APPROACHES TO WEST SYNDROME TREATMENT: WHICH AEDs HELP BETTER?

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Abstract. The study analyzes the effectiveness of short-term and long-term treatment of West syndrome with the help of different antiepileptic drugs (AEDs) (combined therapy with the inclusion of Tetracosactide in comparison with nonhormonal antiepileptic drugs). The RR risk ratio was calculated using Review Manager 5.2 (http://community.cochrane.org). A complete absence of seizures was considered as a favorable outcome. 150 children with confirmed West syndrome who received treatment at A.Yu.Ratner Pediatic Clinical Hospital №8 (Kazan, Russian Federation) were included into a retrospective observational study. 90 children treated with Tetracosactide in combination with AEDs were included into Group I. Group II consisted of 60 children who received any AEDs except Tetracosactide. The results showed that the effectiveness of Tetracosactide with complete absence of seizures as favorable outcome with short-term observation (at least 6 months) is higher than after treatment with other antiepileptic drugs in the absence of difference in safety. Long-term results of treatment (complete clinical remission during three years or more) did not have a significant difference.

Keywords: West syndrome, Tetracosactide, antiepileptic drugs, epilepsy, effectiveness of treatment.

Introduction. In 2015 the International League Against Epilepsy stated that there are currently no recommendations for prescribing antiepileptic drugs for children in the first 3 years of life with epilepsy proved by evidence-based medicine on the level A. The incidence of epilepsy in early childhood is the highest of all age groups. The most common seizures in children during the first three years of life are epileptic spasms and febrile seizures [1]. The authors of the Cochrane review on the treatment of infantile spasms (2013) concluded that most of the available research on the therapy of infantile spasms was methodologically weak and had a high risk of biased results [2]. Based on their findings, the ILAE Commission of Pediatrics recommends the use of Adrenocorticotropic hormone (ACTH) for short-term control of epileptic spasms (level B recommendation), and oral steroids are probably effective in short-term control of spasms (level C recommendation) [1, 2].

Since 1958, adrenocorticotropic hormone therapy (ACTH) has been the preferred method for treating West syndrome [3]. At the same time, researchers refer to the presence of serious side effects in treatment with ACTH. In recent decades, a number of new antiepileptic drugs have been used in clinical practice for the treatment of West syndrome. Preliminary positive results of monotherapy or combined treatment of West syndrome with Lamotrigine, Felbamate, Levetiracetam, Zonisamide, and Topiramate were reported in non-randomized trials conducted primarily by the manufacturers themselves [4–6]. However, subsequent studies did not universally confirm the first positive reports on the high effectiveness of these drugs [7, 8].

Since 2009, the FDA has approved Vigabatrin as a drug for the treatment of infantile spasms in the United States. Outside the USA, a number of prospective studies have compared Vigabatrin with placebo or other methods of treatment [9] and demonstrated that Vigabatrin is effective in the treatment of infantile spasms in most cases regardless of etiology, but it is the most effective in patients with tuberous sclerosis. Vigabatrin, as a rule, was well tolerated. Nevertheless, its use is associated with loss of peripheral vision in some patients [10]. American researchers believe that in children with tuberous sclerosis, Vigabatrin should be considered as an initial therapy for infantile spasms [11]. This drug is a good alternative for patients with an inadequate response to ACTH, or in the presence of contraindications or intolerance to ACTH [12].

Since the first description of infantile spasms, at least 30 drugs for their treatment have been tried and described, but the issue of optimal treatment remains problematic due to the large variability of therapy, uncertain dosing regimens, adverse reactions, incomplete therapeutic response, and, consequently, poor long-term prognosis for psychomotor development and the subsequent development of other types of seizures [2].

West syndrome, especially its symptomatic variant, is the result of polyethiologic, severely affected brain lesions that occurred in the early stages of development. One of the main tasks in its therapy is to relieve the seizures as urgently and fully as possible, since it is the presence of seizures and hypsarrhythmia that adversely affects the development of cognitive and motor functions of a child [13]. Therefore, effective treatment of West syndrome would be considered a therapy that provides complete control of infantile spasms [14]. Currently, there is a large number of antiepileptic drugs and schemes of combination therapy recommended for the treatment of West syndrome. At the same time, none of existing antiepileptic drugs guarantees the onset of rapid and prolonged clinical remission. In addition, many antiepileptic drugs only reduce the number of seizures, without ensuring their complete suppression [15]. The choice of optimal treatment tactics still remains debatable. The effectiveness of various drugs used in the treatment of infantile spasms is also difficult to assess due to the short period of patient observation and the lack of information on long-term results [2]. In 2017, O'Callaghan et al. published a randomized multicenter open-label trial on the study of safety and efficacy of hormonal treatment versus hormonal treatment with Vigabatrin for infantile spasms, which demonstrated the benefit of combined hormone and Vigabatrine treatment compared to monotherapy with hormones.

