Journal of the Neurological Sciences 368 (2016) 140–144

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Intravenous immunoglobulin therapy is rarely effective as the initial treatment in West syndrome: A retrospective study of 70 patients

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ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form 1 July 2016
Accepted 1 July 2016
Available online 4 July 2016

Keywords:
West syndrome
spasms
hypsarrhythmia
Intravenous immunoglobulin therapy
outcome
adverse effect

ABSTRACT

Purpose: To evaluate factors influencing the efficacy and safety of intravenous immunoglobulins (IVIG) therapy for West syndrome.
Methods: We investigated seizure outcomes in 70 patients who received IVIG treatment for West Syndrome during the first 3 months after the onset of epileptic spasms. IVIG was administered for 3 consecutive days (initial IVIG treatment) at dosages ranging from 100 to 500 mg/kg/day. If spasms disappeared within 2 weeks of the initial treatment, maintenance IVIG treatment was commenced. We evaluated seizure outcomes at 2 weeks (initial evaluation), at 2 years (long-term evaluation), and the last visit (last follow-up evaluation) after the initial IVIG treatment. We analyzed dosages of IVIG, age at onset of spasms, treatment lag, and etiologies between responders and non-responders.
Results: Among the patients, 7/70 (10.0%) had cessation of spasms and resolution of hypsarrhythmia at the initial evaluation. Another 6/70 patients (8.6%) were found to have cessation of spasms at the long-term evaluations. The treatment lag in responders was shorter than that in non-responders ($P < 0.01$). There were no significant differences between responders and non-responders in IVIG dosages, age at onset of spasms, and etiologies. Two patients had relapse of partial seizures after cessation of spasms at the last follow-up evaluation. Adverse effects occurred in 2/70 patients.
Conclusions: The efficacy of IVIG was so low that it should not be considered as first-line treatment in West syndrome. IVIG therapy has a good safety profile and we would recommend it for West syndrome cases with drug resistance, severe complications associated with profound brain damage, severe brain atrophy, and in immunocompromised patients.

1. Introduction

West syndrome is an age-related epilepsy disorder of infancy characterized by a combination of epileptic spasms in clusters and a peculiar interictal electroencephalographic (EEG) pattern of hypsarrhythmia. Patients with West syndrome generally have poor long-term neurological outcomes. Adrenocorticotropic hormone (ACTH) and vigabatrin are the only drugs with proven efficacy for the first-line treatment of West syndrome. ACTH is widely used to treat this disorder. However, serious adverse effects including infection, hypertension, electrolyte disturbances, and subdural hematoma sometimes occur, resulting in extended hospital stays and considerable cost. Patients with West syndrome are commonly treated with other first-line treatments in Japan [1]. Vigabatrin was reported to be as effective as ACTH and even better tolerated [2]. However, it raises the risk of visual field loss. Little is known about the efficacy and safety of intravenous immunoglobulins (IVIG) therapy in West syndrome. Some reports showed that IVIG therapy is effective in West syndrome. Subcutaneous immunoglobulin has been found to be effective in patients with severe infantile epilepsy [3]. Furthermore, IVIG therapy was shown to result in complete remission of spasms and normalization of EEGs in patients with West syndrome [4]. However, both the detailed mechanisms of IVIG and the profiles of patients in whom it is effective are unknown. If pediatric neurologists know the features that predict the effectiveness of IVIG in West syndrome, it may help them to understand its appropriate use and place in the treatment regimen. Thus, we investigated the efficacy and adverse effects of IVIG therapy at different dosages in West syndrome. Furthermore, we evaluated whether the age at the

Abbreviations: ACTH, Adrenocorticotrophic hormone; DQ, Developmental quotient; EEG, Electroencephalographic; IQ, Intelligence quotient; IVIG, Intravenous immunoglobulins; SD, Standard deviation.

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http://dx.doi.org/10.1016/j.jns.2016.07.001
0022-510X/

onset of spasms, treatment lag, and etiology influence the efficacy of IVIG therapy.

2. Methods and materials

2.1. Study design

We conducted a retrospective review of the medical records of all patients with West syndrome who had been referred to Saitama Children's Medical Center from July 1993 to May 2012. All patients were treated according to the following protocol in a single center. First, pyridoxal (20–50 mg/kg/day) was administered for 1 week. If no improvement occurred, IVIG (either Venoglobulin-IH [Japan Blood Products Organization, Tokyo, Japan], Glovenin-I [Nihon Pharmaceutical Corporation Limited, Tokyo, Japan], or Venilon-I [Teijin Pharma Limited, Tokyo, Japan]) was administered for 3 consecutive days at dosage ranging from 100 to 500 mg/kg/day and pyridoxal was terminated. Venoglobulin-IH and Glovenin-I are polyethylene glycol treated human normal immunoglobulin. Venilon-I is freeze-dried sulfonated human normal immunoglobulin. If these treatments failed to control the spasms, synthetic ACTH was given intramuscularly at 0.01–0.02 mg/kg/day for 2 weeks, then the amounts were tapered to every other day for 1 week, followed by twice weekly for 1 week.

All patients with West syndrome were treated with IVIG during the first 3 months after the onset of epileptic spasms, after pyridoxal therapy, and before ACTH therapy. All patients received no therapy for two weeks after IVIG therapy. If spasms disappeared within 2 weeks after the initial IVIG treatment, maintenance IVIG treatment was given at intervals of 1–2 weeks, for a maximum of seven repetitions. If spasms relapsed, maintenance IVIG treatment was stopped and ACTH therapy or antiepileptic agents were commenced. Parents were asked to provide written informed consent before IVIG administration. This study was approved by the Saitama Children Medical Center Institutional Review Board.

