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Treatment of Idiopathic West and Lennox-Gastaut Syndromes by Intravenous Administration of Human Polyvalent Immunoglobulins

K. van Rijckevorsel-Harmant[1], M. Delire[2], and M. Rucquoy-Ponsar[3]

[1] Service de Neurophysiologie, Centre Neurologique William Lennox, B-1340 Ottignies
[2] Department of Clinical Research, Hoechst-Behring, B-1060 Brussels
[3] Service de Neuropédiatrie, Centre Neurologique William Lennox, B-1340 Ottignies, Belgium

Summary. A total of 7 patients (3–21 years old) suffering from an intractable "primary" Lennox-Gastaut syndrome (LGS) were treated with i.v. high doses of polyvalent human immunoglobulins. Of these patients 6 improved following such treatment with a decrease in fits and an improvement in the EEG.

Hypotheses about the contribution of the treatment and immunopathological factors in some cases of idiopathic LGS are discussed.

Key words: Immunoglobulins – Intractable epilepsy – Lennox-Gastaut syndrome

Introduction

It is well known that about one-third of the patients with West and Lennox-Gastaut syndromes (LGS) are considered idiopathic (Aicardi 1982). Moreover, some of those cases could be due to an immunological disorder which might explain the beneficial effect of classical corticotropic treatment. In that respect it is interesting to note that Smeraldi et al. (1975, 1978) demonstrated a significantly increased frequency of the HLA-B7 locus in children with the LGS as compared to a normal standard population. This genetic constitution could favour the development of auto-immune disorders, as has been described in some cases of epilepsy (Fontana et al. 1978, Hoshino et al. 1982).

On the other hand, some authors (Shakir et al. 1978; Aarli and Fontana 1980; Tartara et al. 1981; Gilhus and Aarli 1981; Bassanini et al. 1982; Gilhus et al 1982; Ariizumi et al. 1983) have shown a drop in the level of serum IgA in a number of affected children, which could lead to a higher infectious susceptibility.

Accordingly, in this preliminary trial we have tested the eventual benefit of i.v. administration of human immunoglobulins on the clinical and electrical status of children affected by "primary" LGS. It is known that such a treatment can be useful in acute and chronic infectious states (Delire et al. 1980) as well as in some auto-immune diseases (Hoffman and Kappler 1978; Newland et al. 1983).

Offprint requests to: K. van Rijckevorsel-Harmant at the above address

Material and Methods

1. As polyvalent human immunoglobulins (PHI) we used a special preparation (Venimmun, Behringwerke, Marburg, FRG) which is adequate for i.v. administration. The preparation consists of a pool of IgG immunoglobulins from human plasma, treated by the S-sulphonation procedure which, on the one hand, avoids the formation of anti-complementary aggregates and, on the other hand, preserves the normal 7S structure of the native IgG (Gronski et al. 1982). Thus, the preparation retains all the biological properties of the IgG antibodies without any risk of anaphylactic shock secondary to excessive activation of the complement system. The biological half-life of the 5% concentrated IgG lies within the range of 15 days.

2. For the first 2 cases 1 h before the first perfusion of S-sulphonated immunoglobulins, each child was connected to a portable EEG, allowing an uninterrupted registration for 48 h. Then 1 week after this first perfusion of 5 ml/kg, the same procedure was repeated with a continuous EEG registration from 1 h before the perfusion, until 2 days after. The same procedure was repeated again 1 week after the second perfusion, and 1 week after the third perfusion. A fourth and last perfusion of 5 ml/kg took place under the same conditions 3 weeks after the third one. A routine EEG was registered weekly, for 3 weeks, after the last perfusion.

3. For the following 5 cases we administered the perfusions under the same conditions, but performed a continuous EEG only before the first perfusion and in the 3rd month after the last one. Routine EEGs were performed weekly during the entire course of the study.

4. We studied 7 patients (4 males and 3 females), whose ages ranged from 3 to 21 years (mean age 8.71), suffering from epilepsy without evident aetiological factors. They had a normal neurological status except for 2 cases (nos. 5 and 7). The seizures were frequent (> 1 daily), and the EEGs were highly abnormal with slow spike-waves, a poor background rhythm and abundant slow activity. Table 1 summarizes the data of each patient.

