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Research Article

Possibilities of Topiromat in the Treatment of Tics in Children

Zykov VP*, Kashirina EA and Naugolnyh Yu V

Russian Medical Academy of Postgraduate Continuous Education, Moscow, Russia

***Corresponding Author**: Zykov VP, Russian Medical Academy of Postgraduate Continuous Education, Moscow, Russia.

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Abstract

Objective: To evaluate the efficacy of topiramate at a dose of 1–2 mg/kg in 34 patients aged 7–17 with tic hyperkinesis and Tourette syndrome (TS).

Materials and Methods: We performed clinical evaluation of hyperkinesis severity along with the assessment of somatosensory evoked potentials (SSEP) and the analysis of surface electromyography (EMG) data prior to treatment initiation and after 6 weeks of therapy. SSEP investigation was carried out in accordance with a standard protocol. Interpeak latencies on the tracks Cp–Fpz (D, S), Cerv6–Fpz (D, S), Erb'i–Erb'c (D, S) were evaluated in order to determine the afferentation between relevant brain structures: N9–N13, N13–N20, N9–N20. N20–P23 potentials reflected primary activity of somatosensory cortex. The investigation of tic hyperkinesis was conducted using surface EMG of facial muscles (m. orbicularis oculi), the muscles of the shoulder girdle (m. supraspinatus), and the muscles of the upper extremities (m. flexor digitorum superficialis) according to the standard protocol. Interference curve was recorded at rest and after hyperkinesis stimulation with the use of provocative tests. High-amplitude (more than 500 mkV) oscillations were considered as burst activity. The severity of clinical manifestations was evaluated using the Yale Global Tic Severity Scale (1989) and the method of tics counting during 20 minutes (V.P. Zykov, 2009). The control group comprised 15 healthy children matched for sex and age

Results: The use of topiramate in patients with chronic motor/vocal tics and TS has significantly decreased the severity of hyperkinesis manifestations, evaluated both by the Yale Global Tic Severity Scale ($p < 0,05$) and by the method of tics counting during 20 minutes ($p < 0,05$). It also helped to decrease the prevalence of burst activity in EMG while registering hyperkinesis in different muscle groups. SSEP data showed the normalization of interpeak latency values and the decrease of N20–P23 potentials amplitude, which reflects the decline in the activity of brain somatosensory system, represented by thalamo-cortical structures. Conclusion. Surface EMG and SSEP methods can be used for evaluation of treatment efficacy in cases of tic hyperkinesis and TS.

Keywords: *Tic Hyperkinesis; Tourette Syndrome; Yale Global Scale; Somatosensory Evoked Potentials; Surface Electromyography; Topiramate*

Rationale

Tics are the predominant form of hyperkinesis in children. Their prevalence in children is up to 6% [7,8,10,12], with chronic forms diagnosed in 1% of the population, combined with learning violations, anxiety, attention deficit disorder [9]. Chronic tics are known to be transformed into Tourette syndrome [8,16].

One of the most difficult issues is the pharmacological correction of tic hyperkinesis [11]. The pathogenesis of hyperkinetic syndromes is based probably on disturbances in the metabolism of basal ganglia neurotransmitters, in particular, in dopamine reception

disturbances and in frontostrial dysregulation [2]. This is manifested by the GABAergic (the principal central nervous system inhibitor) activation and glutamatergic (the main central nervous system activator) blockade [13-15]. The tic controlling drugs act principally by the dopaminergic metabolism activation, in particular, by postsynaptic D-receptors blocking. Topiramate activates the metabolism of GABA (gamma-aminobutyric acid), the main inhibitory mediator of the neural system [17]. The drug also inhibits the glutamate (main excitatory neurotransmitter) action. Topiramate blocks the voltage-gated Na- and Ca-channels, thus inactivating two main glutamate receptors: cainate (affine to cainate acid) and AMPA (affine to alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) responsible for the synaptic system excitation [13-15].

