The short-term efficacy of combined hormone therapy in West syndrome

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SUMMARY

Background. Effective treatment protocols development for West syndrome (WS) is scientifically and economically significant.

Aim. To evaluate the comparative short term efficacy and tolerability of tetracosactide at a dose of 0.03–0.05 mg/kg and dexamethasone at a dose of 0.3–0.5 mg/kg both combined with valproate at a dose of 30–40 mg/kg/day for WS therapy. The regimen was: 1 injection daily for 10 days, following with 5 injections every other day, then 5 injections every two days, plus a valproate.

Material and Methods. 79 infants (Group 1) received tetracosactide, 18 infants (Group 2) – dexamethasone. The demographic data and the main characteristics of WS were similar in both groups.

Results. The efficacy of tetracosactide exceeded that of dexamethasone: there were more responders to therapy in Group 1: 92.4% vs 72% ($p = 0.0017$). Tetracosactide produced faster results: 50.5% of patients in Group 1 experienced cessation of infantile spasms within the first 5 days of therapy versus 38.7% of patients in Group 2; infantile spasms ceased in 34% of patients in Group 1 on day 6–10, versus 22.2% of patients in Group 2. 74.6% of patients in Group 1 experienced normalization of EEG on day 10, versus 33.3% of patients in Group 2 ($p = 0.04$). A higher percentage of patients treated with dexamethasone exhibited multiregional activity on EEG by day 10. Tolerability was similar in both groups. All adverse effects were of mild to moderate severity

Conclusion. Tetracosactide therapy in combination with average therapeutic doses of valproate proved to be more effective in treating WS than the combination of dexamethasone and valproate.

Key words: Infantile spasms · West syndrome · hormone therapy

BACKGROUND

West syndrome (WS) is one of the most common epileptic encephalopathies. While it affects predominantly infants with various cerebral disorders, it may also present itself in initially healthy children. The absence of adequate therapy which allows to arrest infantile spasms (IS) and hypsarrhythmia in most cases leads to an regression of psychomotor development and severe disabilities. Development of effective treatment protocols for WS is therefore an urgent matter of scientific and economic significance.

The attempts to develop effective treatment of WS has a long history and also connected with geographic peculiarities. For instance, in the USA and India, the adrenocorticotropic hormone (ACTH) has been the drug of first choice, whereas in Europe vigabatrin (VGB) was offered as first-line option alongside with ACTH and prednisone for initial therapy for IS that are symptomatic in etiology (Wheless et al., 2007). Recently treatment methods for WS have been under revision. Currently, preference is given to hormone therapy. The exception are IS in tuberous sclerosis, because of its unparalleled efficacy. It is generally accepted that hormone therapy versus VGB results in a higher rate of IS cessation and EEG normalization, as well as better other treatment outcomes, including cognitive improvement (Lux et al., 2004; Riikonen, 2014; Wilmshurst et al., 2015). Hormone therapy remains largely empirical. The drug choice of hormone type is often defined by its availability in different countries. In the USA the natural ACTH is used, whereas in Europe – its synthetic version, tetracosactide (Riikonen, 2014) is used. In some countries, ACTH or tetracosactide is not approved; therefore corticosteroids (prednisolone, hydrocortisone, and dexamethasone) are mainly used. The data on the efficacy and tolerability of corticosteroids versus ACTH are different (Arya et al., 2012; Go et al., 2012; Jones et al., 2015). Comparative trials on efficacy and tolerability of various hormone therapy protocols are limited. We have used the modified therapy protocol for treatment of WS, originally proposed by Prof. H. Siemes. The protocol included low doses of the hormones and therapeutic doses of valproate concurrently (Siemes, 1997). Despite the lack of any accurate evidence based on the efficacy of valproatefor the treatment of IS, it remains the drug of the first choice for the treatment of different seizure types and epilepsy syndromes.

AIM

The purpose of this study was to evaluate the short-term efficacy (cessation of IS and hypsarrhythmia) of both ACTH (Synacthen Depot) and dexamethasone when combined with sodium valproate (Depakine).