2.2. Etiology

Cryptogenic West syndrome is defined according to the following criteria: 1) clusters of epileptic spasms with onset before the age of 2 years, 2) hypsarrhythmia on EEG, 3) normal pregnancy, normal development, and no eventful past history, including no other types of seizures before the onset of the spasms, 4) no focal abnormalities on neurological examination, 5) normal brain images via computed tomography and/or magnetic resonance imaging. Symptomatic cases were classified into postnatal, perinatal, and prenatal groups. The postnatal group consisted of cases in which the brain insults occurred after 1 month of age. The perinatal group consisted of patients who had experienced brain insults. We divided the perinatal group into two subgroups: term (born after 37 weeks gestation) and preterm (born before 37 weeks gestation). The prenatal group consisted of cases of cerebral dysplasia, chromosomal aberrations, multiple congenital anomalies, intrauterine abnormalities, or inherited disorders. When two or more symptomatic etiologies were suspected, we classified the patients by the first causative factor.

2.3. Outcome

We evaluated seizure outcomes at 2 weeks (initial evaluation), 2 years (long-term evaluation), and the last visit (last follow-up evaluation) after the initial IVIG treatment. The response in the initial evaluation was defined as complete cessation of spasms and resolution of hypsarrhythmia on EEG within 2 weeks after the first-day IVIG treatment. The response in the long-term evaluation was defined as complete cessation of spasms and resolution of hypsarrhythmia on EEG for >2 years after the initial IVIG treatment. Seizure outcome parameters in the last follow-up evaluation were seizure relapse after cessation of spasms, and seizure control until the last visit. The information of seizures including seizure frequency, relapse, and occurrence of new types of seizures was obtained from parents, every 1–3 month for first-year follow-up and every 3–6 month for second-year follow-up. We performed EEG before treatment and after cessation of spasms, and evaluated the resolution of hypsarrhythmia occurring within 2 weeks of the initial IVIG treatment. EEG follow-up examinations of each patient were performed once, at least 6 months after maintenance IVIG treatment was stopped. All EEG were recorded for at least 60 min including wakefulness and sleep. The influence of the following clinical factors on seizure outcomes and adverse effects were compared: dosage of IVIG, age at onset of spasms, treatment lag, and etiology. The definition of period between initial IVIG and cessation as follows: the term "1 day" means that spasms disappeared on the next day after the first-day IVIG treatment. We also evaluated EEG findings and developmental outcomes after IVIG therapy. Intelligence quotient (IQ) and Developmental quotient (DQ) were evaluated by Tanaka-Binet Intelligence Scale, Kyoto Scale of Psychological Development, or Enjoji Scale of Infant Analytical Development in Japanese at the final visit: Normal (IQ & DQ ≥ 75), mild intellectual disability (IQ & DQ ≥ 50, IQ & DQ < 75), moderate intellectual disability (IQ & DQ ≥ 25, IQ & DQ < 50), and severe intellectual disability (IQ & DQ < 25).

2.4. Statistical analysis

Mann-Whitney U and Fisher's exact tests were applied for statistical analysis using statistical software IBM SPSS Statistics 19. A p-value of 0.05 or less was considered to indicate a statistically significant difference.

3. Results

3.1. Patients and etiology

IVIG therapy was administered to 70 patients with West syndrome (41 males, 15 cryptogenic cases). The 55 symptomatic patients were divided into the following groups: prenatal, $n = 28$; preterm, 6; term, 16; and postnatal, 5. The etiologies in the prenatal group were as follows: unknown cause of epileptic spasms ($n = 9$); Down syndrome (4); tuberous sclerosis (3); polymicrogyria (2); cerebral atrophy (2); multiple abnormalities (1); microcephaly (1); hypothalamic hamartoma (1); lissencephaly (1); Aicardi syndrome (1); congenital cytomegalovirus infection (1); suspected antenatal infection (1); and argininosuccinic aciduria (1). In the preterm group, etiologies consisted of neonatal asphyxia ($n = 4$), meconium aspiration syndrome (1), and intraventricular hemorrhage (1). The etiologies in the term group were as follows: lesions due to neonatal asphyxia ($n = 7$); neonatal convulsions (2); unknown (2); twin-to-twin transfusion syndrome (1); neonatal hypoglycemia (1); neonatal polycythemia (1); cerebral parenchyma hemorrhage (1); and cerebral infarction (1). The etiologies in the postnatal group included subdural hematoma ($n = 3$), cerebral infarction (1), and Reye-like syndrome (1). Motor deficits and intellectual disability occurred in 48/70 and 49/70 patients, respectively. Other types of seizures preceded the spasms in 12 cases. Fifty patients were administered Venoglobulin-IH, fifteen were administered Glovenin-I, and five were administered Venilon-I. A dosage of 293 ± 91 (mean ± standard deviation [SD]) mg/kg/day IVIG was administered for 3 consecutive days (initial IVIG treatment). The age at the onset of spasms was 5.9 ± 3.0 (mean ± SD) months, ranging from 1 to 15 months. The treatment lag between the onset of spasms and IVIG therapy was 38.5 ± 19.5 (mean ± SD) days, ranging from 7 to 87 days. The duration of follow-up was 103.4 ± 58.7 (mean ± SD) months, ranging from 25 to 232 months. All patients were followed up for >2 years. Sodium valproate was given to 7/70 patients before pyridoxal therapy.