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Vigabatrin and high-dose prednisolone therapy for patients with West syndrome

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Highlights:

- The treatment protocol for West syndrome using vigabatrin (maximum dose of 150 mg/kg/day) and prednisolone (maximum dose of 60 mg/day) was studied observationally to determine its efficacy and safety.
- The treatment protocol that included vigabatrin and prednisolone therapy for West syndrome showed resolution of spasms and a BASED score ≤ 2 in 72.7% of patients, with no serious adverse effects.
- The mental and psychomotor age quotients were higher at the time of diagnosis and remained significantly higher 6 months after diagnosis in the patients who responded to the therapy.

Abstract

Objective

Hormonal therapy and vigabatrin are now accepted as the first-line or standard therapies for West syndrome (WS). However, the superiority of these drugs in terms of monotherapy or combination therapy is still in question. In this study, we designed a treatment protocol for WS and prospectively assessed the efficacy of these therapies in controlling spasms, stabilizing electroencephalography (EEG), and allowing for developmental catch-up.

Methods

In patients diagnosed with WS, vigabatrin was first administered alone for 2 weeks, and then prednisolone was administered in combination with vigabatrin if patients did not respond to

vigabatrin. The detailed drug administration protocol was as follows: vigabatrin 50 mg/kg/day for 1 day, followed by vigabatrin 100 mg/kg/day for 3 days, vigabatrin 150 mg/kg/day if spasms were still present or the burden of amplitudes and epileptiform discharges (BASED) score on EEG was ≥3 on day 5; 40 mg/day of prednisolone was added if spasms were still present or the BASED score was ≥3 on day 14. The prednisolone dose was increased to 60 mg/day if spasms were still present or the BASED score was ≥3 on day 21.

Results

Sixty-six patients newly diagnosed with WS (median seizure onset age: 5.7 [IQR, 4.1-7.1] months, median age at diagnosis: 6.6 [IQR, 5.4-8.1] months, n = 40 [60.6%] boys) were subjected to the vigabatrin and prednisolone therapy protocol. Of the 66 patients, 22 (33.3%) patients showed resolution of spasms and a BASED score of ≤2 after vigabatrin alone, and 26 (39.4%) patients showed resolution of spasms and a BASED score of ≤2 after a combination of vigabatrin and prednisolone, for a total of 48 (72.7%) patients who were responsive to the protocol without relapse for at least 7 months after WS diagnosis. The mental and psychomotor age quotients were higher at the time of diagnosis and remained significantly higher 6 months after the diagnosis in responsive patients ($p < 0.001$). No serious adverse reactions leading to discontinuation or reduction of drug doses were observed.

Conclusion

Using a treatment protocol involving vigabatrin and prednisolone for WS, 72.7% of patients showed resolution of spasms and a BASED score of ≤ 2. This study also found that this

drug administration protocol was safe. However, further studies are warranted as this study describes results from observational study with limited sample size.

Abbreviations:

WS: West syndrome

EEG: electroencephalogram

ACTH: adrenocorticotrophic hormone

BASED: Burden of Amplitudes and Epileptiform Discharges

IQR: interquartile range

MRI: magnetic resonance imaging

GABA: gamma-aminobutyric acid

Keywords:

West syndrome; infantile spasms; treatment; vigabatrin; prednisolone

1. Introduction

West syndrome (WS) is a developmental and epileptic encephalopathy of infancy, characterized by the triad of epileptic spasms, hypsarrhythmia on interictal electroencephalogram (EEG), and developmental arrest or psychomotor delay.(Pellock et al., 2010) The most devastating facet of WS is the rapid neuro-developmental regress that occurs upon the onset of this disorder,

which can worsen with delayed or ineffective treatment.(Koo et al., 1993) Adrenocorticotrophic hormone (ACTH), oral corticosteroids, and vigabatrin are accepted as the standard first-line therapies for WS in the United States and Europe despite the various side effects of these drugs.(Demarest et al., 2017; Riikonen, 2014) The superior treatment, in terms of efficacy, among ACTH, oral corticosteroids, and vigabatrin, is still controversial.(Lux et al., 2005; Mohamed et al., 2011) One recent study showed that hormonal treatment with vigabatrin was more effective than hormonal treatment alone.(O'Callaghan et al., 2017)

We designed a treatment protocol for WS based on previous studies in which vigabatrin was first administered alone for 2 weeks, and then prednisolone was added to vigabatrin treatment after 2 weeks if the patients were unresponsive to vigabatrin. We prospectively assessed the efficacy of these treatment protocols in controlling spasms, stabilizing EEG, and allowing for developmental catch-up.