The efficacy is not studied of topiramate use in the tics treatment in the Russian pediatric population with a surface electromyographic assessment of the clinical change of hyperkinesis.

In the literature we have found only a few studies of evoked potential in childhood. Zykov V.P. and Safonov D.A. (2009) diagnosed the cerebral visual disturbances in patients with early childhood epilepsy by the visual evoked potential (VEP) with the latency lengthening and the main component P100 amplitude reduction, a prognostic criterion of the severe symptomatic epilepsy in young children [5].

Several authors have studied the muscles bioelectric activity in tic hyperkinesis in children by surface electromyography (EMG). Shanko G.G. (1990) and Zykov V.P., Malyshev Y.I. (2002) provided EMG data on the firing activity in tics. Firing activity is formed by the pulses flow from cortical and subcortical structures to the spinal motoneurons (Yusevich Yu.S., 1958, 1972, Bilyk V.D., 1964. 1972) [1].

The combination of surface electromyography and somatosensory evoked potentials will objectify the hyperkinesis and test the thalamocortical interactions in tics and Tourette syndrome.

Aim

To test the clinical efficacy of topiramate in patients with tics and Tourette syndrome.

Materials and Methods

Totally 34 patients with tic hyperkinesis were studied, aged from 6 to 17 years. Chronic motor or vocal tics were found in 22 subjects, 12 subjects were diagnosed with Tourette syndrome according to DSM-IV and Tourette Syndrome Classification Study Group recommendations, 1993. Topiramate therapy was performed in 30 patients (10 patients with Tourette syndrome and 20 patients with chronic motor or vocal tics). The Yale Global Tic Severity Scale assessed the clinical severity with the determination of total and combined tic severity [18], and also by 20-minute tics self-counting [7]. The control group comprised 15 healthy children of comparable sex and age. Somatosensory evoked potential (SSEP) were studied with Skybox Neuro-MVP-5 (from Neurosoft, Ivanovo, Russia) by the standard technique. On Cp-Fpz (D. S), Cerv6-Fpz (D, S), and Erb'i-Erb'c (D, S) routes, the inter-peak latencies were evaluated to determine the time of afferent signal conduction between the corresponding brain structures: N9-N13 (pulse propagation time from Erb's point to trunk), N13-N20 (pulse propagation time from the lower brainstem to the cortex), N9-N20 (pulse propagation time from Erb's point to the cortex). N20-P23 potentials reflected the primary activation of the somatosensory cortex [3,4]. The 2.5-30 ms inter-peak latencies elongation from normal values was considered pathological reflecting the delay of impulse conduction between the corresponding nervous structures [3]. For example, elongation of inter-peak latency N13-N20 was interpreted as a delay between the caudal parts of the brainstem and the cortex.

The study of tic hyperkinesis was carried out using the method of surface electromyography (EMG) from facial muscles (m. orbicularis oculi), the thoracic girdle muscles (m. supraspinatus), upper limb muscles (m. flexor digitorum superficialis) by the standard technique [4]. The interference curve was recorded in the EMG interference mode: the rest mode and the functional tests mode with hyperkinesis

stimulation by 10 blinks and 10 finger flexions/extensions test (Zykov V.P.) [7]. Firing activity was noted when high-amplitude curve flares of over 500 μV intensity were recorded. The duration of the firing activity did not exceed 100 msec (Gonce M., 1986) [19].

To correct tics, topiramate was used to influence the tic hyperkinesis development. SSEP and surface EMG parameters were recorded twice: before the treatment and after the 6 weeks of the treatment.

Results and Discussion

Tics were represented by various motor and vocal hyperkineses (Table 1).