5. *Case no. 1: D.O. 02.08.1981.* This 3-year-old boy presented no problems until June 1982, when he was 10 months

Table 1. Clinical and EEG data of patients before and 3 months after the last perfusion of Ig

Cases	Age (years)	Sex	Before Ig i.v.			3rd month after Ig i.v.	
			EEG		Fits	EEG	Fits
1. D.O.	3	♂	Background rhythm Slow SW	delta +++	+++	alpha ∅	∅
2. B.T.	6	♂	Background rhythm Slow SW	theta +++	+++	theta ∅	∅
3. D.E.	4	♀	Background rhythm Slow SW	delta +	+++	delta +	++
4. J.S.	5	♀	Background rhythm Slow SW	delta +++	+++	alpha ±	+
5. B.M.[a]	4	♂	Background rhythm Slow SW	theta ±	+	alpha ±	±
6. L.P.	21	♂	Background rhythm Slow SW	theta +++	+++	theta (alpha) +	+
7. D.S.[b]	18	♀	Background rhythm Slow SW	theta +++	+++	theta (alpha) +	++

+++: ≥1 daily or ≥90% of the EEG; ++: ≥1 weekly or 60%–89% of the EEG; +: 1–4 monthly or 6%–59% of the EEG; ±: rarely or ≤5% of the EEG; ∅: not present

[a] slight microcephaly; [b] chromosomal aberration: Ring chromosome 17.

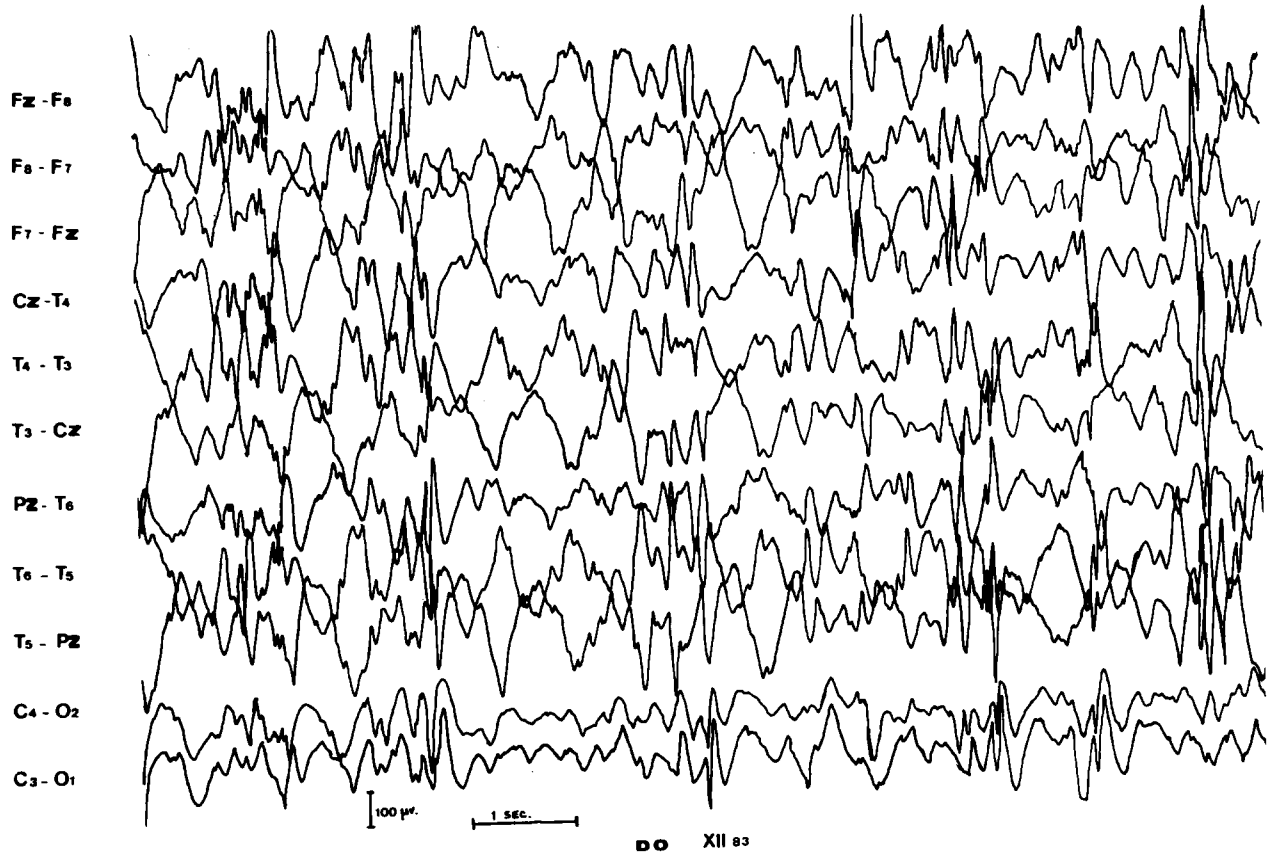

Fig. 1. Routine EEG of case 1 before treatment with i.v. PHI. Note the high amplitude and the abundance of slow spike-waves

old. At that time, the mother noticed a few spasms just after awaking. In July 1982, the mother also noted a regression in the psychomotor development of her son. At this date, the boy presented typical symptoms of West's syndrome and was treated with ACTH for 3 weeks. His development was unremarkable, except for recurrent upper respiratory tract infections, until January 1983, when the mother again noted some spasms. However, the EEGs remained normal until May 1983. At this time, the mother noted clonic seizures and spasms in extension.