2. Methods

2.1 Patients

WS patients diagnosed with both clinical spasms and hypsarrhythmia on EEG whose parents/guardians agreed to participate were enrolled for this prospective study at Severance Children's Hospital. Patients were excluded if they had a diagnosis of tuberous sclerosis or if they were on other antiepileptic medications at the time of diagnosis. Patients with tuberous sclerosis were excluded from the study, as vigabatrin is a well-established first-line therapy for WS patients with tuberous sclerosis. Patients who were on other antiepileptic medications at the time of diagnosis were excluded to eliminate any possible confounding factors since this study was not a randomized controlled study. A total of 66 patients were enrolled, and the sample size was based on previous studies (single center studies which assessed efficacy of medical treatment in WS patients) due the observational nature of this study. Informed consent was obtained from the patients' parents/guardians, and the Institutional Review Board of Severance Hospital approved the study protocol. This study is registered with Clinical Research Information Service (cris.nih.go.kr).

To evaluate the etiology of WS after diagnosis, all patients received brain magnetic resonance imaging (MRI) and metabolic work-ups including plasma lactate and pyruvate, plasma and cerebrospinal fluid amino acids, and urine organic acids. Patients whose brain MRI and metabolic test results were negative were subject to genetic evaluation using a targeted NGS gene panel study comprising 172 genes for developmental and epileptic encephalopathy. Selected patients were subject to array CGH or multiplex ligation-dependent probe amplification.

2.2 Assessments during the treatment protocol

2.2.1 Spasms

Parents or caregivers were instructed to complete a seizure diary. Specifically, the number of clusters of spasms, the greatest number of spasms in a given cluster, and/or the longest duration of a cluster was recorded daily. Parents or caregivers were also advised to record any events that might be adverse reactions of vigabatrin or prednisolone.

2.2.2 Electroencephalography

All subjects were examined using a video-EEG monitoring system with electrodes placed according to the international 10-20 system. EEG was recorded for a minimum duration of 4 hours; sleep tracing without the use of sedatives was always included. Two pediatric neurologists certified by the Korean Board of EEG and Clinical Neurophysiology, one aware of clinical information of patients and one unaware, reviewed the EEGs. EEG records were graded using the Burden of Amplitudes and Epileptiform Discharges (BASED) scoring system proposed by Mytinger et al.(Mytinger et al., 2015) The BASED scores were graded as described in Table 1. There was no disagreement in the BASED scores between the two EEG reviewers. According to the BASED scoring system, scores of 4 and 5 represent hypsarrhythmia. A BASED score ≤ 2 was targeted as the treatment goal to aim for stricter control of the disease.

If clinical spasms were present, treatment was increased without EEG confirmation. However, if clinical spasms were not present for more than 24 hours or if their presence was uncertain, EEG was recorded whenever a decision was required for treatment. If patients did not show clinical spasms and showed BASED score ≤ 2 four weeks following initiation of the protocol they were considered well treated, and EEG was performed every 1 to 2 months to detect

worsening of the condition until the final assessment point of the trial, which was 7 months after treatment initiation.

2.2.3 Developmental function

Developmental function of the patients was evaluated within 1 week of diagnosis and 6 to 7 months after treatment initiation using the Bayley Scales of Infant and Toddler Development, second edition, which is the latest version with valid Korean translation.(Bayley, 1993) The mental age and psychomotor age quotients were calculated by dividing the mental age and psychomotor age assessed from the Bayley scales by the chronological age of each patient, respectively.

2.3 Treatment protocol and patient grouping (Figure 1)

Patients were first administered vigabatrin at the time of their initial diagnosis of WS. Vigabatrin was first administered at a dose of 50 mg/kg/day for 1 day and was then increased to 100 mg/kg/day. After 3 days of vigabatrin administration at a dose of 100 mg/kg/day, patients remained on that dose of vigabatrin if they did not experience spasms for more than 24 hours and had a BASED score ≤ 2. The vigabatrin dose of 100 mg/kg/day was maintained until 5 months after the initiation of treatment and then tapered out over 1 month. If patients continued to experience spasms or had a BASED score ≥ 3, the dose of vigabatrin was increased to 150 mg/kg/day. Two weeks after the start of the treatment protocol, patients who did not experience spasms over a 24-hour period and had a BASED score ≤ 2 remained on a vigabatrin dose of 150 mg/kg/day until 5 months after initiation of treatment. Vigabatrin was then tapered out over 1 month. Prednisolone at a dose of 40 mg/day was added to vigabatrin in the patients not effectively treated by vigabatrin alone.

After 7 days of prednisolone (40 mg/day), the patients who did not show spasms over a period of 24 hours and who had a BASED score ≤ 2 remained on the dose for 7 more days. The drugs were then tapered over 2 weeks. Otherwise, the prednisolone dose was increased to 60 mg/day and administered for another 7 days, and then tapered over 2 weeks. In both cases, high-dose prednisolone (40 mg/day or 60 mg/day) was administered for 2 weeks and then tapered over 2 weeks. Vigabatrin was administered twice daily, and prednisolone four times daily. The doses of vigabatrin were adjusted according to the change in patients' weight at a maximum interval of 1 month. Cimetidine was prescribed alongside prednisolone.

In patients who received prednisolone, 150 mg/kg/day vigabatrin was maintained until 2 months after the initiation of vigabatrin treatment and then tapered out over 1 month. In summary, 100 or 150 mg/kg/day of vigabatrin was maintained for 5 months and then tapered over 1 month in the patients who did not receive prednisolone (vigabatrin responders), while 150 mg/kg/day vigabatrin was maintained for 2 months and then tapered over 1 month in the patients who were unresponsive to vigabatrin and received prednisolone.

