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Effect of anti-epileptic drugs on serum immunoglobulin levels in children

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Abstract

Epilepsy is one of the most frequent neurological disorders. Despite the advances and improvements in treatment of seizure disorders, immunologic alterations related to anticonvulsant drugs have been described. The aim of this paper is to assess the effect of some anti-epileptic drugs on serum immunoglobulin levels in epileptic patients.

Seventy-one patients with epilepsy were included in the study. Participants were divided into three groups based on their treatment with carbamazepine (n = 33), sodium valproate (n = 22) or phenobarbital (n = 16) as monotherapy. Three samples were taken from each patient and serum immunoglobulin levels were measured before treatment, 3 months and 6 months after therapy.

Overall, eleven patients out of 71 (15.5%) had a decrease in at least one serum immunoglobulin level (more than 2SD below age-matched control). In the patients receiving carbamazepine, 8 patients (24.2%) showed significant decline in at least one immunoglobulin (3 cases in IgA and 5 cases in IgG). In the group of treated with sodium valproate, 2 patients showed significant decrease in serum IgA level. Results of the last group indicated a significant reduction in serum IgG concentration only in one patient. No patient at all showed significant decrease in serum IgM level.

This study suggests that anti-epileptic drugs could reduce serum immunoglobulins, especially IgA and IgG; among them carbamazepine effect is of more concern.

Key words: antiepileptic drugs; epilepsy; immunoglobulin; IgA.

Introduction

Epilepsy and epileptic syndromes are common neurological diseases, which represent an important public health problem that has given rise to marked social and healthcare concerns (Berg, 1995). Epilepsy which is one of the most frequent neurologic disorders in all children through the age of 16 years (Berg *et al.*, 1994; Camfield *et al.*, 1996), is known as a common comorbid condition in children with developmental disabilities (Sillanpaa *et al.*, 1998; D'Amelio *et al.*, 2002). Also, patients with epilepsy have an increased risk of sudden death and mortality (Leestma *et al.*, 1989; Derby *et al.*, 1996; Callenbach *et al.*, 2001). Advances and improvements in the diagnosis and treatment of seizure disorders have been made during recent years and now the majority of patients with childhood-onset epilepsy attain remission (Annegers *et al.*, 1979; Camfield *et al.*, 1993; Casetta *et al.*, 1997; Aktekin *et al.*, 2006; Sillanpää *et al.*, 2006; Sillanpää *et al.*, 2006; Camfield *et al.*, 2007). The most widely used drugs for epilepsy are phenobarbital, carbamazepine, sodium valproate and phenytoin as well as new drugs which have been introduced in the recent years (Kälviäinen *et al.*, 1993; Glauser *et al.*, 2006).

Despite the therapeutic effectiveness of anti-epileptic drugs (AEDs) in children with epilepsy, these drugs could be associated with some adverse events, including behavioral problems and changes in serum immunoglobulin levels (Glauser, 2004; Sanker, 2004). Several documented studies (Aarli, 1976; Gilhus *et al.*, 1982; Bardana *et al.*, 1983; Ranua *et al.*, 2005) have shown that antiepileptic drugs can decrease serum immunoglobulin levels in children treated with these drugs. Among anti-epileptic drugs, phenytoin is known to have a reducing effect on serum immunoglobulins (Aarli *et al.*, 1983). The most common reported reduced immunoglobulin is IgA (Aarli, 1993), especially with phenytoin treatment (Bardana *et al.*, 1983; Ruff *et al.*, 1987; De Ponti *et al.*, 1993). Carbamazepine (Sorrell *et al.*, 1975; Pacifici *et al.*, 1991; De Ponti

et al., 1993; Basaran *et al.*, 1994; Castro *et al.*, 2001) and sodium valproate (Garzón *et al.*, 1985; Lenti *et al.*, 1991; Hemingway *et al.*, 1999) are also associated with changes in both humoral and cellular immunity. Furthermore, some studies reported that reduction of serum immunoglobulins caused by AEDs is associated with increased susceptibility to recurrent infections (Aarli, 1993; Aarli, 2000).

In this study we measured serum IgA, IgG, and IgM levels in a cohort of epileptic patients in comparison with age and gender-matched controls.

Patients and methods

Patients

In this survey, 71 patients with epilepsy were selected as subjects of this study. Diagnosis of epilepsy was based on approved standard criteria, including medical history, physical findings, and electroencephalography (Wilson *et al.*, 2004; Winckler *et al.*, 2004). Patients receiving immunosuppressive drugs or patients younger than 2 years old were excluded from this study. Based on patients' condition and physicians' decision, patients were treated with carbamazepine, phenobarbital or sodium valproate as monotherapy. The study was conducted at the Outpatient Department of Neurology in Children Medical Center Hospital Affiliated with Tehran University of Medical Sciences (TUMS). This study was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences and also written informed consent was taken from the adult patients and children's parent(s).