Semiotics of tics	Tourette syndrome, %	Chronic motor or vocal tics, %
Blinking	65%	80%
Eye squeeze	34%	50%
Opening the mouth with the mandibular advancement	50%	55%
Head lag	15%	20%
Head turns to the side	35%	
Shoulder movement	80%	65%
Lateral arm throwing, flexion and extension of hand and fingers	80%	14%
Startling	28%	20%
Bouncing, squatting	15%	-
Ritual gestures	6%	-
Abdominal muscle contraction	60%	10%
Sniffing	60%	75%
Coughing	65%	80%
Pronunciation of vowel sounds	20%	40%
Echolalia	5%	-
Coprolalia	2%	-

Table 1

In all subjects, tic hyperkinesis had a long course with periods of exacerbation and partial remission. Yale Global Tic Severity Scale estimates the signs score 70.7 ± 10.5 points (0-100 points) in patients with Tourette syndrome and the corresponding 20-minute (Zykov V.P., 2009) motor tics score of 130.8 ± 45.5 episodes and vocal score of 80.3 ± 25.8 episodes. Patients with chronic motor or vocal tics scored 40.5 ± 8.7 (0-100) points on Yale Global Tic Severity Scale, with 20-minute tics counting of 85.5 ± 25.7 motor hyperkineses and 56.7 ± 18.9 vocal tics.

In the SSEP with the inter-peak latencies study (Figure 1), a significant lengthening was found of the pulse propagation (ms) along the N13-N20 route in chronic motor or vocal tics patients to 9.8 ± 2.3 ms (5.3 ± 0.3, $p<0.05$ with the control group) and in Tourette syndrome patients to 15.1 ± 2.2 ms (5.3 ± 0.3, $p<0.01$ with the control group).

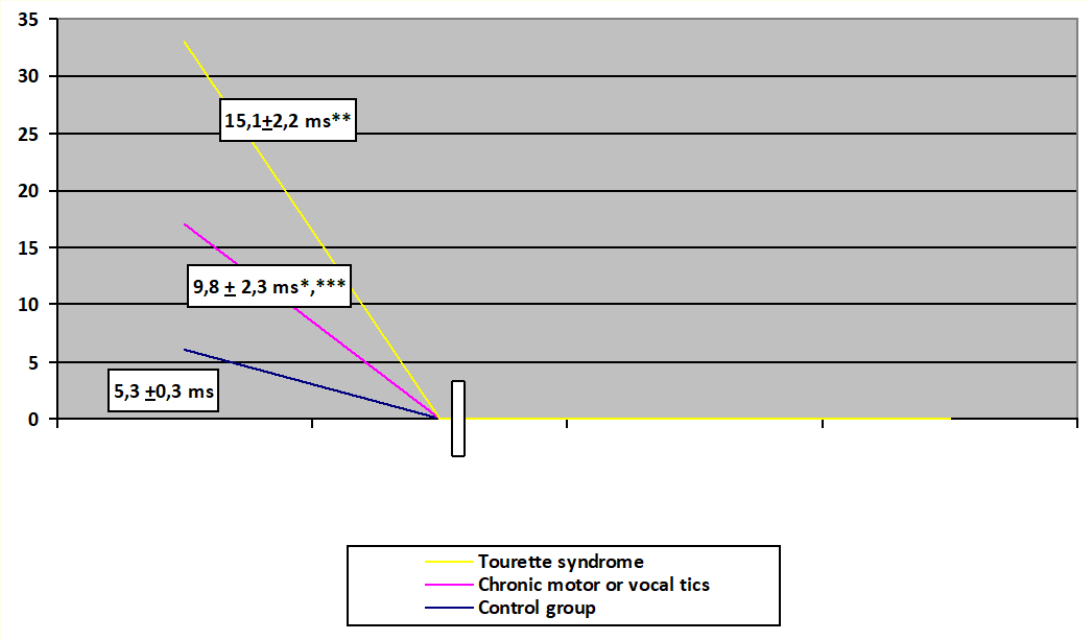

Figure 1: *N13-N20 inter-peak latencies (caused by somatosensory evoked potential) in patients with chronic motor or vocal tics and Tourette syndrome.*
*<0.05 vs. control group; ** p <0.01 vs. control group.*