If spasms recurred or a BASED score ≥ 3 was noted during follow-up EEG, which was performed every 1 to 2 months in the patients who received vigabatrin only, prednisolone therapy was administered as the standard protocol without changing the total duration of vigabatrin therapy. If spasms did not recur and the BASED score remained ≤ 2 until 7 months after treatment, i.e., until 1 month after discontinuation of vigabatrin, patients were labeled "vigabatrin responsive." If spasms did not recur and the BASED score remained ≤ 2 until 7 months after the treatment, patients were labeled "prednisolone responsive." Patients whose spasms were not controlled or whose BASED score remained ≥ 3 after prednisolone therapy were labeled "unresponsive" and were administered other antiepileptic medications or dietary therapy.

2.4 Monitoring for adverse reactions

Following their WS diagnosis, patients were admitted for monitoring of possible adverse reactions to vigabatrin at the start of the treatment protocol. Patients were generally admitted during the 4-6 days of vigabatrin dose escalation. Patients who underwent prednisolone therapy were re-admitted for 2-3 days at the initiation of the 40 mg/day dose of prednisolone. Patients subject to the 60 mg/day dose of prednisolone were re-admitted and stayed in the hospital throughout the 1-week course of 60 mg/day prednisolone.

Possible adverse reactions were listed in the study consent form and parents were educated to monitor for and document any suspected events, and to report them immediately. During hospitalization, patients were closely monitored, including by laboratory tests, for possible adverse reactions. While patients were on high-dose prednisolone, their blood pressure was monitored three times per day, the blood glucose levels were monitored at least once per day, and other laboratory examinations, including complete blood counts and routine chemistry tests, were performed once per week.

2.5 Statistical analysis

Data from the statistical analyses are expressed as medians and interquartile ranges (IQRs) for continuous and ordinal variables, and as counts and percentages for categorical variables. The 2 groups were compared using chi-squared or Fisher's exact tests for categorical and ordinal data, and the Mann-Whitney U-test for non-parametric continuous data. $p < 0.05$ was considered significant. The Statistical Package for the Social Sciences (version 23.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

3. Results

3.1 Patient characteristics

Sixty-nine patients who were newly diagnosed with WS between March 2016 and June 2017 at Severance Children's Hospital, and who were not on other antiepileptic medications at the time of diagnosis and whose parents agreed to participate in the study were included. After brain MRI, 3 tuberous sclerosis patients were excluded, leaving a total of 66 eligible patients who were subject to the vigabatrin and prednisolone therapy protocol trial. No patients were lost to follow-up during the 7-month period.

Among the 66 patients, 40 (60.6%) patients were boys. The median age at seizure onset was 5.7 (IQR, 4.1-7.1) months, the median age at diagnosis/treatment was 6.6 (IQR, 5.4-8.1) months, and the median lead-time from seizure onset to diagnosis/initiation of treatment was 15 (IQR, 7-48) days (Table 2). Twenty (30.3%) patients had structural etiologies, including 3 with lissencephaly, 2 with polymicrogyria, 1 with polymicrogyria-pachygyria, 3 with focal cortical dysplasia, 1 with multifocal posthemorrhagic encephalomalacia due to protein C deficiency, 1 with porencephaly, and 9 with hypoxic-ischemic encephalopathy. Two patients had metabolic etiology, both of whom had mitochondrial disorders. Among the remaining 44 patients, 12 had identified mutations – 3 with copy number variations and 9 with monogenic mutations. The final 32 patients were defined as the unknown etiology group.

The median mental age quotient was 0.55 (IQR, 0.01-0.78), and the median psychomotor age quotient was 0.57 (IQR, 0.17-0.79).

3.2 Treatment outcome

Among the 66 patients, 8 (12.1%) showed resolution of spasms and achieved a BASED score ≤ 2 with 100 mg/kg/day of vigabatrin, and 14 (21.2%) showed resolution of spasms and a BASED score ≤ 2 with 150 mg/kg/day of vigabatrin. These findings resulted in a total of 22 (33.3%) patients being defined as "vigabatrin responsive" (Figure 2). This patient group included those who continued to remain spasm free with a BASED score ≤ 2 until the final follow-up (7 months after diagnosis). The 7 patients who proceeded to prednisolone treatment due to the recurrence of spasms or worsening of the BASED score to ≥ 3 later were not included in this group.

The remaining 44 patients did not respond to vigabatrin and were also administered prednisolone. Spasm resolution and BASED scores ≤ 2 were achieved after 1 week of 40 mg/day prednisolone in 15 (22.7%) patients, and after 1 additional week of 60 mg/day prednisolone in 13 (19.7%) patients. However, 2 (3.0%) patients showed worsening of the BASED score to ≥ 3 after tapering of prednisolone, resulting in a total of 26 (39.4%) patients who were defined as 'prednisolone responsive.'