Methods

Venous blood was drawn from each patient and serum samples were stored at -20°C in different aliquots till the time of analysis. Three samples were taken from each patient and serum immunoglobulin levels were measured as follow: before onset of treatment, 3 months after therapy and 6 months after therapy. In all patients, serum immunoglobulin (IgA, IgM and IgG) levels were measured using nephelometry technique (Behring Nephelometer, Behringwerke, Marburg, Germany) (Cuilliere *et al.*, 1991). IgA deficiency was defined if serum IgA was less than 7 mg/dl in patients older than 4 years old (Hammarström *et al.*, 2000). Reduced serum immunoglobulin levels were identified if the serum level was below the age-adjusted 5th percentile in comparison to healthy controls (Stiehm *et al.*, 1966).

Results

Seventy one children with epilepsy (42 boys and 29 girls), aged 2.5-16 years (median age of 8 years), were enrolled in this study. The median period from first episode of seizure till starting treatment was 30 days. The most common seizure type was generalized tonic clonic seizure, identified in 47 patients (66.2%), followed by partial (9 cases), atonic (8 cases), absence (4 cases) and mixed type seizures (3 cases).

According to type of administrated drugs, patients were classified into 3 groups; in the first group, 33 patients were treated with carbamazepine. The second group (22 patients) and the third group (16 patients) were treated with sodium valproate and phenobarbital, respectively. Again, among the patients in all groups generalized seizure was the most prevalent. However, in carbamazepine treated patients, the second most common seizure type was partial seizure (7 patients, 21%) while in sodium valproate and phenobarbital group it was atonic seizure (6 and 1 patients, respectively).

After using antiepileptic drugs (AEDs) for 6 months, 11 children among 71 studied patients (15.5%), showed reduction in at least one of immunoglobulin levels (Table 1).

From 33 patients taking carbamazepine in the first group, 8 patients (24.2%) showed significant decrease in at least one serum immunoglobulin level [reduction more than 2SD compared with age-matched normal values was considered significant (Aarli, 1976). Of these eight patients, IgA was declined in three patients and IgG in the other five patients. In the patients taking sodium valproate, two cases out of 22 (9%) showed significant decrease in serum IgA level and no other significant changes in serum immunoglobulin concentration were observed. Among 16 patients taking phenobarbital, only a 9-year old boy was found to have reduced serum IgG level. Serum concentrations of AEDs for all patients were measured after six months of therapy, which were in the therapeutic levels. It should be noted that these patients with such immunoglobulin defects did not experience any episode of infection.

Discussion

Epilepsy is a multifactorial paroxysmal brain disorder, in which both environmental and genetic factors are implicated. Involvement of the immune system has been suggested to contribute in the pathogenesis of some forms of epilepsy such as Rasmussen's encephalitis, Lennox-Gastaut syndrome

Table 1

Immunologic findings in patients showing reduction in immunoglobulin levels

Patient number	Age (year)	Sex (F/M)	Drug	Seizure type	Reduced Immunoglobulin (mg/dL)			Age-matched (mg/dL) Ig level (Stiehm and Fudenberg 1966)	Decrease (mg/dL)*
					Ig	Before	After 6 months		
1	7	Male	CBZ	GTCS	IgA	222	25	124 ± 45	197
2	8.5	Female	CBZ	ATONIC	IgA	110	31	124 ± 45	79
3	10	Male	CBZ	GTCS	IgG	601	412	1124 ± 235	189
4	8.5	Female	CBZ	GTCS	IgG	605	394	923 ± 256	211
5	10	Male	CBZ	PS	IgG	988	466	1124 ± 235	522
6	9	Female	CBZ	GTCS	IgG	752	644	1124 ± 235	108
7	12	Male	CBZ	GTCS	IgG	702	580	946 ± 124	122
8	10	Male	CBZ	PS	IgA	207	7	131 ± 60	200
9	9	Male	PHB	GTCS	IgG	560	500	1124 ± 235	60
10	6	Female	VPA	PS	IgA	54	26	124 ± 45	28
11	6	Female	VPA	ATONIC	IgA	60	40	124 ± 45	20

CBZ = carbamazepine; VPA = valproic acid; PHB = Phenobarbital; PS = Partial Seizure; GTCS = Generalized Tonic Clonic Seizure;
* All these patients had a significant decrease exceeding 10% of initial Ig level.

and Landau-Kleffner syndrome (Haraldsson *et al.*, 1992; Rogers *et al.*, 1994; van Engelen *et al.*, 1995; Connolly *et al.*, 1999). Changes in serum immunoglobulin concentrations in patients with epilepsy have been reported since the 1970s; however, few data are published on the effect of new AEDs on the immune system. Many studies have reported aberrant levels of one or more immunoglobulin (sub)classes in epileptic patients, but the data are inconsistent and sometimes conflicting. This is probably due to heterogeneity of patient populations with regard to epileptic syndrome, age at onset of seizures, and concurrent treatment with AEDs (Billiau *et al.*, 2005).