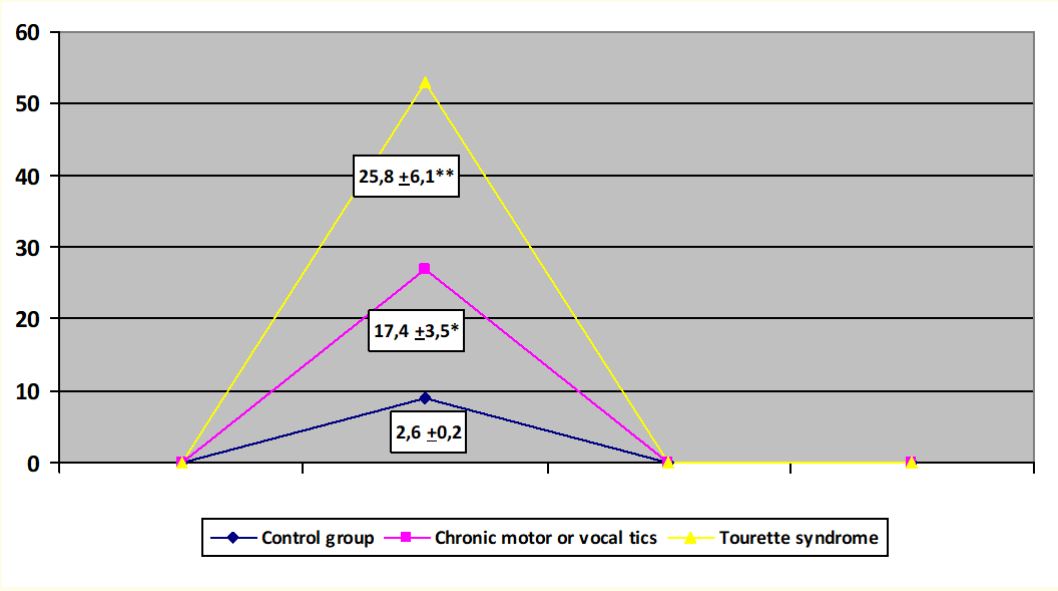

Figure 2: *Amplitude of the somatosensory cortex (somatosensory evoked potentials).*
**p<0.01 vs. control; **p<0.001 vs. control.*

The N20-P23 amplitude (μV) showed a significant activation of the somatosensory cortical zone (Figure 2) from 2.6 ± 0.2 μV in the control group to 17.4 ± 3.5 μV ($p < 0.01$) in patients with motor or vocal tics and to 25.8 ± 6.1 μV in patients with Tourette syndrome ($p<0.001$). Maximum values were recorded in Tourette syndrome ($p<0.05$).

The N20-P23 potential amplitude (25.8 ± 6.1 μV) in patients with Tourette syndrome correlated ($p<0.004$) with Yale Global Tic Severity Scale (70.5 ± 10.5 points of combined motor and vocal tics severity).

Tic hyperkinesis was recorded by surface electromyography as firing activity (high-amplitude curve flashes) in several samples. Table 2 shows the firing activity (μV) amplitude change at the surface electromyography from different muscle groups at Tourette syndrome and chronic motor or vocal tics.

Muscle groups EMG, interference mode	Tourette syndrome (TS), amplitude, μV	Chronic motor or vocal tics (CMV), Amplitude, μV	Indices in the control group (amplitude, μV)	Reliability (p value<)
EMG interference mode (rest mode), m. Flexor Digitorum Superficialis	1624.5 ± 108.3 μV* (duration 75.3 ± 0.6 ms)	992.5 ± 219μV** (79.3 ± 4.4)	122.7 ± 47.82 μV	*p<0.001 (TS vs. control group) **p<0.01 (CMV vs. control group)
EMG interference mode with functional tests m. Flexor Digitorum Superficialis	2150.3 ± 315.4 μV* (duration 95.6 ± 15.4 ms)	1334.7 ± 56.5 μV** (duration 55.9 ms)	550.4 ± 78.9 μV	*p<0.001 (TS vs. control group) **p<0.001 (CMV vs. control group)
EMG interference mode (rest mode), m. Supraspinatus	138289.5μV* (49.9 ± 5.5 ms)	1099 ± 115μV** (duration 55.6 ± 10.5 ms)	122.7 ± 47.82 μV	*p<0.001 (TS vs. control group) **p<0.001 (CMV vs. control group)
EMG interference mode with functional tests m. Supraspinatus	2010.5 ± 66.4 μV* (duration 78.3 ± 0.7 ms)	1678.3 ± 66.4 μB** (duration 88.4 ± 34.3 ms)	550.4 ± 78.9 μV	*p<0.001 (TS vs. control group) **p<0.001 (CMV vs. control group)