However, the authors again evaluated the effectiveness of therapy only in the case of short-term follow-up: the maximum follow-up was 18 months [16].

The purpose of this study was to provide a comparative retrospective assessment of short-term and long-term outcomes of combined therapy with the inclusion of Tetracosactide in comparison with other antiepileptic drugs (AEDs) in West syndrome.

Materials and methods. We conducted a retrospective analysis of the pharmacotherapy in 150 children who received inpatient West syndrome treatment in 2000–2015 at A.Yu.Ratner Pediatric Clinical Hospital No. 8 (Kazan, Russia). The inclusion criteria: a) proved diagnosis of West syndrome, b) the presence of antiepileptic treatment (mono- or poly-therapy). The outpatient phase of the study was conducted at the Cabinet for the Diagnosis and Treatment of Epilepsy and Paroxysmal Conditions where the additional information was obtained on the catamnesis of children who were first diagnosed with West syndrome while at the hospital. Duration of observation: not less than 3.5 years. Average age of children: 4 – 14.5 years old. The onset of the disease: 60 children – at 6 months; 82 children – prior to 1 year; 8 children – after they turned 1 year old.

The work was performed within the frames of research on clinical neurology and epilepsy conducted at Kazan Federal University [17–20].

The research involved pharmacoepidemiological, analytical, and statistical methods. The results were processed using the Microsoft Excel program package. The risk ratios (RR) and their confidence intervals (CIs) were calculated using the Revman 5.0 Software program. A favorable outcome of the treatment was clinical remission (complete absence of seizures of any type). In the statistical processing of the results, differences at $p<0.05$ were considered reliable.

Results. In patients included into the study, 141 of 150 (94%) were diagnosed with a symptomatic West syndrome; 6% (9/150) had a cryptogenic variant of the West syndrome. The gender distribution of patients with West syndrome was somewhat dominated by boys: 93 (62%) male and 57 (38%) female children.

All children with West syndrome were divided into 2 groups. Group I (study group) included 90 children with West syndrome (60% of the total number of patients) who received Tetracosactide (a synthetic analog of ACTH; international non-proprietary name Synacthen Depot) for the reduction of infantile spasms in combination with other AEDs. Tetracosactide (Synacthen Depot) was administered intramuscularly in doses according to the manufacturer's instructions (https://www.rlsnet.ru/mnn_index_id_1193.htm).

The course of Tetracosactide injections was performed in patients either simultaneously with the onset of AED therapy (for example, with valproic acid preparations) or after inefficient use of various AEDs. In this case, therapy with valproate or other AEDs remained as supporting.

Group II (comparison group) included 60 children with West syndrome (40% of the total number of patients) who took AEDs, except Tetracosactide, as mono- or poly-therapy to relieve infantile spasms. The mono- and poly-therapy variants used in the treatment of West syndrome in children in groups I and II are presented in Table 1 and Table 2.

Table 1. Treatment options in Group I

Type of mono- and poly-therapy in group I (studies)	Number of patients, abs/n (%)
VA*, Tetracosactide	76 (85%)
VA, Topiramate, Tetracosactide	7 (8%)
VA, Carbamazepine, Tetracosactide	3 (3%)
VA, Levetiracetam, Tetracosactide	1 (1%)
VA, Levetiracetam, Topiramate, Tetracosactide	1 (1%)
VA, Ethosuximide, Tetracosactide	1 (1%)
VA, Carbamazepine, Levetiracetam, Vigabatrin, Tetracosactide	1 (1%)

* VA – Valproic acid

Table 2. Treatment options in Group II

Type of mono- and poly-therapy in Group II	Number of patients, abs/n=60 (%)
Valproic acid	24 (40%)
Topiramate	1 (2%)
VA*, Succinamide	2 (3%)
VA, Carbamazepine	1 (2%)
VA, Topiramate	9 (15%)
VA, Benzodiazepine	2 (3%)
VA, Levetiracetam	2 (3%)
VA, barbiturates	3 (5%)
VA, 2 or more antiepileptic drugs	16 (27%)

* VA – Valproic acid

All patients in both groups were comparable in age, sex, neurological status, gestational age at birth, and severity of the disease.

A comparative analysis of the remission onset from the start of treatment in the two study groups showed that significantly faster complete remission was achieved when introducing Tetracosactide in patients with West syndrome.

After 2 weeks of Tetracosactide treatment, seizures in 68 patients (76% of the total number of patients) stopped. In Group II, only 1 patient (4% of the total number of patients) had a favorable outcome. When comparing risk ratio parameters, the effectiveness of Tetracosactide 2 weeks from the start of treatment in Group I is significantly higher than in Group II, RR=45.33; 95% CI [6.47–317.71], p=0.0001.