MATERIALS AND METHODS

Study design

A single center retrospective comparative observational study was used as it closely resembling routine clinical practice. The study population comprised 131 children aged between 2 and 18 months, followed at the Novosibirsk City Center for Epilepsy and the Novosibirsk City Neurology Center "Sibneiromed" between 1999 and 2009. Observation period in the study was approximately 45 days, with the majority of patients continuing follow up at the same facility for up to 10 years.

Study inclusion criteria:
1. 2–18 months of age.
2. Infantile spasms.
3. Hypsarrhythmia on interictal EEG.
4. Developmental delay or regression.

IS were characterized as brief severe axial muscles contractions (flexors, extensor, or mixed), lasting fractions of a second, in clusters (5 to 50 per cluster), with multiple clusters daily, often upon awakening. IS were either symmetric or asymmetric, with head and eye deviation, or only in one side of the body. In rare scenarios we observed only a brief upward eye deviation with typical for IS ictal EEG pattern (Engel, 2001).

Hypsarrhythmia was defined as "*…random high-voltage slow waves and spikes. These spikes vary from moment to moment, both in location and duration. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally, the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the petit mal variant type. … The abnormality is almost continual…*" (Gibbs and Gibbs, 1952). Hypsarrhythmia was either classical or modified, the latter of several types: synchronized, asymmetrical, with sustained regional pattern, high amplitude asynchronous, or with suppression-burst pattern. Hypsarrhythmia was diagnosed by EEG during wakefulness and sleep. We recorded bioelectrical brain activity and ECG simultaneously, using

Neurotravel and Encephalan-131-01 encephalographs. EEG results were evaluated by us.

According to the ILAE the classic triad of WS is rare. Due to early diagnosis and treatment, classical hypsarrhythmia is practically never found. Nowadays modified hypsarrhythmia or multiregional epileptiform discharges are more often registered. There are also some difficulties in defining regression in children who have developmental delay and early debut IS. Taking into consideration the fact mentioned above, when describing the syndrome, it is currently recommended to use the term "infantile spasms". The name "West syndrome" is used only in rare cases (Pavone et al., 2015; Howell et al., 2016). However, due to the retrospective nature of the study, we continue to use the historical term "West syndrome".

Exclusion criteria:
1. Atypical infantile spasms (IS with developmental retardation or regression without hypsarrhythmia, or hypsarrhythmia with developmental retardation without IS).
2. Absence of developmental delay or regression.
3. Use of antiepileptic drugs (AEDs) and/or hormones prior to the follow up.
4. Use of other AEDs, excluded valproic acid, and hormones (tetracosactide and dexamethasone).
5. Hypersensitivity to valproic acid or liver disease.
6. Presence of infection disease accompanied by fever at the start of therapy.
7. Acute or chronic progredient diseases of CNS and other systems that could potentially compromise therapy outcomes.
8. Non compliance.

97 out of 131 patients matched all inclusion and exclusion criteria. 34 patients were not included.

Treatment

None of the patients had previously received therapy. At the start of therapy, the majority of patients received a combination of oral sodium valproate and intramuscular injections of tetracosactide, while a minority of patients received a combination of oral sodium valproate and intramuscular injections of dexamethasone. 79 infants (Group 1), 53 males and 26 females, received synthetic ACTH, while 18 infants (Group 2), 13 males and 5 females, received dexamethasone. The hormone therapy choices were dictated by drug availability in the healthcare system.

All patients received standard doses. Sodium valproate (Depakene syrup, Sanofi, France) was administered at a daily dose of 30–40 mg/kg/d. The initial dose was 10 mg/kg/d, with a 10 mg/kg dose increase every second day according to H. Siemes treatment protocol. Tetracosactide (Synacthen Depot, Novartis, USA) therapy at a daily dose of 0.03–0.05 mg/kg or dexamethasone (Dexasone, Polfa, Poland) therapy at a daily dose of 0.3–0.5 mg/kg were administered intramuscularly, according to the following schedule: one injection daily for 10 days, followed by 5 alternate-day injections, followed by 5 injections every third day. Patients were concurrently administered diuretics on the days of hormone injections and received potassium, calcium and vitamin D daily. Other AEDs were not used.