Table 2

The firing activity (μV) amplitude change at the surface electromyography from different muscle groups at Tourette syndrome and chronic motor or vocal tics before the treatment.

The amplitude of the firing activity was maximal in the Tourette syndrome group ($p<0.05$). The spontaneous firing activity was found from common surface digital flexor in patients with motor or vocal tics (991.4 ± 37.6 μV) and in patients with Tourette syndrome (1138.7 ± 44.1 μV). A similar trend was observed when recording surface EMG with m. orbicularis oculi in interference samples at rest and in provocative tests with the greatest manifestation in patients with Tourette syndrome.

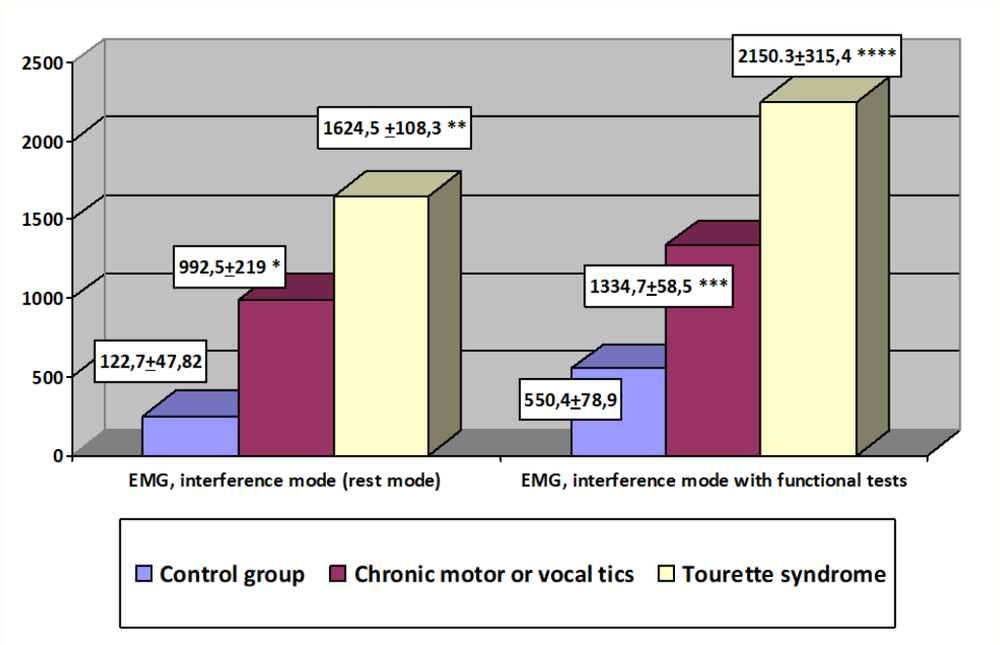

Figure 3: *EMG, interference mode: m. flexor digitorum superficialis on the right; sleep mode and functional tests in patients with chronic motor or vocal tics and Tourette syndrome.*

**p<0.01 vs. control group; **p<0.001 vs. control group in the EMG interference mode (rest mode)*

****p<0.001 vs. control group; ****p<0.001 vs. control group in the EMG interference mode with functional tests (amplitude of volley activity, μV)*

Topiramate induced positive changes in the form of a clinical reduction of tic hyperkinesis according to Yale Global Tic Severity Scale in children with chronic motor or vocal tics and Tourette syndrome (Figure 4) correlated to the 20-minute tics self-counting.