Of the 18 (27.3%) unresponsive patients, 7 (10.6%) showed spasm cessation. Of these 7 patients, 5 (7.6%) had a BASED score of 3. As BASED scores of 4 and 5 represent hypsarrhythmia, 53 (80.3%) patients showed spasm cessation and resolution of hypsarrhythmia on EEG. Of the remaining patients, 6 (9.1%) showed improvements in the BASED scores from 5 to 4, representing a partial response to the treatment protocol.

In summary, 48 (72.7%) patients achieved seizure freedom and an EEG BASED score ≤ 2 with vigabatrin and prednisolone treatment; these effects persisted until the final follow-up conducted 7 months after WS diagnosis.

3.3 Comparison of clinical variables between responsive and unresponsive patients

When vigabatrin- or prednisolone-responsive patients were compared with unresponsive patients, no significant differences in sex, age at seizure onset, age at diagnosis/treatment, lead-time since seizure onset to diagnosis/treatment, or etiology were found (Table 2).

The median of mental age quotient and psychomotor age quotient were 0.67 (IQR, 0.38-0.86) and 0.68 (IQR, 0.39-0.81) in responsive patients, while the median of mental age quotient and psychomotor age quotient was 0.01 (IQR, 0.01-0.24) and 0.01 (IQR, 0.01-0.43) in unresponsive patients. The mental age quotient and psychomotor age quotient were each significantly higher in responsive patients than in unresponsive patients ($p < 0.001$ in both).

3.4 Developmental function after 6 months of treatment

The median mental and psychomotor age quotients were 0.74 (IQR, 0.60-0.86) and 0.76 (IQR, 0.56-0.94) in responsive patients, respectively, and 0.03 (IQR, 0.01-0.35) and 0.06 (0.01-0.44) in unresponsive patients, respectively, after 6 months of treatment (Table 2). The mental and psychomotor age quotients remained significantly higher in responsive patients over time ($p < 0.001$ for both). The change in mental and psychomotor age quotient from the time of diagnosis to 6 months after treatment, calculated by subtracting the mental or psychomotor age quotient at 6 months from the corresponding quotient at the time of diagnosis, were higher in responsive patients than in unresponsive patients, though the difference was not statistically significant.

When the data from the 22 vigabatrin responders were compared with the 26 combination vigabatrin and prednisolone responders, the mental and motor age quotients at the beginning of treatment were significantly higher in vigabatrin responders (mental age quotients: median 0.76, IQR 0.58-0.95, vs. median 0.56, IQR 0.15-0.78, $p = 0.036$; motor age quotients: median 0.77, IQR

0.60-0.95, vs. median 0.58, IQR 0.26-0.77, p = 0.015). However, the extent of developmental improvement (i.e., the difference after 6 months of treatment) in terms of mental and motor age quotients was not significantly different between the two groups.

3.5 Adverse reactions

In terms of adverse reactions, drowsiness was observed in 17 (25.8%) patients after administration of 100 mg/kg/day vigabatrin, in 2 (3.4%) patients after increasing the vigabatrin dose to 150 mg/kg/day, and in 1 (2.3%) patient after the addition of 40 mg/day of prednisolone (Table 3). Feeding difficulty was observed in 8 patients who received vigabatrin, but this effect was attributable to drowsiness in all cases. Irritability was noted in 1 (1.5%) patient after administration of 100 mg/kg/day vigabatrin, in 5 (11.4%) patients after the addition of 40 mg/day prednisolone, and in 9 (31.0%) patients after the dose of prednisolone was increased to 60 mg/day. No other adverse reactions were reported in the patients who received vigabatrin only.

Sleep disturbance was observed in 6 (13.6%) and 2 (6.9%) patients after the addition of 40 and 60 mg/day of prednisolone, respectively. Eighteen (40.9%) patients showed increased appetite, and 1 (2.3%) patient showed cushingoid facies with increased weight after adding 40 mg/day of prednisolone to vigabatrin. After increasing the dose of prednisolone to 60 mg/day, increased appetite was observed in 5 (17.2%) patients, cushingoid facies with increased weight in 3 (10.3%) patients, thrombocytosis in 3 (10.3%) patients, leukocytosis in 1 (3.4%) patient, and infection (pneumonia) in 1 (3.4%) patient. The adverse reactions were all reversible, and serious adverse reactions resulting in discontinuation of the medication did not occur in all cases.

4. Discussion

Using a stepwise treatment protocol of vigabatrin followed by prednisolone based on the presence of clinical spasms or a BASED score ≥ 3, the resolution of clinical spasms and a BASED score ≤ 2 EEG were achieved in 48 (72.7%) patients. These patients included 8 (12.1%) who achieved resolution of clinical spasms and a BASED score ≤ 2 and remained in that state until 7 months following initiation of 100 mg/kg/day vigabatrin, 14 (21.2%) who achieved resolution of clinical spasms and a BASED score ≤ 2 after 150 mg/kg/day vigabatrin, 15 (22.7%) who achieved these results after 40 mg/day prednisolone, and 11 (16.7%) who achieved these results after 60 mg/day prednisolone. The clinical variable found to be associated with treatment responsiveness was that of developmental function, as unresponsive patients had lower mental and psychomotor age quotients at the time of initiation of treatment than responsive patients.

