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

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A B S T R A C T
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.

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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...
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], Glivenon-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 Glivenon-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 < 75, ≤ 75), moderate intellectual disability (IQ & DQ < 25, ≤ 25), 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 Glivenon-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.
3.2. Efficacy of IVIG

Following IVIG treatment, 7/70 (10.0%) patients had cessation of spasms within 2 weeks after the initial IVIG treatment and no relapses occurred for >2 weeks after complete cessation. There were no significant differences in efficacy among three kinds of IVIG preparations. Table 1 shows the characteristics of the patients who responded to initial IVIG treatment. Spasms disappeared within 3.6 ± 4.1 (mean ± SD) days after the initial IVIG treatment. Among the seven patients who responded to initial IVIG treatment, four were given maintenance IVIG treatment every 1–2 weeks, seven times in total. Patient 6 was not given maintenance treatment due to an adverse effect (hypertension) from the initial IVIG treatment; however, this patient did not relapse for >2 years. Patient 7 received maintenance IVIG treatment nine times; it was administered for 3 consecutive days every 2 weeks, three times. The patient had complete cessation of spasms for >2 years after the initial IVIG treatment. Following initial IVIG treatment, 1/7 (14.3%) patients had relapse of spasms within a month after initial IVIG treatment, and 6/7 (85.7%) patients had cessation of spasms for >2 years. Patient 4 who had a relapse of spasms after IVIG showed resistance to ACTH therapy and antiepileptic drugs. Two patients had relapse of partial seizures after cessation of spasms in the last follow-up evaluation: Patient 1 had partial seizures at the age of 2 years and 10 months, which were treated with carbamazepine. Patient 3 had partial seizures at the age of 1 year and 4 months, which were resistant to valproate and topiramate. They did not experience a relapse of spasms. Intellectual disability was found in 6/7 (85.7%) patients who had cessation of spasms in the initial evaluation at the last visit (Table 1). Cryptogenic patients showed better cognitive outcomes than symptomatic cases.

3.3. Efficacy of IVIG in dosages, age at the onset of spasms, treatment lag, and etiology

We analyzed dosages of IVIG, age at onset of spasms, treatment lag, and etiologies between responders (n = 7) and non-responders (63) (Table 2). 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.

3.4. EEG follow-up examinations

Hypsarrhythmia was resolved in all patients who responded to initial IVIG treatment within 2 weeks. The EEGs of five patients who had cessation of spasms for >2 years showed resolution of hypsarrhythmia after the final maintenance IVIG treatment. The EEGs of three patients were recorded within 3 months of the final maintenance IVIG treatment, and two were recorded within 5 months. The EEG of one patient who had cessation of spasms for >2 years without maintenance IVIG treatment showed resolution of hypsarrhythmia, recorded within 2 months of the initial IVIG treatment. The EEGs of 6 patients who had cessation of spasms for >2 years showed normalization in 3, focal discharges in the left frontal region in 1, in the left centro-parietal region in 1, and in the right frontal and centro-temporal regions with low voltage waves in the left hemisphere in 1. One patient who had a relapse of spasms after IVIG showed hypsarrhythmia.

3.5. Adverse effects

A total of 251 IVIG infusions were administered for West syndrome. The adverse effect rate was 2/251 (0.8%). One patient became hypertensive and one developed aseptic meningitis as an adverse effect after the initial IVIG treatment. These adverse effects resolved after discontinuation of IVIG therapy.

No patients died during the follow up period.

4. Discussion

4.1. Efficacy of IVIG therapy for West syndrome

To the best of our knowledge, this is the first study of IVIG therapy on a large number of patients with West syndrome. This study provided reliable information of IVIG therapy for West syndrome. In this study, initial IVIG treatment was effective in 10.0% of patients with West syndrome. Table 3 showed the various rates of efficacy after IVIG therapy for West syndrome in previous studies [4–8]. Complete cessation of spasms occurred in 21.4–63.6% patients. The efficacy of IVIG therapy in our study was lower than that in previous studies, which might be caused by small number of cases in previous study. Most patients in