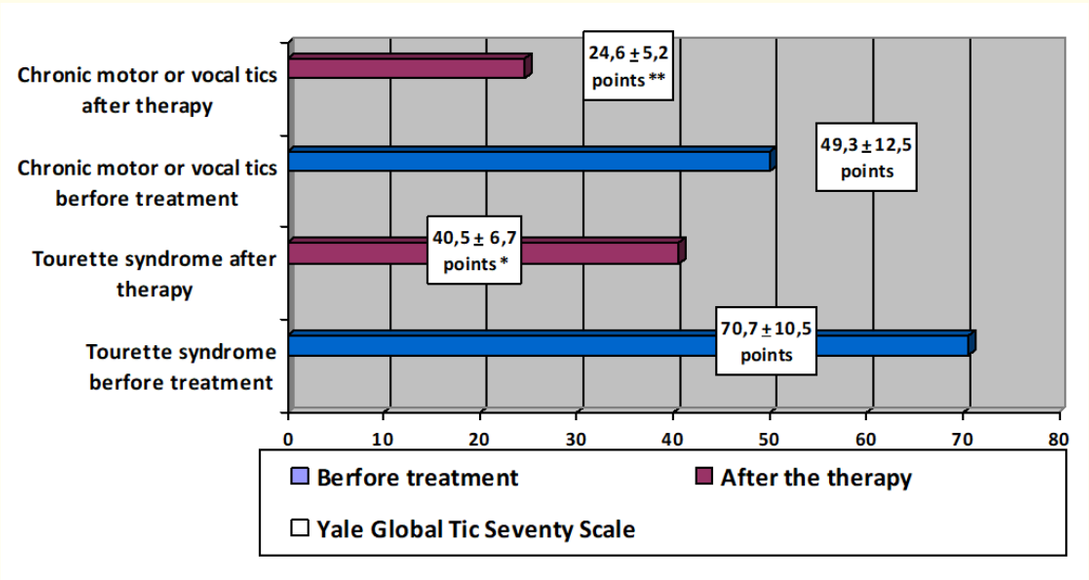

Figure 4: *Clinical changes of tics by Yale Global Tic Severity Scale on the background of topiramate therapy*

**p <0.05, clinical assessment according to Yale Global Tic Severity Scale in patients with Tourette syndrome after the therapy.*

***p <0.05, clinical assessment according to Yale Global Tic Severity Scale in patients with chronic motor or vocal tics after the therapy.*

Figure 5 shows the evoked somatosensory evoked potential change against the topiramate treatment. Both in motor or vocal tics and in Tourette syndrome groups, a significant normalization was found of inter-peak latencies (ms). A significant decrease in amplitude (μV) was found in children with chronic motor or vocal tics. Patients with Tourette syndrome had no significant changes in the somatosensory cortical amplitude.