ACTH, prednisolone, and vigabatrin are considered to be the standard or first-line medications for WS due to their superior efficacy in the resolution of spasms and hypsarrhythmia on EEG compared with other conventional antiepileptic drugs.(Demarest et al., 2017; Knupp et al., 2016) Various studies have shown hormonal therapy to have a more rapid clinical and electrical response than vigabatrin.(Granstrom et al., 1999; Lux et al., 2004; Mohamed et al., 2011) However, studies with a longer follow-up duration have shown no significant difference in the relapse-free responder rate between hormonal therapy and vigabatrin; this can be attributed to the shorter duration of hormonal therapy administration (1 month) compared with that of vigabatrin therapy (6 months). As a result, the superiority between vigabatrin and hormonal therapy is still unclear.(Darke et al., 2010; Lux et al., 2005; Pellock et al., 2010) After failing to respond to a first-line medication, administration of another first-line medication with a different mechanism of

action (i.e., hormones vs. vigabatrin) has been shown to result in a higher response rate than the use of other nonstandard medications.(Knupp et al., 2016) Additionally, a recent study showed that steroid and vigabatrin combination therapy was more effective in controlling spasms than hormonal therapy alone.(O'Callaghan et al., 2017) Based on these findings, a protocol implementing a sequential trial of vigabatrin and prednisolone was designed and tested in this study.

Serious and drug-specific adverse reactions of vigabatrin are peripheral visual field defects and vigabatrin-associated brain abnormalities on MRI. The occurrence of vigabatrin-induced retinal damage resulting in irreversible peripheral visual field defects has been found to be associated with duration of vigabatrin administration, and generally appears as soon as 3 months after the initiation of vigabatrin.(Maguire et al., 2010; Riikonen et al., 2015; Willmore et al., 2009) Therefore, it is recommended that the duration of vigabatrin treatment be limited to less than 3 months in patients who are non-responsive to vigabatrin.(Willmore et al., 2009) Patients who remained spasm-free with vigabatrin for 6 months have been shown to remain spasm free without relapse after discontinuing vigabatrin, and minimization of vigabatrin treatment to less than 6 months has been shown to reduce the prevalence of vigabatrin-induced retinal damage in patients with infantile spasms.(Appleton, 1998, Westall et al., 2014; Willmore et al., 2009) Based on such studies, the protocol adopted for the present study used a vigabatrin treatment duration of 6 months in vigabatrin responders and 3 months in vigabatrin non-responders.

Vigabatrin-associated brain abnormalities on MRI are reversible and appear as mostly asymptomatic signal changes in the thalami, basal ganglia, brainstem, and cerebellar nuclei.(Hussain et al., 2017) The risk of vigabatrin-associated brain abnormalities on MRI has been shown to be peak dose-dependent. An increased risk has been observed with the use of a high

vigabatrin dosage (> 175 mg/kg/day); but the risk was not found to be associated with the cumulative dose.(Hussain et al., 2017) However, low dose (18-36 mg/kg/day) vigabatrin is less effective in controlling spasms than high dose (100-148 mg/kg/day) vigabatrin.(Elterman et al., 2010) Therefore, in the treatment protocol used in this study, we limited the maximum dosage of vigabatrin to 150 mg/kg/day.

Potential prednisolone-specific serious adverse reactions include high blood pressure, infection, gastrointestinal bleeding, and adrenal insufficiency.(Riikonen, 2014) These severe potential adverse reactions are often reversible or treatable if detected early. Furthermore, the recommended duration of hormonal therapy is 1 month, as the effects of hormonal therapy remain permanently following the cessation of 2-4 weeks of treatment. This short therapy duration is favorable in terms of reducing adverse reactions.(Baram et al., 1996; Pellock et al., 2010) In terms of dosage, higher dose (4 mg/kg/day) prednisolone was more effective in controlling spasms than lower dose (2 mg/kg/day) prednisolone.(Chellamuthu et al., 2014) High-dose prednisolone (up to 60 mg/day) has been shown to be safe in various studies.(Knupp et al., 2016; Lux et al., 2004; O'Callaghan et al., 2017) Therefore, in this study, we adopted a dosing schedule of 40 mg/day for 1 week followed by 40 or 60 mg/day for 1 week, and then tapered the dose off over the next 2 weeks, resulting in a total steroid treatment duration of 4 weeks.