<p>| Table 1 |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>Age at initial IVIG (m)</th>
<th>Period between initial IVIG and cessation</th>
<th>Maintenance IVIG treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dosage of IVIG (mg/kg/d)</td>
<td>Duration of infusion (d)</td>
<td>Interval of infusion (w)</td>
</tr>
<tr>
<td>1</td>
<td>IVH</td>
<td>7</td>
<td>373.1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>brain atrophy</td>
<td>11</td>
<td>3.0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>subdural hematoma</td>
<td>8</td>
<td>263.2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>TS</td>
<td>5</td>
<td>301.2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>cryptogenic</td>
<td>6</td>
<td>280.9</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>HIE</td>
<td>6</td>
<td>138.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>cryptogenic</td>
<td>6</td>
<td>347.2</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2

Comparison between responders and non-responders in dosages of IVIG, age at the onset of spasms, treatment lag, etiology and adverse effect.

<table>
<thead>
<tr>
<th>Responder</th>
<th>Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage of IVIG (mg/kg/day)</td>
<td>289.6 ± 75.6</td>
</tr>
<tr>
<td>Age at the onset of spasms (m)</td>
<td>6.4 ± 2.4</td>
</tr>
<tr>
<td>Treatment lag (d)</td>
<td>22.4 ± 8.5*</td>
</tr>
<tr>
<td>Cryptogenic: Symptomatic</td>
<td>2: 5</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>1 (14.3%)</td>
</tr>
</tbody>
</table>

* Significant differences between the two groups as determined by Mann-Whitney U test.
previous studies were treated with IVIG therapy after ACTH and multi-
drug therapies. Our study demonstrated the efficacy of IVIG ther-
apy if given early and provided a useful prediction of its efficacy as
monotherapy for West syndrome. This is the most reliable information
of IVIG therapy for West syndrome.

### 4.2. Period between initial IVIG treatment and cessation of spasms

Most patients had complete cessation of spasms within a week of
the initial IVIG treatment in our study. In previous studies, spasms
usually disappeared within a few days (Table 3) and the average period
between initial vigabatrin treatment and complete cessation was 4 days
[9,10]. The periods between initial ACTH treatment and complete cessa-
tion of spasms were within a week[11]. These results are similar to the
previous studies of IVIG therapy to West syndrome.

### 4.3. Seizure and cognitive outcomes

The treatment lag in responders was shorter than that in non-
responders in our study. Thus, a short treatment lag may lead to a
more favorable seizure outcome following IVIG therapy for West syn-
drome. Symptomatic patients responded to IVIG similarly to cryptogen-
ic patients, without adverse effects (Table 2). IVIG was more effective for
cryptogenic than symptomatic West syndrome in previous studies [4,5,
8]. However, these studies were conducted on small numbers of pa-
tients. Patients with cryptogenic West syndrome who had cessation of
spasms for 2 years had better cognitive outcomes in our study. Early
diagnosis and prompt treatment with an effective therapy produces a
more favorable cognitive outcome, particularly in cryptogenic West syn-
drome [14,15]. Furthermore, cryptogenic patients who had cessa-
tion of spasms after IVIG therapy showed improved DQ scores [4]. Com-
plete cessation in the early phases and in cryptogenic West syndrome
are factors related to favorable cognitive outcomes following IVIG
therapy.

### 4.4. Dosage of IVIG

Table 3 showed the various dosage of IVIG for West syndrome in
previous studies [4–8], but appropriate dosages, number, and interval
of infusion were not considered. Most of them administered IVIG at
100–500 mg/kg/day for 2–6 weeks for 6–16 times without serious adverse
effects. Dosages of IVIG were not correlated positively with efficacy in our study: There were no significant differences between re-
ponders and non-responders in dosages of IVIG. It is interesting to note
that the patient 6 who was administered in lower dosage of IVIG (138.9 mg/kg/day for 3 consecutive days) did not have relapse without
maintenance IVIG treatment (Table 1). The other factors which associ-
ate with cessation of spasms should be investigated other than dosage.
Further investigation is required to make treatment protocol: dosage, number, and interval of infusion.

