

High-Dose Intravenous Immunoglobulin Treatment in Intractable Childhood Epilepsy

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Abstract: Rationale: Intractable childhood epilepsy is characterised by convulsions, which are resistant to treatment with adequate dosage, combination and duration of appropriate anticonvulsant drugs. Many clinical and experimental studies support the role of the immune mechanism in the pathogenesis of childhood epilepsy. The purpose of the present study is to ascertain the possible efficacy of intravenous immunoglobulin in the treatment of intractable childhood epilepsy.

Methods: The children aged 4-8 years suffering from intractable childhood epilepsy were treated with high-dose intravenous immunoglobulin (400 mg/kg) 5 times in the first week, on the 15th and 30th days. The treatments were repeated every 4 weeks for 6 months. The cases were as follows: infantile or epileptic spasms (5 cases), myoclonic epilepsy (1 case), secondary generalised simple partial seizure (1 case), secondary generalised complex partial seizure (1 case),

and myoclonic absence (2 cases). The cases were followed up for 6 months to 2 years. Clinical examinations, electroencephalograms and computed tomography findings were evaluated in all cases. Response to treatment was evaluated by estimating the reduction in clinically observed seizures.

Results: One child had complete remission, 2 had partial response with 75% reduction in seizure frequency, 3 had 50% reduction in seizure frequency and the remaining 4 cases had no response. There were no side effects due to intravenous immunoglobulin administration.

Conclusions: We conclude that intravenous immunoglobulin is a safe therapy and may have beneficial effects in intractable epilepsies, but controlled, multicentre studies are needed to elucidate the pathogenesis and the effects of this therapy.

Key Words: intractable epilepsy, IVIG, gammaglobulin treatment

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Introduction

Recurrent seizures are a significant cause of childhood morbidity. It is estimated that 10-20% of childhood epilepsies are intractable and cannot be controlled after an adequate trial of first-line conventional antiepileptic drug treatment (1).

Immunological mechanisms have been suspected in the pathogenesis of epileptic seizures in some patients and in experimental animal models of epilepsy. The effects of globulin treatment in epilepsy were first studied by Pechadre et al. in 1977 (2). They observed the disappearance of seizures and EEG improvement in epileptic children treated with intramuscular immunoglobulin for allergic seasonal diseases. Since the initial report, IVIG has been employed in intractable epilepsy, West and Lennox-Gastaut Syndromes (LGS).

Material and method

The study group included 10 children, 8 boys and 2 girls between 4 and 8 years old (mean 5.9 years) with intractable epilepsy. The patients had been treated with most of the accepted anticonvulsive drugs in various combinations. Clinical details are given in Table I. The selection criteria were as follows: the patient had to have been diagnosed at least one year previously and he had to have had at least 1 seizure per month during the previous 6 months. Response to treatment was evaluated by estimating the reduction in clinically observed seizures; the patients were evaluated every 3 weeks.

Complete remission was defined as cessation of all seizures. A positive result was defined as a 50% or greater reduction in seizure frequency.

IVIG was administered in 400 mg/kg doses 5 times during the first week. Single doses were repeated once during the 2nd week and the 4th week, and then at 4-week intervals for 6 months (Figure 1). Clinical and EEG evaluations were performed before and after the gammaglobulin administrations.

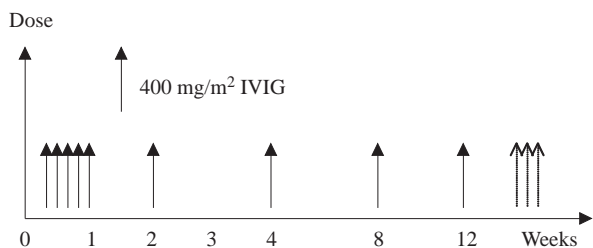


Figure 1. IVIG treatment schedule of intractable childhood epilepsy.

Results

One patient had complete remission, 2 had a 75% reduction and 3 had a 50% reduction in seizure frequency.

Sixty percent of the patients responded to IVIG therapy. All of the patients with cryptogenic etiology responded to IVIG therapy. The results of the study are summarised in Table 1.

The levels of Ig A, G, M, E and Ig G subclasses were normal in all patients. No side effects due to IVIG treatment were observed. EEG evaluations were performed before and after gamma globulin administrations. EEG improvement was noted in patients 1,2 and 3.

Discussion

Walker was among the first to hypothesize that immunological mechanisms are involved in the pathogenesis of epileptic events (3). Animal models in which seizure activity produced by the administration of specific antibodies supports that view. Plioplys et al. found high anti-CNS antibodies on frontal cortex immunoblasts in epileptic patients (4). A high kappa/lambda ratio caused by the high concentration of the kappa chain was found in children with therapy-resistant epilepsy (5). Pechadre et al. first examined the clinical effects of gamma globulin in 1977 (2). Since 1977 many studies have been done in which IVIG was administered to children with intractable epilepsy. In 24 studies, none with a placebo-controlled design, 368 patients with intractable epilepsy receiving IVIG were identified between 1977 and 1993 (6). Their ages ranged from 1 to 35 years (mean 7.3 years). The

Table 1. Clinical details of the intractable childhood epilepsy patients in study and the effects of IVIG treatment.