When designing the protocol, as mentioned above, we selected the doses and durations of vigabatrin and prednisolone administration in order to show their full efficacy while minimizing adverse reactions. Combination vigabatrin and prednisolone therapy has been shown to be more effective than vigabatrin or prednisolone monotherapy; however, we implemented a sequential approach to filter out patients who responded to monotherapy.(O'Callaghan et al., 2017) Vigabatrin monotherapy was administered before prednisolone therapy, as acute serious adverse

reactions with fatal consequences due to high-dose prednisolone, such as infection, sepsis, hypertension, and gastrointestinal bleeding, could not have been foreseen or avoided by adjusting the protocol. Additionally, a higher relapse rate has been reported with prednisolone, presumably due to its shorter administration duration. (Darke et al., 2010; Lux et al., 2005) The longer tolerable administration duration of vigabatrin of 3 to 6 months, a duration sufficient to suppress neuronal hyperexcitable period in WS patients, also contributed to the selection of vigabatrin as the first drug in the protocol. Further studies comparing the switch from vigabatrin to prednisolone after a 2-week trial with vigabatrin are warranted to confirm the role of vigabatrin in patients whose spasms and hypsarrhythmia were not completely controlled by it. By adapting the stepwise approach of vigabatrin and prednisolone, patients who would benefit from vigabatrin monotherapy alone can be selected, and unnecessary exposure to the potential adverse reactions of high-dose prednisolone can be avoided.

Patients were admitted to hospital when medications were introduced or doses were adjusted in order to closely monitor for possible adverse reactions. However, as the protocol did not result in any serious adverse reactions, admission seems unnecessary except in cases where special concerns are present.

It has been reported that the patients who initially received ACTH showed better cognitive outcomes than those who received vigabatrin in the unknown etiology subgroup, and this finding is supposedly attributable to the more rapid action of hormonal therapy in the cessation of infantile spasms.(Darke et al., 2010; Lux et al., 2005) In this study, the mental and motor age quotients of the vigabatrin responders at the time of diagnosis were higher than the vigabatrin plus prednisolone responders, indicating that patients with lighter disease burden may show a faster response to the first treatment. Also, patients who achieved clinical electrical responses showed more

improvements in developmental function following 6 months of treatment than those who did not achieve clinical and electrical cessation of spasms and hypsarrhythmia; however, this difference did not reach statistical significance. Furthermore, as the extent of developmental improvements did not differ between the vigabatrin and vigabatrin plus prednisolone responders, the 2-week delay to the introduction of hormonal therapy may not affect developmental outcomes, at least in the short-term. However, as both groups went through the same treatment protocol, it is not possible to assess the direct effect of this treatment protocol on development, as partial effects cannot be ruled out for the unresponsive patients. Additionally, re-assessments after longer follow-up durations are needed in order to evaluate the definite trends in developmental functioning. In addition, the etiologies and baseline developmental states that critically affect developmental progress were too heterogeneous on which to draw comparisons.

This study was limited by its lack of a control group and patient randomization, as well as its small sample size. For these reasons, patients with tuberous sclerosis and patients who had been on other antiepileptic medications who were regarded as having possible confounding factors to the treatment protocol response were excluded; this may have generated selection bias.

In conclusion, using the vigabatrin and prednisolone treatment protocol for WS, 72.7% of patients showed spasm resolution and BASED scores ≤ 2. The present findings also demonstrate that the safety of this treatment protocol. However, randomized controlled study investigating the efficacy of this protocol compared to vigabatrin, hormonal therapy, or combination therapy is needed. Also, different stepwise approach of switching vigabatrin to hormonal therapy should be investigated to verify our hypotheses of role of vigabatrin in reducing relapse rate after discontinuation of hormonal therapy.

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Conflict of Interest:

The authors have no conflicts of interest relevant to this article to disclose.

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Figure legends

Figure 1. Schematic flow of the vigabatrin and prednisolone treatment protocol for West syndrome.