Further, response to therapy (2 months from the start of treatment) was also better in children receiving Tetracosactide: 69 of 90 patients (77%) achieved clinical remission in Group I and only 13 of 60 patients (22%) had a favorable outcome (absence of epileptic seizures) in Group II, RR=3.54; 95% CI [2.16–5.8], p<0.00001. Similarly, we calculated the risk ratio (the number of patients with full remission) 6 months later: 69 of 90 (77%) in Group I, 36 of 60 (60%) in Group II, RR=1.28 95% CI [1.01–1.62]; p=0.04.

In children with West syndrome in Group II (comparison group), the time to remission was more uncertain and the number of patients in remission reached the same level as in Group I only 1 year after treatment: 71 of 90 (79%) in Group I, 43 of 60 patients (72%) in Group II, RR=1.10 95% CI [0.91–1.33]; p=0.33. In the analysis of long-term outcomes (with complete clinical remission after 3 years considered the favorable outcome), the number of patients without seizures also did not differ statistically in the two groups: 62 of 90 patients (69%) in Group I and 37 of 60 patients (62%) in Group II, RR=1.12; 95% CI [0.88–1.42], p=0.75.

Analysis of undesirable drug reactions in the treatment with antiepileptic drugs in both groups showed the following: in Group I, 26 of 90 children (29%) had various side effects during the period of the treatment with Tetracosactide. The most common complaints were anxiety, crying (19 out of 90, 21%), Cushing's syndrome (6 out of 90, 7%), and weakness and drowsiness (5 out of 90, 6%).

A single child (1/90; 1%) manifested meningoencephalitis during the treatment with Tetracosactide. However, in the catamnesis, we did not observe any residual phenomena. In Group II, adverse events were reported in 11 of 60 patients (18%). The spectrum of side effects in the treatment of certain AEDs recorded in the treatment of children in the second group is presented in Table 3.

Table 3. Side effects of AEDs in Group II (comparison group)

AED	Side effects	Number of patients who had side effects/number of patients taking this AED (%)
Valproic acid	Abdominal pain, nausea, vomiting, drowsiness, allergic reactions	10/59 (17%)
Levetiracetam	Expressed anxiety, crying	2/3 (33%)
Topiramate	Refusal to eat, weight loss, inhibition, drowsiness, severe anxiety, sleep disturbance, increased salivation	6/11 (55%)
Clonazepam	Lethargy, drowsiness, excessive drooling	4/5 (80%)
Carbamazepine	Allergic reaction, drowsiness, vomiting, respiratory disorders, sleep disorders, increased excitability	5/8 (63%)

Discussion. We calculated the risk ratios in Group I and Group II where the indicator was an unfavorable outcome: the number of patients with side effects. Risk Ratio RR=1.58; 95% CI [0.84–1.58], (p=0.15) indicates that there is no reliable difference between these groups with respect to AED safety.

The literature mentions the marked adverse reactions observed in the treatment of ACTH, such as fulminant infection, immunosuppression, arterial hypertension [21]. However, in this group of children, such severe reactions were not observed when introducing Tetracosactide into the regimen. This can be explained by the fact that the minimum doses of Tetracosactide recommended in the instructions for the drug were used for treatment.

Despite the fact that the long-term results of therapy of children with West syndrome with inclusion of Tetracosactide in the regimen of therapy do not differ from the results of the use of antiepileptic drugs without the use of Tetracosactide, rapid cessation of seizures (within the first two weeks after the start of treatment) and their complete absence during 1 year from the start of treatment in most patients with Tetracosactide treatment has a great importance for the psychomotor development of the patients.

The results obtained make it possible to determine the tactics for treating patients with West syndrome. The principal property of the therapeutic agent that determines the long-term prognosis for the development of cognitive and motor functions in children with West syndrome is a rapid and complete control of seizures and inhibition of hypsarrhythmia on the EEG, which provides the introduction of adrenocorticotropic hormone into the treatment regimen of these patients. The cessation of infantile spasms almost immediately after the introduction of Tetracosactide into the treatment regimen allows early rehabilitation of these children, reduces the severity of cognitive and motor

disorders, reduces the need for antiepileptic drugs in poly-therapy, and, as a result, the risk of a large number of unwanted drug reactions.

Conclusion. A comparative analysis of the treatment effectiveness in two groups (Group I with the use of Tetracosactide and Group II without the use of Tetracosactide) showed that the effectiveness of Tetracosactide (with complete absence of seizures as favorable outcome) with short-term observation (at least 6 months) is higher than when treated with other antiepileptic drugs in the absence of difference in safety; and with long-term follow-up (three years or more), the effectiveness of Tetracosactide is comparable to that of other antiepileptic drugs.

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