All the patients were hospitalized for the whole period of hormone therapy and were under twenty-four hour observation. Counting of seizures was carried out by parents and medical staff.

Efficacy

Primary endpoints were:
1. Percentage of patients with IS cessation by day 5.
2. Percentage of patients with IS cessation by day 10/11.
3. Percentage of patients with cessation of hypsarrhythmia on EEG by day 10/11.

Secondary endpoints were:
1. Percentage of patients with IS cessation at hormone therapy completion.
2. Percentage of patients with ongoing IS at hormone therapy completion.
3. Percentage of patients with epileptic discharges in EEG by day 10/11.

Safety

Safety was assessed by recording spontaneously reported adverse events throughout the study. Additionally, hematology, blood chemistry panel, and ECG were performed every 10^{th} days during the first month of therapy. The presence of side effects was assessed according to records in patient clinical chart.

Data processing

Student's t-test for alternate groups and χ^2 test were used to determine statistical differences between the groups.

Study design limitations

The major limitation was concurrent administering

Table 1. Demographic data in treatment groups

	No. of patients	
	Group 1 (tetracosactide + valproate)	Group 2 (dexamethasone + valproate)
Total	79	18
Median age (months)	5.8	7.3
Male	53	13
Female	26	5
Male vs Female	2.04	2.6

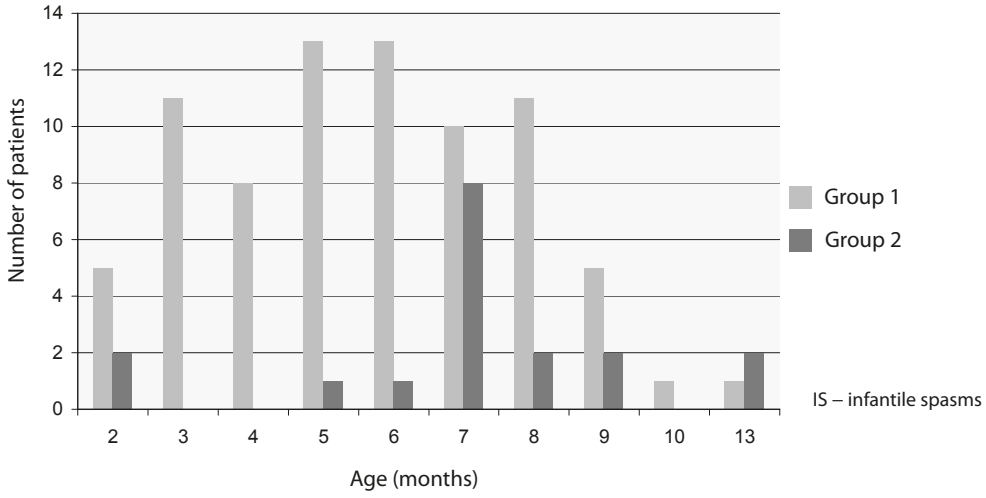

Figure 1. IS onset age

of valproate and hormones, because at the start of the study in 1999 this type of formula was common. However, the titration rate and the maximum valproate therapeutic dose of 30–40 mg/kg were identical in both study groups. We believe that it made it possible to assess the efficacy of tetracosactide versus dexamethasone. With concurrent administering of therapies, the difficulty lies in determining adverse effects. Definitely, video EEG monitoring is ideal for determining the number of seizures, as there may be hidden IS. Unfortunately, we did not have such a possibility at that time. Another design limitation was unequal numbers of patients in the groups due to the retrospective nature of the study. Also in this study it was possible to estimate only the short-term efficacy of this protocol.

Ethical Committee

Voluntary informed consent, approved by the Local Ethics Committee, was received for each patient.

RESULTS

Study groups

Overall, we provided initial treatment to 97 children with WS. The follow-up period lasted from one month to ten years. In the course of the study, patients were divided into 2 groups based on the type of hormone therapy.

Demographic data and medical history data are shown in Table 1.

The onset of IS in Group 1 occurred at the age range of 2–14 months, however, in the majority of cases onset occurring at 5–6 months; the onset of IS in Group 2 occurred at the same age range of 2–14 months, however, in the majority of cases onset occured at 7 months (Figure 1).