The EEG was then typical of LGS (Fig. 1). The child received many different anti-epileptic drugs, always at therapeutic levels, administered alone or in association. Neither clinical nor electrical improvement was noted. He presented 7–8 atonic seizures a day and at least 3–5 spasms in extension, and there was no further progress in his psychomotor develop-

ment. The mother also noted that the situation worsened every time her child presented some infection. In December 1983, we suggested treatment with i.v. polyvalent immunoglobulin perfusion.

Table 2 summarizes the therapeutic and EEG evolution from December 1983 until December 1984. First, the fits decreased, then from the 3rd month after the last perfusion, the fits disappeared and the EEG was normal until November 1984 (Fig. 2). At this time, we noted some spasms and slow spike-waves in the left temporal region of the EEG. But we were able to control these fits and we observed no psychomotor stagnation or regression.

Table 2. Summary of treatment and EEG findings of the first 2 cases during and after Ig treatment

Before Ig treatment		Ig treatment	After Ig treatment	
Day ∅		Week 1 to 6	3 Months	1 Year
Case 1. D.O.				
Treatment	Valproate	→	↓ and ∅	Valproate
	Carbamazepine	→	Progabide	→
	Clobazam	→		
EEG	Occ rhythm 4–5	↑	8	→
	delta ++	↓	↓	→
	slow SW +++	↓	∅	+ (left)
	fast activity +	∅	∅	∅
Case 2. B.T.				
Treatment	Phenobarbitone	→	→	→
	Clonazepam	→	→	→
			Progabide	↓
			Premoline	↓
EEG	Occ rhythm 4–6	→	6–8	6
	delta ++	↓	↓	→
	slow SW ++	↓	∅	rarely
	fast activity +	∅	∅	∅

→ no change, ∅ not present
+++ ≥ 90% of the EEG; ++ 60%–89% of the EEG; + 6%–59% of the EEG

6. Case no. 2: B.T. 21.05.1978. This 6-year-old boy had no problems until 6 months of life when he presented a hyperthermic convulsion and, a few months later, spasms in flexion. He received ACTH in 1981, but the fits persisted with tonic-clonic convulsions and absences. The parents noted stagnation in the psychological development after 1 year of age. He had received clonazepam and phenobarbitone since October 1983 but without any evident improvement. In March 1984, with no change in anti-epileptic drugs, treatment with i.v. polyvalent immunoglobulin perfusion was initiated. Table 2 shows his therapeutic and EEG evolution from February 1984 until February 1985. As in the first case, we noted a real improvement from the 3rd month after the last perfusion until September 1984. At this time, the EEGs showed generalized spike-waves during intermittent light stimulation, and clinically we noted occasional tonic-clonic seizures.

Results

All patients, except for case 3, were improved by this treatment at both clinical and EEG levels. We noted a decrease in frequency of fits, and an improvement in psychomotor performances. The EEGs showed a more abundant and faster background rhythm with a decrease in slow activity and slow spike-waves. It seemed that the improvement of psychomotor development was more dependent on a faster background rhythm than on a decrease in the paroxysmal activity.

Discussion

Among the cases of "primary" LGS, a certain proportion could find origin in some disturbance of the immune network,