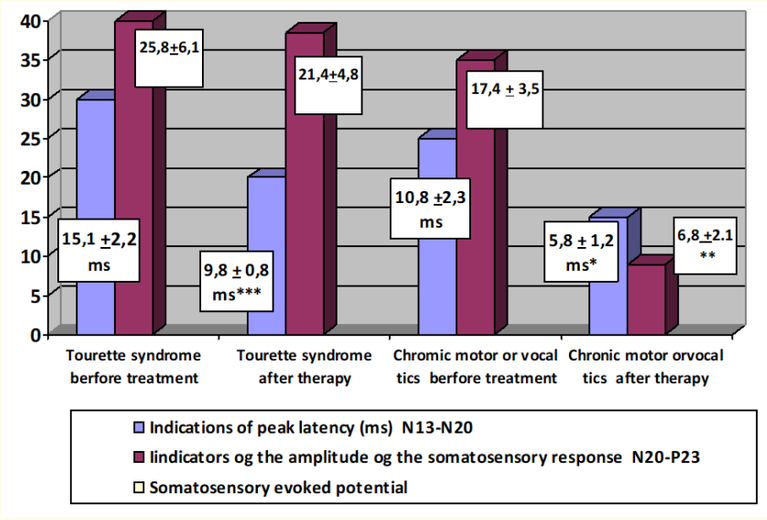

Figure 5: *The somatosensory evoked potential change against the topiramate treatment.*
**p<0.05; **p<0.01, somatosensory evoked potentials before and after the treatment of the tic patients;*
****p<0.05, somatosensory evoked potential before and after the treatment in the Tourette syndrome patients.*

Topiramate reduced significantly the severity of tic hyperkinesis reflected in the firing activity in the surface EMG in interference mode (rest mode) and in the functional tests with m. flexor digitorum superficialis (Figure 6). A similar pattern was observed in the study using surface EMG of other muscle groups (m. orbicularis oculi and m. supraspinatus).

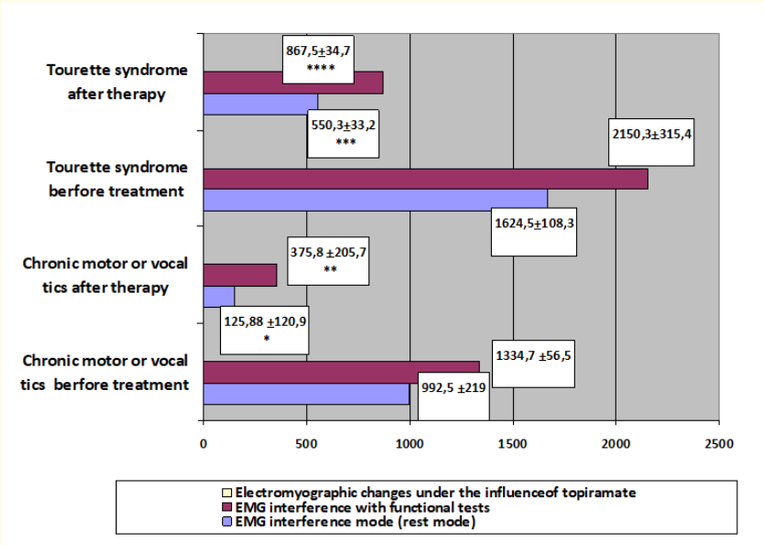

Figure 6: *Surface electromyographic changes in m. flexor digitorum superficialis under the influence of topiramate in children with chronic motor or vocal ticks and Tourette syndrome.*
**p<0.05 between the EMG interference mode at rest before and after the topiramate treatment in children with chronic motor or vocal ticks.*
**p<0.01 between the EMG interference mode with the functional tests before and after the topiramate treatment in children with motor or vocal ticks.*
**p<0.01 between the EMG interference mode at rest before and after the topiramate treatment in children with Tourette syndrome.*
**p<0.01 between the EMG interference mode with the functional tests before and after the topiramate treatment in children with Tourette syndrome.*

The results of topiramate therapy were studied 6 months after the start. At this point, a positive effect of treatment was noted in 50% of the patients (n=8) and an increase in tics in the shoulder and facial muscles was also noted in other 50% of the patients (n=8) reflected by total tics count and YGTSS: 41.12 ± 54.88 motor tics and 29.5 ± 50.56 vocal tics in 20 minutes, corresponding to 25.25 ± 11.7 total and 44.87 ± 22.83 combined severity points on the YGTSS scale. The number of tics increase in the patients 6 months after the therapy coincided with the firing activity in facial, shoulder, and upper limb muscles and with the sensorimotor response amplitude.

However, the background bioelectrical activity amplitude decreased in the facial and shoulder muscles and the firing amplitude decreased significantly in the facial muscles ($p<0.01$, $p<0.05$) compared to the initial data before the course of therapy.