The changes observed on serum immunoglobulin concentrations in patients treated with AEDs deserve consideration, because of their frequency and possible clinical repercussions. Nevertheless, the clinical significance of these reported changes is debatable. However, increased susceptibility to respiratory infections has also been postulated (Aarli, 1993; Aarli, 2000). As such immunoglobulin defect is consequence of adverse drug reactions to the AEDs, it is considered as a temporary event, which is recovered after discontinuing the specific drug. Although phenytoin is the drug most extensively studied because of its somehow apparent effect on the immune system as induction of transient selective IgA deficiency (Gilhus *et al.*, 1981), other AEDs can also have similar effects. Immunologic abnormalities could be due to either direct effect of epilepsy on immune system (Bardana *et al.*, 1983; Aarli *et al.*, 1983; Aarli, 1993) or effect of AEDs on serum immunoglobulin levels (Leestma *et al.*, 1989; Derby *et al.*, 1996; Callenbach *et al.*, 2001; D'Amelio *et al.*, 2002).

This study focuses on a cohort of children with at least one unprovoked epileptic seizure followed prospectively and treated with AEDs. This study seeks to assess effects of AEDs on serum immunoglobulins. Our study showed that carbamazepine, sodium valproate and phenobarbital can affect the serum immunoglobulins, especially IgA and IgG. A significant decrease of at least one serum immunoglobulin level 6 months after initiation of treatment with AEDs was found in 15.5% of the patients. Among three drugs, the reduction was more common with carbamazepine, which was much higher than sodium valproate or phenobarbital.

These changes in immunoglobulin levels can be due to the consumption of AEDs. Regarding the decrease of IgA serum concentration in carbamazepine group, our study seems to be in agreement with some earlier studies (Sorrell *et al.*, 1975; Gilhus *et al.*, 1982; Castro *et al.*, 2001; Callenbach *et al.*, 2003; Ranua *et al.*, 2005). Callenbach et al in a study on children with epilepsy (34 cases) showed that carbamazepine can cause a significant reduction in serum IgA and IgG level, while there was significant reduction in serum IgA and significant increase in serum IgG in patients treated with valproic acid (Cal-

lenbach *et al.*, 2003). In our study, 9% of patients in carbamazepine (3 of 33) and valproate (2 of 22) groups showed significant reduction in serum IgA level. In addition, our findings indicated that such adverse reaction is more common in carbamazepine and valproate groups, which is in contrast to a study by Ranua et al (Ranua *et al.*, 2005). In that cohort study (958 adult patients), effects of AEDs on serum immunoglobulins were assessed, and the frequency of low serum IgA in lamotrigine treated patients (8.6%) was higher than carbamazepine group or sodium valproate groups (7.9% and 5.5%, respectively). Moreover, the results of that study showed no significant changes in serum IgG and IgM levels, while 15% of our patients treated with carbamazepine appeared to have significant reduction in serum IgG level. Furthermore, our data are contradictory to other reports in adults (Pacifici *et al.*, 1991) and children (Lenti *et al.*, 1991), which showed no effect of carbamazepine treatment on serum concentrations of any of the major immunoglobulin isotypes. Explanation of these discrepancies of results could be due to variable composition of the study population, the usually small size of the study groups, and the variable duration of medication.

There is a little data available in the literature on the effect of valproic acid on the concentration of serum immunoglobulin levels. Our results showed that IgA deficiency is the only defect seen in children treated with sodium valproate as monotherapy. Contrarily, other studies showed no significant changes in their concentrations (Garzón *et al.*, 1985; Lenti *et al.*, 1991; Hemingway *et al.*, 1999). Again, the same limitations, as we mentioned previously, could be blamed for these opposite findings.

The clinical significance of low serum IgA concentration is controversial. IgA deficiency could be seen either symptomatic or asymptomatic. Although approximately one third of individuals with IgA deficiency can be associated with recurrent respiratory tract infections (Aghamohammadi *et al.*, 2009), possibly due to changes in nasal secretion and secretory IgA formation (Gilhus *et al.*, 1977), most affected individuals are asymptomatic (Aghamohammadi *et al.*, 2008; Hanson *et al.*, 1988). Previous studies suggested that symptoms of primary IgA deficiency can also occur in epileptic patients whose immune system is altered by the medications or by the epilepsy per se (Gilhus *et al.*, 1981; Castro *et al.*, 2001). Other studies reported that patient with IgG deficiency induced by carbamazepine developed an infection or recurrent infections with systemic symptoms such as fever, rash or hepatosplenomegaly (Castro *et al.*, 2001; Voutsinas *et al.*, 2001); however, in some case reports, patients with IgG deficiency after carbamazepine therapy have been asymptomatic (Go, 2004). Nevertheless, our results showed that all epileptic children treated with AEDs were asymptomatic during treatment.

To our best knowledge, this is the first time that the effect of AEDs on serum immunoglobulins is studied in our region. There appear to be considerable body of evidence supporting the reducing effect of AEDs on serum immunoglobulin levels and this is a good practice to monitor serum immunoglobulins before and after treatment. Agreeably, our study displayed this effect of AEDs on serum immunoglobulins and humoral immunity. Our studied patients did not experience infections, in spite of reduced levels of immunoglobulin. However, considering the fact that IgA deficiency can lead to variety of symptoms in some individuals, evaluation of immunoglobulin levels in patients taking AEDs and careful monitoring of those with reduced levels of immunoglobulins could be recommended.

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