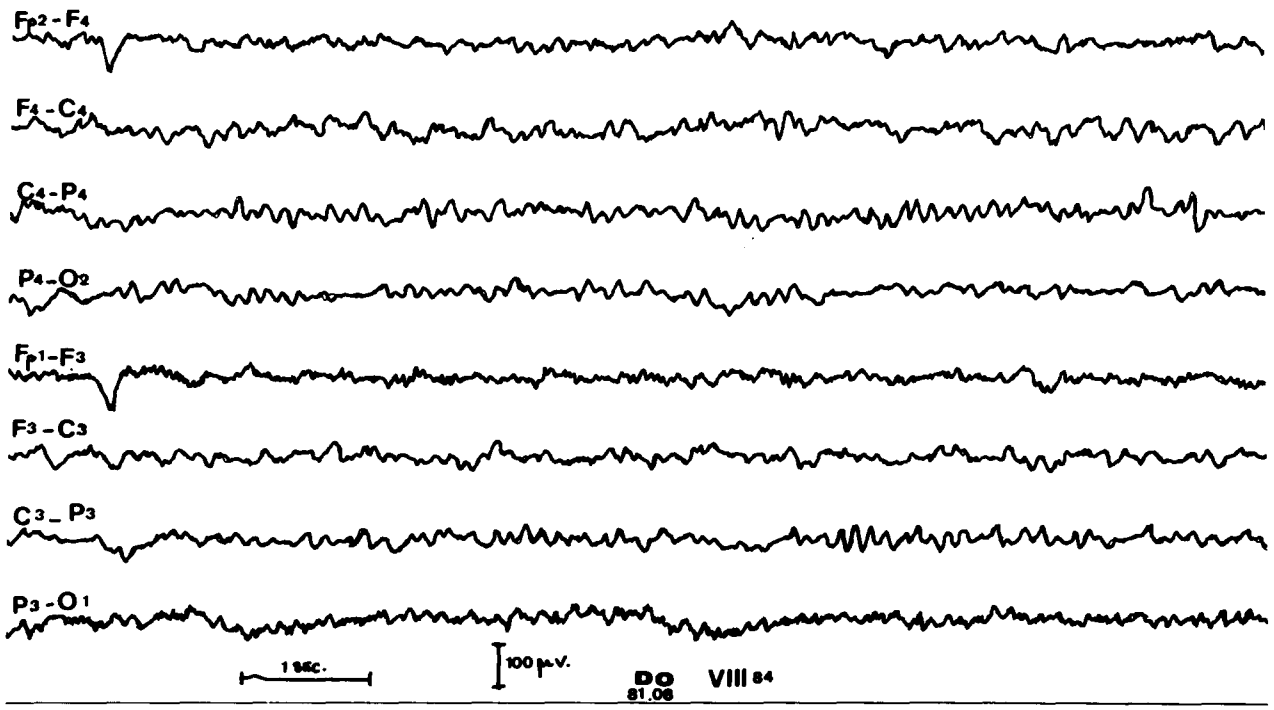

Fig. 2. Routine EEG of case 1, 4 months after the last perfusion of i.v. PHI. This EEG is actually normal

either through an imbalance leading to the pathological production of auto-antibodies specific to brain tissue structures, or through a genetically predisposed abnormal susceptibility to various bacterial and/or viral particles.

Both disturbances could be linked to an abnormal segregation of some haplotypes of the major histocompatibility complex in the population of patients and their parents. Indeed, some authors (Smeraldi et al. 1975, 1978) have shown that children with LGS were lacking the HLA-A12 locus, although the HLA-B7 was found in higher frequency as compared to a normal reference population. Moreover, other investigators (Shakir et al. 1978; Aarli and Fontana 1980; Tartara et al. 1981; Gilhus and Aarli 1981; Bassanini et al. 1982; Ariizumi et al. 1983) have demonstrated that some affected children had a decrease in serum IgA, which again could impair the defence mechanisms towards infectious agents. It is, however, impossible to distinguish whether this defect is of primary origin or secondary to previous anti-epileptic treatment i.e. hydantoins; but some studies (Seager et al. 1975; Fontana et al. 1978; Bassanini et al. 1982) have reported a low level of IgA in epileptic patients, even without or before treatment. For many years, the administration of PHI has been used for anti-infectious therapy as it provides the host organisms with a broad spectrum of high affinity specific antibodies (Delire et al. 1980). On the other hand, high doses of 7S IgG are known to play an immunosuppressive role by means of the Fc part of the antibody (Hoffman and Kappler 1978; Stockinger and Lemmel 1978). This leads to a non-specific blockage of the endogeneous antibody synthesis, and, thus, to a subsequent drop in the production of auto-antibodies, as already proved for some auto-immune diseases (Newland et al. 1983).

Taking all these considerations into account, we habe assessed the effect on the clinical and electrical status of 7 cases of LGS, with i.v. perfusions of a preparation of S-sulphonated PHI. It is of interest to note that the patient D.O. (case 1) was suffering from recurrent upper respiratory tract infections and had a slight decrease in serum IgA level.

The infectious situation dramatically improved during the course of immunoglobulin perfusions, as compared to the same period of the previous year (December to March). It seems that patients with a low level of IgA (Ariizumi et al. 1983) (case 1) responded better to the treatment, but further cases are needed to confirm this first impression.

Conclusion

Our work is obviously preliminary, but the results described in this paper are sufficiently encouraging to convince us to enlarge the trial to a larger number of patients suffering from "primary" West's syndrome and LGS.

The data expected from this larger investigation should provide us with more information and hopefully a definitive judgement concerning the usefulness of i.v. PHI in the treatment of these severe childhood epilepsies.

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