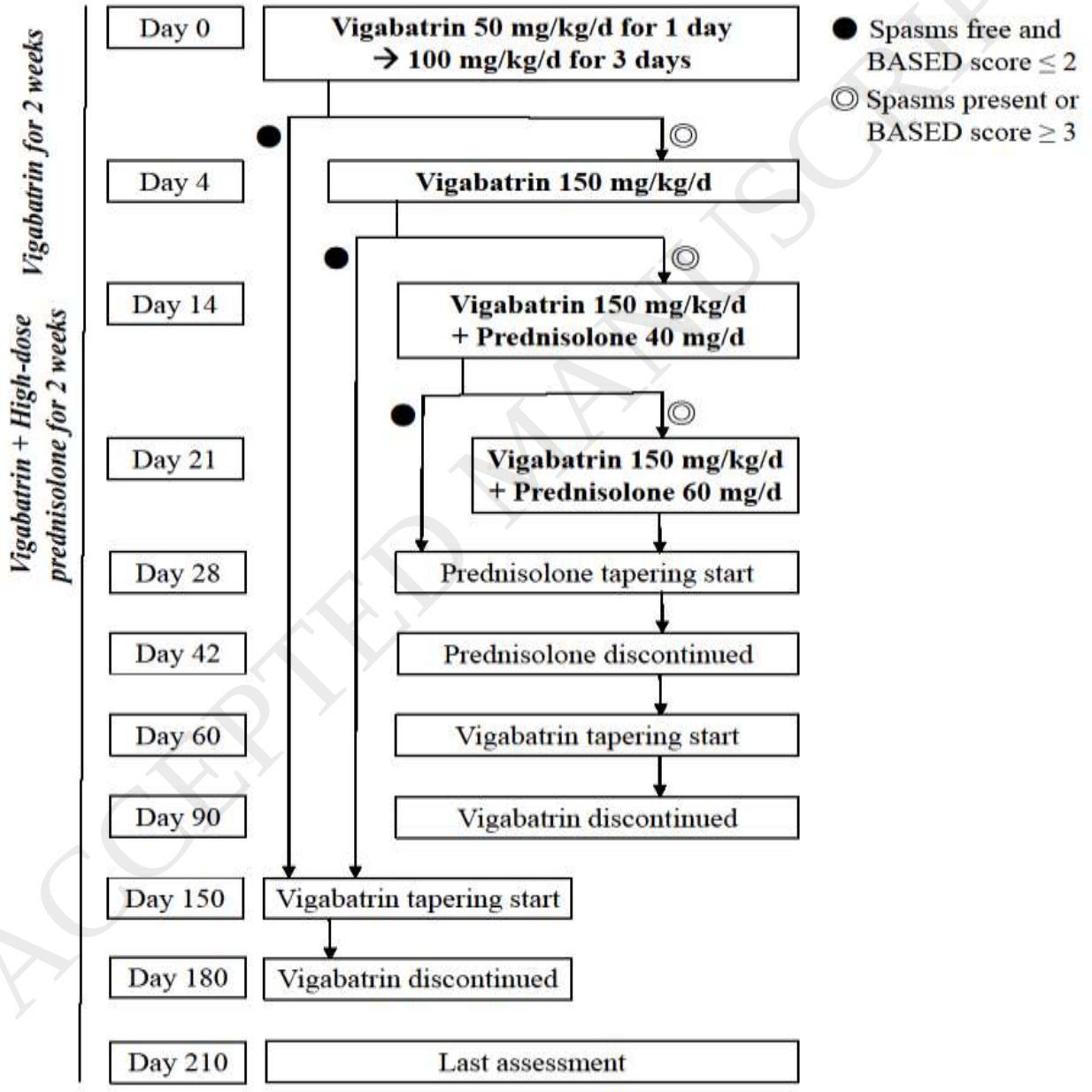
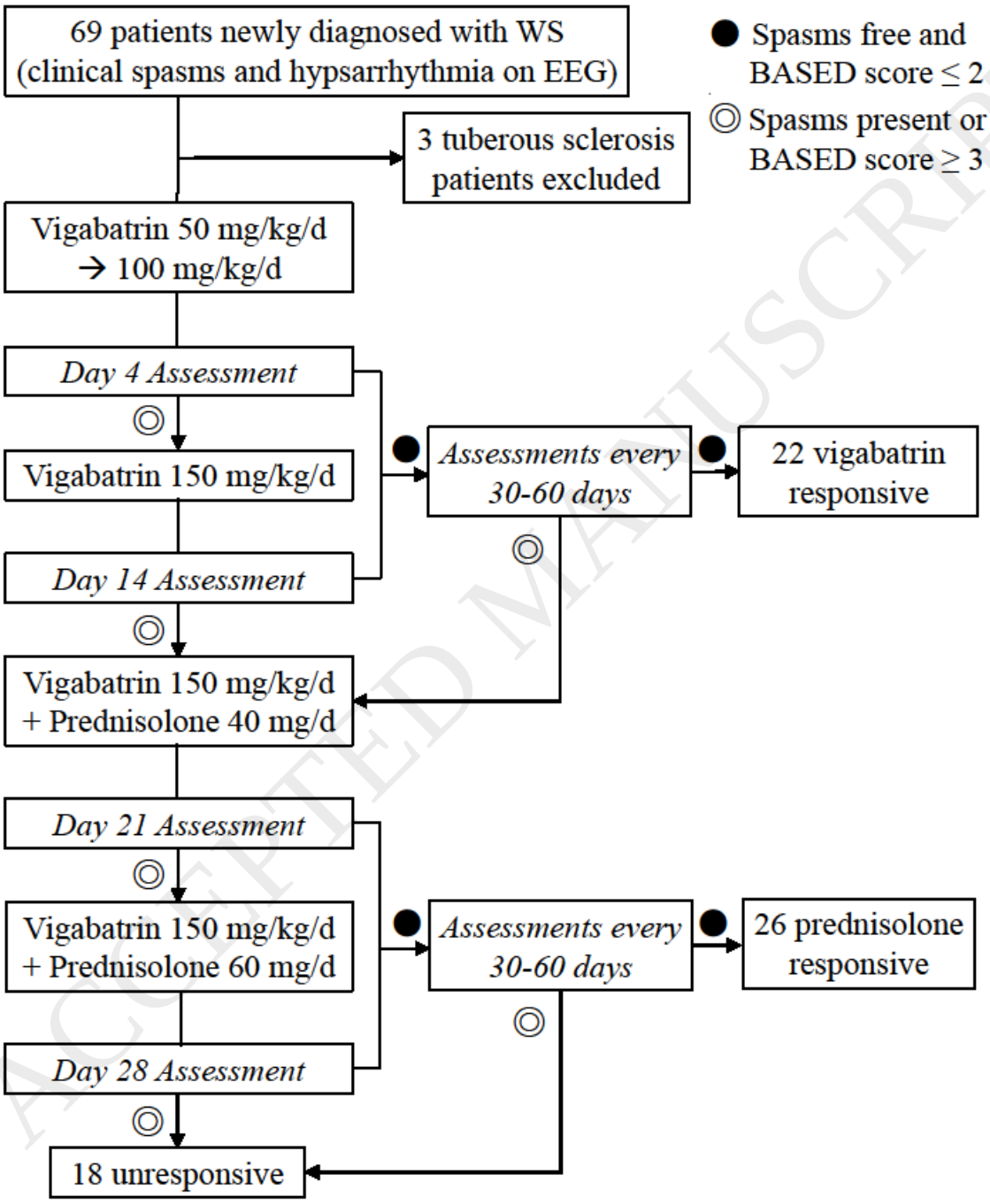