### 4.5. Adverse effects of IVIG

The adverse effect rate of IVIG therapy was low and no serious ad-
verse effects occurred in our study. Moreover, IVIG therapy for patients
with West syndrome and intractable epilepsy produced no serious ad-
verse effects in previous studies [4–8,16]. IVIG therapy demonstrated that it is safe and effective in some children with intractable seizures
[17]. Long-term, high-dosage IVIG for patients with multiple sclerosis
showed short-term and long-term safety without serious adverse ef-
ects [18]. In the adverse effects of ACTH therapy, Infection was reported
in 14% of patients [19]. A patient who was treated with ACTH therapy
had tuberculosis of the lung and died despite anti-tuberculosis therapy
[20]. Patients with congenital cytomegalovirus infection died during
ACTH therapy, because of generalized cytomegalovirus infection [21].
IVIG therapy, therefore, has a good safety profile and we would recom-
end it for West syndrome cases with drug resistance, severe complica-
tions associated with profound brain damage, severe brain atrophy, and
in immunocompromised patients.

### 4.6. Mechanisms of IVIG

Proposal mechanisms of IVIG in autoimmune and inflammatory
disease are blockage of Fc receptors, decrease in inflammation, induc-
tion of antiinflammatory of the cytokine release, and modulation of
B cell and T cell function [22]. The full mechanisms of IVIG in treatment

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**Table 3**

Previous studies of IVIG therapy to West syndrome.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Age mean (y, range)</th>
<th>Dosage of IVIG</th>
<th>Total number of infusion</th>
<th>Interval of infusion (w)</th>
<th>Complete cessation of spasms (n,%)</th>
<th>Period between initial IVIG and cessation of spasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariizumi, et al. (1987)</td>
<td>WS 11</td>
<td>0.55 (0.25–1)</td>
<td>0.1-0.4 g/kg/d</td>
<td>6-10</td>
<td>2-3</td>
<td>7 (63.6%)</td>
<td>&lt; 14 d in 4 cases ≥ 14 d in 3 cases</td>
</tr>
<tr>
<td>Echenne, et al. (1991)</td>
<td>WS 19</td>
<td>NA (NA)</td>
<td>0.4 g/kg/d for 5 d or 1 g/kg/d for 2 d</td>
<td>1-8</td>
<td>NA</td>
<td>1/3 (33.3%)</td>
<td>2-20 d</td>
</tr>
<tr>
<td>Van Engelen, et al. (1994)</td>
<td>WS 3 LGS 12</td>
<td>3.6 (1-6)</td>
<td>0.5 g/kg/d</td>
<td>11</td>
<td>0.15-2</td>
<td>7 (10.0%)</td>
<td>a few weeks to 6 m</td>
</tr>
<tr>
<td>Mikati, et al. (2010)</td>
<td>WS 9 LGS 17</td>
<td>9.94 (8.1-10.1)</td>
<td>0.1-0.5 g/kg/d</td>
<td>16</td>
<td>0.15-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geva-Dayan, et al. (2012)</td>
<td>WS 14 ESES 12</td>
<td>1.1 (0.2-7.5)</td>
<td>initial 2 g/kg/2-5 d then 0.5-2 g/kg/d</td>
<td>9.5</td>
<td>4-6</td>
<td>WS 3/14 (21.4%) 75% (75%)</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>WS 70</td>
<td>0.49 (0.1-1.3)</td>
<td>0.1-0.5 g/kg/d</td>
<td>3-12</td>
<td>0.15-2</td>
<td>7 (10.0%)</td>
<td>3.6 ± 4.1 d</td>
</tr>
</tbody>
</table>

*Table 3* showed the various dosage of IVIG for West syndrome.
of West syndrome are still unknown. Immunoglobulin G crossed blood brain barrier in patients with cryptogenic West syndrome or Lennox Gastaut syndrome [23]. However there were no significant differences in the initial, long-term, and last follow-up evaluations among different IVIG dosages in our study. Some studies showed humoral deficiencies and abnormality of cell mediated immunity in West syndrome [24, 25]. IVIG may modify immunological dysfunctions of West syndrome. Our study could not provide us with information to explain the propensity of IVIG for improving patients with West syndrome. Further investigation is required to elucidate the mechanisms of IVIG.

5. Conclusion

Intravenous immunoglobulin therapy is low efficacy and inadequate therapy as the initial treatment in West syndrome. The efficacy of IVIG was not high, but it had long-term effects without serious adverse effects or the need for antiepileptic drugs. 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. We can evaluate efficacy early in IVIG therapy. Patients with short treatment lag showed better seizure outcomes. If spasms did not respond to first-line treatment, we recommend IVIG therapy for West syndrome. Our study demonstrates the most reliable information of IVIG therapy for West syndrome.

Disclosures


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