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IMMUNE GLOBULIN TREATMENT IN INTRACTABLE EPILEPSY OF CHILDHOOD*

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SUMMARY: Türkay S, Baskın E, Dener Ş, Gültekin A, Tanzer F, Sekreter E. (Departments of Pediatrics and Neurology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey). Immune globulin treatment in intractable epilepsy of childhood. Turk J Pediatr 1996; 38: 301-305.

Six children suffering from epilepsy refractory to conventional anti-convulsive therapy were treated with high-dose intravenous immune globulin (IVIG) (200 mg/kg three times per week, repeated after three weeks). In four children clinical and EEG findings markedly improved, while a partial response was noted in the other cases. These results suggest that high-dose intravenous immune globulin may have a beneficial effect in the treatment of intractable epilepsy. *Key words: intractable epilepsy, intravenous immune globulin (IVIG).*

High-dose intravenous immune globulin (IVIG) has been used successfully in the treatment of various immune-mediated diseases[1-3]. Intractable childhood epilepsy is characterized by convulsions which are resistant to treatment with adequate dosages of appropriate anticonvulsant drugs[4-6]. IVIG therapy has also been tried by several groups in so-called intractable childhood epilepsy on the hypothesis that the immune mechanism may play a role in triggering or maintaining this severe form of epilepsy[5-10]. We too decided to treat six patients with intractable epilepsy with high-dose IVIG.

Material and Methods

The study group consisted of six children between the ages of five and 13 years. Two of them were male. All children suffered from frequent daily seizures. All patients had been treated with a variety of anti-convulsant drugs (valproic acid, carbamazepine, phenobarbital, clonazepam) in various combinations. In all cases the epilepsy was accepted to be resistant to these drugs. These patients had had seizures for a long time, as seen in Table I.

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Table I:
Clinical Features of Patients

Patient No.	Age (years)	Neurological findings	Mental status	Etiology	Age at onset of seizures	Type of seizure	Cranial tomography
1	8	Normal	Moderate retardation	Idiopathic	4 months	Left partial generalized tonic-clonic	Normal
2	13	Normal	Profound retardation	Idiopathic	3 months	Generalized tonic-clonic	Cortical Atrophy
3	5	Microcephaly, spasticity quadriparesis	Profound retardation	Idiopathic	3 weeks	Myoclonic generalized tonic-clonic	Cortical Atrophy
4	7	Spasticity, quadriplegia	Moderate retardation	Neonatal sepsis	2 weeks	Myoclonic jerks	Cortical atrophy
5	9	Normal	Borderline	Neonatal asphyxia	1 week	Generalized tonic-clonic	Normal
6	12	Normal	Moderate retardation	Idiopathic	1 year	Myoclonic jerks, atonic akinetic	Normal

Table II: Effect of Immune Globulin Treatment on EEG and Seizures of Patients

Patient No.	Therapy of admission	EEG before treatment	No. of seizures before treatment	EEG after treatment	No. of after treatment	Duration of follow-up
1	Valproic acid, carbamazepine	Normal	2-3/day, tonic-clonic	Normal	1-2/week, tonic-clonic	4months
2	Phenobarbital, valproic acid	Generalized slowing, generalized bursts of high slow waves	3-4/day, general tonic-clonic	Generalized slowing	1-2/day, clonic	6 months
3	Clonazepam, phenobarbital	Slow, irregular, generalized bursts of high slow waves and polyspike activity (Lennox-Gastaut)	10-15/day myoclonic jerks	Slow activity, single spike	3-4/week, akinetic, atonic	9 months
4	Phenobarbital, valproic acid, clonazepam	General slowing	7-8/day myoclonic jerks	No change	2-3/week, tonic-clonic	1 year
5	Valproic acid, carbamazepine	Normal	9-10/week, general tonic-clonic	Normal	2-3/week, atonic-akinetic	18 months
6	Phenobarbital, valproic acid, clonazepam carbamazepine	low, irregular polyspike activity (Lennox-Gestaut)	2-7/day, atonic-akinetic	No change	1-2 day, atonic-akinetic	8 months

Clinical and laboratory investigations (EEG evaluations and serum IgG, A and M levels) were performed before and three weeks after immune globulin administration. IVIG (Sandoglobulin) was administered at a dose of 200 mg/kg over a period of six hours. This was repeated twice at 48-hour intervals for a total of three doses (600 mg/kg). No adverse reactions were observed. This procedure was performed again three weeks later. None of the patients became seizure free. The patients were followed up for a period of four to 16 months.

Results

In our of six patients the number of attacks decreased dramatically and a marked improvement in EEG findings was noted. The others showed partial improvement (Table II). Serum immunoglobulin G, A and M levels were within normal limits in all children, but other immunological tests could not be studied.

Discussion

The etiology of intractable epilepsy is still unknown, but a disregulation of the immune system may play a role. Several studies have proposed an immunological basis for intractable epilepsy[1,3,7]. While some researchers have been able to document underlying immune defects in these patients, others did not determine any immunological abnormalities even in cases with an observed beneficial effect of IVIG[4,7,10-12]. In previous studies the efficacy of IVIG was found to be approximately 50 percent[5-10]. However, in one study[13], IVIG treatment was associated with minimal improvement. The number of our cases is very limited, but four patients markedly improved. All children had some evidence of mental retardation. In four of six children, decreased frequency of seizures as well as improved behavior and psychologic performance were observed. We were unable to show any immune dysfunction in our patients.

Reported laboratory investigations in favor of an immunological component in human epilepsy include: impaired humoral immunity (predominantly IgA and IgG_2 deficencies)[13,14], lower kappa/lambda ratios of serum IgG and serum IgM[14], an increased incidence of antibodies against the frontal cortex[15], an increased percentage of B-cells[16], decreased percentage of T-cells[17], and differences in HLA class II antigen frequencies compared with the general population[18]. The IgA deficiency found in five to 10 percent of patients with epilepsy is usually drug-induced, but such patients can have subnormal IgA levels before treatment[19]. Disturbances of the IgA immune system have been described in association with a variety of drugs, such as certain gold preparations, d-penicillamine benoxaprofen[20], and long-term anticonvulsant administration[21,22]. One report concluded that at present epileptics do not seem to require special immunological or clinical monitoring[19].

In humans, IVIG has been reported to be beneficial for more than 35 diseases that may be produced by immunopathology[23]. The mechanism of action of IVIG in intractable epilepsy remains unclear. Two main theories have been proposed. The first suggests that the correction of some undiagnosed immunological abberration by IVIG my influence the convulsive activity[1,12]. The second theory for the mode of action of IVIG is the occurrence of an idiotype-anti-idiotype interaction[1,4,24]. IVIG may be effective in the treatment of an auto-immune disease by providing a source of anti-idiotypic antibodies. This possibility is based on the observation that cross-reactive idiotypes can be suppressed by administering anti-idiotypic antibodies. By selective reduction of the concentration of pathogenic antibodies, auto-immune disease may be effectively treated[1,2]. The main component of the IVIG preparation (the IgG molecule) crosses the blood cerebrospinal fluid (CSF) barrier, significantly increases the CSF IgG concentration, and is likely to reach the brain and act centrally[25].

We concluded that although the mechanism is still obscure, high doses of immune globulin may be useful in the treatment of selected children with intractable epilepsy unresponsive to anticonvulsants. However, there is a need for multicenter controlled studies to evaluate the pathogenesis and the possible effect of this therapy, and to clarify the exact indication and dosage of IVIG in therapeutically refractory epilepsy.

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