Patient No	Age, Sex	Neurological Presentation	Etiology	Age of Onset	Mental State	Type of Seizures	Medication Before IVIG	Follow-Up	Seizure Reduction
1	8, F	normal	idio	4 yr	normal	SP secondary general	4,2,9	18 mo	100 %
2	5, F	normal	idio	3 yr	MR	myoclonic absence, GTC	1,6,2,7,9	11 mo	75 %
3	4, M	normal	symp	2 yr	MR	myoclonic absence, GTC	1,2,3,6,7,9	10 mo	75 %
4	7, M	normal	symp	1 yr	normal	secondary general CP	6,4,2,8,9,10	6 mo	50 %
5	4, M	normal	idio	1,5 yr	MR	myoclonic, GTC	6,10,4,3,8,2	12 mo	50 %
6	6, M	normal	symp	6 mo	MR	InSp, EpSp, GTC	1,6,2,3,9,8	6 mo	50 %
7	8, M	Mic, SpQp	symp	6 mo	PR	InSp, EpSp, tonic	1,2,3,5,9	24 mo	26 %
8	8, M	Mic, SpQp	symp	1 yr	PR	InSp, EpSp, CP	1,6,2,4,9,8	12 mo	NR
9	4, M	normal	symp	1 yr	MR	InSp, EpSp	1,6,2,3,8	12 mo	NR
10	5, M	hemiparesis	symp	1 yr	MR	InSp, secondary general CP	1,2,4,9	12 mo	NR

F=female, M=male, Mic=Microcephaly SpQp=spastic quadriplegia, idio=idiopathic, symp=symptomatic, MR=moderate retardation, PR=profound retardation, GTC=general tonic clonic, InSp=infantile spasm, EpSp=epileptic spasm, CP=complex partial, SP=simple partial, NR=no response, yr=years, mo=months 1=ACTH, 2=Valproate, 3=clonazepam, 4=carbamazepine, 5=phenytoin, 6=barbiturate, 7=ethosuximide, 8=vigabatrin, 9=lamotrigine, 10=eptantoin

female/male ratio was 0.6. The total dose of IVIG varied between 0.3 and 6.8 g/kg for a period of 0.15 to 12 months. In our study we used a total IVIG dose of 4.8 g/kg over 6 months. In the literature review the percentage of patients with complete seizure remission was 23%. All these studies were heterogeneous as to patient inclusion criteria, type of IVIG preparation used, protocol of administration, follow-up period and criteria for evaluation of response. The mean seizure reduction reported by the authors ranges from 0% to 90%. As yet only two blind, placebo-controlled studies have been published. Illum et al. studied the efficacy of IVIG in 10 Lennox-Gastaut syndrome cases. This was the first single-blind placebo-controlled study. The study compared the add-on antiepileptic efficacy of IVIG infusion (400 mg/kg dose) to a placebo (0.9% sodium chloride). Complete disappearance of seizures and significant EEG improvement was observed in 2 of the children only after infusions of IVIG (7). In 1994 von Rijckvorsel-Harmant et al. reported the first double-blind dose-finding clinical study. Sixty-one epileptic patients (adults and children with Lennox-Gastaut Syndrome, West Syndrome and other forms of epilepsy) were assigned to 1 of 4 different groups. They received either a placebo or one of three different doses of IVIG (100, 250, 400 mg/kg per perfusion). A decrease of more than 50% in seizure frequency was observed in 27.8% of the patients in the placebo group and of 52.5% in the IVIG treatment group. This difference was not statistically significant. No significant dose-effect relationship was found (8).

There is no dose protocol in IVIG treatment. In the literature, all studies have different dose schedules. Illum et al. reported disappointing results from 10 Lennox-Gastaut syndrome cases treated in an add-on, placebo-controlled, single-blind trial. The cases received two 400 mg/kg doses of IVIG at an interval of 2 weeks and a washout period of 4 weeks. The total observation period was 14 weeks (7). Some patients responded immediately but most had an 8 to 12 week delay before any significant improvement, as previously published (8,9). We administered IVIG doses of 400 mg/kg per day 5 times during the first week and on the days 15 and 30. This dose was repeated at 4-week intervals for 6 months. The follow-up period was 6-24 months in our study. In some previous studies the follow-up period was 12-15 months or less. Van Rijckvorsel et al. reported a complete

response for 7-11 months (9). Sandstedt et al. reported that the improvement lasted for the entire follow-up of 12 months (10). Both immediate (2,7,10-14) and late responses to IVIG therapy have been reported. Late onset of response with complete remission after 2-6 months has been reported in several studies with long-term treatment and follow-up periods (8,15-18). Duse et al. and Sterio et al. found a decrease in the daily number of seizures over 6 months of IVIG treatment (17,18). EEG improvement was noted in several studies (2,8,10-19). Bedini et al. and Illum et al. found no correlation between electroencephalographic findings and clinical changes (7,14). We noted EEG improvement in 3 of our cases.

Disorders of immunoglobulins have been associated with epilepsy. In one study increased intrathecal production of Ig G was reported in infantile spasm cases. The CSF:serum Ig G index was elevated. This observation is consistent with the possible role of an autoimmune mechanism in infantile spasms. Ig A deficiency is seen in 2-5% of epileptic patients. Low serum concentrations of Ig A are found in 10-20% of these patients (20,21). Ig A deficiency has also been determined in children with epilepsy prior to any antiepileptic drugs (21,22). A high incidence of Ig G2 deficiency in patients with intractable epilepsy has been reported in several studies (7,15,17,18). Sandstedt et al. are the only researchers to have measured intrathecal immunosynthesis, and they found a correlation between defects in intrathecal immunosynthesis and clinical improvement (10). We found no immunological abnormalities in our patients. Some studies have claimed that beneficial effects were seen in children with underlying immune dysfunction. Duse et al. reported that the effect of IVIG was restricted to patients with IgG2 deficiency (18). In the literature review, between the years 1977 and 1993, 25% of the 368 cases had IgG2 deficiency (6). We found no side effects of IVIG in our patients. In the literature none of the studies reported the need of cessation of IVIG administration due to adverse effects.

The studies carried out so far support the efficacy of IVIG in the treatment of intractable epilepsy. Ideal dosage and treatment schedules are difficult to define. The response rates were similar in most studies.

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