The description of epileptic syndrome by study group is shown in Table 2.

Tables 1 and 2 demonstrate that despite the unequal

Table 2. Description of epileptic syndrome in treatment groups

	Number of patients %	
	Group 1 (tetracosactide + valproate) n = 79	**Group 2 (dexamethasone + valproate) n = 18**
Epilepsy etiology		
Hypoxic Ischemic Neonatal Encephalopathy	51 (64.6%)	13 (72.2%)
Malformations of cerebral cortical development	11 (13.9%)	2 (11.1%)
Metabolic disorders	5 (6.3%)	0
Chromosomal disorders	2 (2.5%)	0
Neuroinfections	2 (2.5%)	0
Cerebral hemorrhage	1 (1.3)	1 (5.5%)
Cryptogenic IS	7 (8.9%)	2 (11.1%)
Spasm types		
Flexor IS	48 (60.7%)	12 (66.6%)
Extensor IS	12 (15.1%)	3 (16.6%)
Asymmetrical IS	4 (5.1%)	1 (5.5%)
Combination of IS	15 (18.9%)	2 (11.1%)
Clusters daily		
Up to 5	61 (77.2%)	15 (83.3%)
Up to 10	13 (16.5%)	1 (5.5%)
> 10	5 (6.3%)	2 (11.1%)
Spasms per cluster		
Up to 5	1 (1.2%)	0
Up to 10	46 (58.2%)	11 (61%)
Dozens	32 (40.5%)	7 (39%)
Hypsarrhythmia types		
classical	21 (26.6%)	3 (16.6%)
synchronized	17 (21.5%)	5 (28%)
asymmetric	5 (6.3%)	0
with a consistent focus	13 (16.4%)	3 (16.6%)
high amplitude asynchronous	4 (5.1%)	1 (5.5%)
suppression-burst pattern	16 (24.1%)	6 (33.3%)

IS = infantile spasms

numbers of patients in Group 1 and 2, the demographic data (age, gender) and the descriptions of epileptic syndrome (age at onset, types and frequency of IS, and hypsarrhythmia types) were similar in both groups.

Efficacy of hormone therapy

The results of hormone therapy are shown in Table 3. Thus, it can be seen from Table 3 that in most cases IS ceased during the first 5 days of hormone therapy. The protocol that included tetracosactide proved to be more effective for IS cessation. Also the disappearance of hypsarrhythmia is achieved in most cases during the first 10 days of hormone treatment. And herein the protocol included tetracosactide showed its greater efficacy. Epileptiform discharges on EEG (multiregional, focal and hypsarrhythmia) remained more often in patients of Group 2.

Tolerability

The data on adverse effects are summarized in Table 4. Appetite increase and weight gain are predictable and unpreventable adverse effects of hormone therapy, and were not taken into account in comparing tetracosactide versus dexamethasone. Treatment had no adverse effects in 32/79 (40.5%) of patients on tetracosactide, and in more than 50% of patients on dexamethasone: 10/18 (55.6%).

Most adverse effects were mild, occurring on the second week of hormone therapy, and did not require suspension or cessation of therapy.

Table 3. Efficacy of hormone therapy treatment groups

	Number of patients (%)	
	Group 1 (tetracosactide + valproate) n = 79	**Group 2 (dexamethasone + valproate) n = 18**
Cessation of IS		
First 5 days of therapy	40 (50.6%)	7 (38.7%)
Days 6–10	24 (34%)	4 (22.2%)
Days 11–30	9 (11.4%)	2 (11.1%)
IS ongoing		
	6 (7.6%) (p = 0.0017)	5 (28%) (p = 0.0017)
EEG on Days 10-11 of hormone therapy		
Without epileptiform discharges	59 (74.7%) (p = 0.4)	7 (38.9%) (p = 0.04)
Multiregional epileptiform discharges	1 (1.3%)	6 (33.3%)
Focal epileptiform discharges	14 (17.7)%	3 (16.7%)
Hypsarrhythmia	5 (6.%)	2 (11.1%)

