved

	Those with EEG findings resolved after treatment (n:4)		Those with EEG findings not resolved after treatment (n:16)	p-value	
Sex Female	2(50)		8 (50)	1.0	

Seizure type Focal to bilateral tonic-clonic seizures	1 (25)		2 (12.5)	0.51	
Number of drugs before treatment >2 <2	3 (75) 1 (25)		8 (50) 8 (50)	0.59	
Those with abnormal MRI	2 (50)		3 (18.8)	0.25	

Discussion:

Neuroinflammation plays a role in the pathogenesis of many neurological disorders[9]. Inflammatory conditions in the central nervous system increase the risk of epileptic seizure[10]. Moreover, some studies suggested that epileptic seizures may trigger neuroinflammation and may lead to a progression of epileptogenesis[11]. These results indicate that, in addition to antiseizure drugs , immunomodulatory treatments could be utilized in the management of epilepsy. Intravenous (IV) methylprednisolone is a well established, safe immunomodulatory treatment used for various inflammatory neurological diseases[12-15]. High-dose IV corticosteroid therapy is a recognized treatment approach for several neurological syndromes, such as multiple sclerosis. Recent studies reported that this therapy may prevent epilepsy related side effects and achieve long term treatment efficacy in the field of epilepsy[16-19]. The action mechanism of corticosteroids in epilepsy is complex and has not been fully explained yet. Potential neuromodulatory effects of corticosteroids include correcting deficiencies or dysfunctions in enzymes, addressing intracellular and extracellular electrolyte imbalances, increasing intracellular glucose levels, modulating intracellular adenosine levels, and contributing to neuronal lipid production[20]. Corticosteroids primarily modulate neurotransmitters, particularly gamma aminobutyric acid (GABA), to achieve acute seizure inhibition. However, previous studies indicated that antiepileptic effects cease if the medication is discontinued, leading to an increase in seizure frequency and drug resistance. This result suggests that corticosteroids not only provide acute seizure control but also contribute to the reestablishment of homeostatic mechanisms in the brain[21-22]. Approximately one third of epilepsy cases involve seizures that are resistant to antiseizure drugs with focal impaired awareness seizures comprising the majority of these cases[23]. In the light of all this information, when we evaluated the effectiveness of pulse methylprednisolone treatment as a single cure in patients with focal impaired awareness seizures in our study,a significant decrease in seizure frequency (over 50%) was observed in four patients after treatment,with one patient achieving complete seizure freedom.These results suggest that methylprednisolone therapy could serve as a beneficial treatment option for drug resistant epilepsies.In four of nine patients who had epileptiform discharges on EEG before treatment,epileptiform activity findings disappeared after treatment.However, these patients did not have a significant decrease in seizure frequency, supporting previous studies indicating that IV methylprednisolone may have a transient suppressive effect on seizure activity, which diminishes over time[24]. In our study,the fact that no statistically significant difference was observed in the number of seizures

after a single course of IV methylprednisolone treatment,does not completely eliminate the idea that the underlying cause may be a neuroinflammatory pathology in patients with refractory focal impaired awareness seizures .It suggests that a more effective response may be obtained in the treatment of these seizures,if corticosteroid treatment is continued in repeated doses.However,since the study population was small, the treatment results need to be repeated in studies with a larger patient population in order to generalize these findings.

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