Figure 2. Outcomes of the vigabatrin and prednisolone treatment protocol.



Tables

Table 1. Burden of Amplitudes and Epileptiform Discharges (BASED) score

BASED score	**Description**
0	Normal
1	Non-epileptiform abnormality
2	< 3 spike foci and no background slow waves of ≥ 200 μV
3	Multifocal spikes in < 50% of one-second bins* and no background slow waves of ≥ 200 μV, or no multifocal spikes but background slow waves of ≥ 200 μV
4	Multifocal spikes in < 50% of one-second bins*, and background slow waves of ≥ 200 μV
5	Multifocal spikes in ≥ 50% of one-second bins*, or background slow waves of ≥ 300 μV in 2 or more head regions

Adapted from Mytinger et al.(Mytinger et al., 2015)

BASED scores, which range from 2 to 5, are based on the most severely abnormal five-minute epoch.

*The percentage of one-second bins that include one or more spikes

Table 2. Patients demographics and comparison of the clinical characteristics between responsive (including both vigabatrin- and prednisolone-responsive) patients and unresponsive patients.

	Total (n = 66)	**Responsive (n = 48)**	**Unresponsive (n = 18)**	***p***
Sex (male)	40 (60.6%)	31 (64.6%)	9 (50.0%)	0.280
Age at seizure onset (months)	5.7 (4.1-7.1)	5.7 (4.2-6.9)	3.7 (5.7-7.5)	0.746
Age at diagnosis/treatment (months)	6.6 (5.4-8.1)	6.4 (5.2-7.9)	7.6 (5.7-9.2)	0.150
Lead-time from seizure onset to treatment (days)	15 (7-48)	15 (7-33)	29 (9-107)	0.327
Etiology				0.388
Structural	20 (30.3%)	14 (29.2%)	6 (33.3%)	
Metabolic	2 (3.0%)	1 (2.1%)	1 (5.6%)	
Genetic	12 (18.2%)	7 (14.6%)	5 (27.8%)	
Unknown	32 (48.5%)	26 (54.2%)	6 (33.3%)	
Developmental function at diagnosis				
Mental age quotient	0.55 (0.01-0.78)	0.67 (0.38-0.86)	0.01 (0.01-0.24)	< 0.001
Psychomotor age quotient	0.57 (0.17-0.79)	0.68 (0.39-0.81)	0.01 (0.01-0.43)	< 0.001
Developmental function 6 months after treatment				
Mental age quotient	0.63 (0.23-0.83)	0.74 (0.60-0.86)	0.03 (0.01-0.35)	< 0.001
Psychomotor age quotient	0.67 (0.34-0.86)	0.76 (0.56-0.94)	0.06 (0.01-0.44)	< 0.001

Difference in mental/psychomotor age quotients after 6 months*				
Mental age quotient	0.00 (-0.02-0.16)	0.02 (-0.01-0.22)	0.00 (-0.05-0.01)	0.067
Psychomotor age quotient	0.00 (-0.06-0.22)	0.02 (-0.06-0.31)	0.00 (-0.07-0.02)	0.110

Data are expressed as number (percent) or median (interquartile range).

*Calculated as (mental or psychomotor age quotient 6 months after treatment) – (mental or psychomotor age at time of diagnosis).

Table 3. Adverse reactions observed after starting or increasing the dose of vigabatrin or prednisolone.

Existing adverse reactions due to previous medications are not included.

	Vigabatrin 100 mg/kg/day (n = 66)	**Vigabatrin 150 mg/kg/day (n = 58)**	**Prednisolone 40 mg/day (n = 44)**	**Prednisolone 60 mg/day (n = 29)**
Drowsiness	17 (25.8%)	2 (3.4%)	1 (2.3%)	-
Sleep disturbance	-	-	6 (13.6%)	2 (6.9%)
Irritability	1 (1.5%)	-	5 (11.4%)	9 (31.0%)
Increased appetite	-	-	18 (40.9%)	5 (17.2%)
Thrombocytosis	-	-	-	3 (10.3%)
Leukocytosis	-	-	-	1 (3.4%)
Infection	-	-	-	1 (3.4%)

Data are expressed as number (percent).