IS = infantile spasms

Table 4. Adverse effects and their frequency in hormone therapy combined with valproates

	Number of patients (%)	
	Group 1 (tetracosactide + valproate) n = 79	**Group 2 (dexamethasone + valproate) n = 18**
Upper respiratory infections	21 (26.6%)	4 (22.2%)
Mucous membrane candidiasis	16 (20.2%)	1 (5.5%)
Hypopotassemia	12 (15.1%)	2 (11.1%)
Hypocalcemia	3 (3.8%)	1 (5.5%)
Thrombocytopenia	5 (6.3%)	0
Hyponatremia	0	1 (5.5%)

DISCUSSION

There is no single globally accepted treatment protocol for West syndrome. Epilepsy centers in different countries follow individual treatment protocols, varying in chosen medications, their doses and therapy duration. The common goal is to ensure cessation of IS and normalization of electroencephalograms. Similar therapy principles – start of treatment as soon as possible, minimal therapeutic dose of hormones with maximum efficacy – are widely used (Pellock et el., 2010; Riikonen, 2014). There are more data on efficacy and tolerability of natural ACTH and its synthetic analogue, tetracosactide (Synacthen Depot), in the treatment of IS, comparing with efficacy and tolerability of corticosteroids (Riikonen, 2014; Wilmshurst et al., 2015). However, effective doses of the biologically equivalent ACTH and tetracosactide vary from 0.2 mg in Japan to 0.6 mg in the USA. Frequency of ACTH or tetracosactide administration also varies: once daily or once every other day. There are no clear guidelines for therapy discontinuation: whether it should be gradual or immediate. Until recently, the general view was that the efficacy of tetracosactide is higher than that of corticosteroids (Pellock et el., 2010; Arya et al., 2012; Go et al., 2012; Riikonen, 2014; Shumiloff et al., 2013; Wilmshurst et al., 2015), while most recent research demonstrates higher efficacy of prednisolone versus tetracosactide (Wanigasinghe et al., 2015).

We compared two therapy protocols. In the first one, tetracosactide was administered together with gradually increased therapeutic doses of valproates, and in the second protocol, we administered dexamethasone. Titration and doses of valproate were identical in both groups, so we believe that it is possible to compare the efficacy and of tolerability of the two hormones. The efficacy of tetracosactide exceeded that of dexamethasone, i.e. the percentage of responders to therapy was significantly higher in Group 1: 92.4% vs 72% (p = 0.0017). Tetracosactide produced faster results in higher percentage of cases: 50.5% of patients in Group

1 experienced cessation of IS within the first 5 days of therapy versus 38.7% of patients in Group 2; IS ceased in 34% of patients in Group 1 (treated with tetracosactide) on days 6 through 10, versus 22.2% of patients in Group 2 (treated with dexamethasone). 74.6% of patients in Group 1 had normalization of EEG on day 10, versus 33.3% of patients in Group 2 ($p = 0.04$). A higher percentage of patients treated with dexamethasone exhibited multiregional activity in EEG by day 10. Both protocols of hormone therapy demonstrated similar tolerability in patients. All patients in both groups displayed increased appetite and weight gain. Other adverse effects were demonstrated in 50% of cases, most frequently, upper respiratory infections and mucous membrane candidiasis. All adverse effects were of mild and moderate severity, and did not require therapy discontinuation.

CONCLUSIONS

Tetracosactide (Synacthen Depot) therapy in combination with average therapeutic doses of valproates is more effective in treating WS than the combination of dexamethasone and valproate. Tetracosactide doses of 0.03–0.05 mg/kg daily according to the treatment protocol are effective and well tolerable. Adverse effects are predictable and easily amenable to correction. Tolerability is similar in both treatment protocols, with adverse effects that do not lead to the discontinuation of therapy. Presented protocol leads to quick cessation of IS and hypsarrhythmia, it lasts for 35 days. A doctor who chooses any of the protocols for hormonal treatment of IS can plan the duration of therapy, its cost, necessary exams and their frequency during treatment and concomitant therapy as well as the expected efficacy and tolerability of the protocol.

CONFLICT OF INTEREST DISCLOSURE

The authors have no conflict of interest to declare.

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