Thus, topiramate reduced the clinical manifestations of tic hyperkinesis in patients with chronic motor or vocal tics and Tourette syndrome by Yale Global Tic Severity Scale and by 20-minute tics counting.

In patients with chronic motor-vocal tics and Tourette syndrome, topiramate reduced significantly the firing activity from different muscle groups, according to surface EMG. Maximal effect was recorded in patients with chronic motor or vocal tics.

Topiramate normalized the inter-peak latencies and amplitude parameters in the study of somatosensory evoked potential in patients with chronic motor or vocal tics and Tourette syndrome. Maximal effect was also recorded in patients with chronic motor or vocal tics.

Conclusion

Our study showed that 6 months of the 1-2 mg/kg topiramate therapy did not induce a complete regression of tic hyperkinesis in 50% of the patients. Loss of the effect of the initial dose suggests the average daily topiramate dose increase, requiring an additional research.

To assess the tic and Tourette syndrome therapy effect, surface electromyography and somatosensory evoked potentials can be recommended.

Our study shows the effectiveness of topiramate in the treatment of tics and Tourette's syndrome in children in the Russian population.

On the background of treatment with topiramate, a significant decrease in the clinical manifestations of TIC hyperkinesis and a decrease in the AML amplitude of volley discharges on EMG coinciding with the clinical manifestations of tics was registered. The decrease in the amplitude of the sensorimotor response of BSSP led to regression of clinical and Electromyographic parameters in patients with tics.

So, patients with chronic motor and vocal tics, patients with Tourette's syndrome had a positive clinical dynamics in the form of reducing the TIC hyperkinesis on a scale of severity of tics YGTSS ($p<0.05$) that correlated with the method of counting ticks at 20 minutes ($p<0.05$) after 6 weeks of treatment.

Reduction of clinical manifestations of ticose hypecrinesis in patients with tics coincided with the data of Electromyographic study. There was a significant ($p<0.01$, $p<0.05$) decrease in the amplitude of volley activity of the studied muscle groups (flashes of the high amplitude curve) in various EMG regimes against the background of topiramate use in patients with motor-vocal tics and in patients with Tourette's syndrome.

Against the background of topiramate therapy, a significant decrease in the amplitude parameters of the sensorimotor response was revealed in the study of the somatosensory caused potentials in patients with chronic motor-vocal tics ($p<0.01$) and not significant – in patients with Tourette's syndrome.

We observed 16 patients with tics who received topiramate for 6 months. No positive clinical dynamics was observed in 8 patients (Tourette's syndrome – 5 patients, chronic motor-vocal tics – 3 patients). Clinical remission was registered in 8 patients with tics, of which Tourette's syndrome was diagnosed in 2 patients, chronic motor-vocal tics-in 6 patients.

In the group of patients with tics with negative clinical dynamics after 6 months from the beginning of therapy, there was a significant increase in the background amplitude of bioelectric activity of muscles and AML amplitude OF the studied muscles in the EMG mode at rest and in the EMG mode when performing AF ($p<0.01$, $p<0.05$) in comparison with the group of patients with positive clinical dynamics.

A significant increase in the amplitude of the somatosensory response on the right N20-P23 D (22.65 ± 11.03 mV) and on the left N20-P23 S (37.41 ± 14.98 mV) was determined in the group with negative dynamics in comparison with the group with positive dynamics ($p<0.01$) in the study of BSSP.

Thus, the data of our study indicate the effect of topiramate on the excitability of the parietal zone of the brain. The positive clinical effect of the drug was associated with inhibition of the high-amplitude somatosensory response of the left parietal the somatosensory caused potentials in patients with tics. However, the administration of topiramate at a dose of 1-2 mg/kg did not lead to a complete regression of ticose hypecrinesis in 50% of patients after 6 months of therapy (62,5% of them - patients with Tourette's syndrome). The loss of the effect of the initial dose of the drug allows us to raise the question of increasing the average daily dosages of topiramate, which requires additional research.

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