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DIAGNOSIS AND TREATMENT OF TICS DISORDERS IN CHILDREN (REVIEW)

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Abstract. Tics disorders are a pressing issue due to their high incidence, reaching 1–6% in the pediatric population, comorbidity with attention deficit disorder, stereotypies, anxiety, learning disabilities, mood swings, and sleep disorders. The article discusses new provisions of ICD-11 on the transfer of tics and Tourette syndrome (TS) from the section of mental disorders to the neurological section. The main pathogenetic model is an imbalance of dopamine, GABA, and glutamate mediators in the cortex-thalamus- striatum -cortex system. We have discovered for the first time electromyographic patterns of tics, which include spindle-shaped and diamond-shaped burst activity, which allows us to objectify the severity and prognosis of the disease, as well as expand our understanding of the neurophysiological aspects of tics. According to electromyography data, clear differences were found between the groups of patients with motor, motor-vocal tics and TS, the parameters of the initial background of muscle bioelectric activity, the number of serial (cluster) volleys and their amplitude showed a direct correlation with the severity of hyperkinesis according to the Yale tic severity scale YGSST. Aminophenylbutyric acid can be used as a first-line drug at the onset of tics in preschool and primary school children. At the stage of symptom expression, it is advisable to begin treatment with Anvifen , in the absence of symptom dynamics, switch to treatment with anticonvulsants and neuroleptics.
Key words: hyperkinesis, motor tics, vocal tics, Tourette syndrome.

Introduction

Tic disorders are a pressing issue due to their high incidence, reaching 1–6% in the pediatric population, comorbidity with attention deficit disorder, stereotypies, anxiety, learning disabilities, mood swings, and sleep disorders [1, 2].
A tic is a stereotypical hyperkinesis involving various muscle groups, resembles voluntary movements or sounds, intensifies with emotional and physical stress, and disappears during sleep [3]. In the latest version of the International Classification of Diseases (ICD-11) [4], which is presented for discussion, tic disorders and Tourette syndrome (TS) have been transferred from the mental disorders section to the nervous system diseases section. The ICD-11 project will be approved by the WHO General Assembly in May 2019. A full transition to the new version is planned for 2022. It should be noted that this innovation is justified, since parents primarily turn to a child neurologist when tic hyperkinesis appears, and not to a psychiatrist.

Primary tics

Primary tics are considered hereditary, from a clinical standpoint it is advisable to compile pedigrees, search for relatives who had tics in childhood or are currently observed. In some cases, retrospective hyperkinesis of the proband's relatives allows us to present an individual prognosis for the patient. TS are considered as multiple generalized motor tics, one or more vocal tics,

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occurring over 12 months with a remission of no more than 3 months. Hyperkinesis significantly worsens professional activity (in adults) or school and college education (in children). There are difficulties in differential diagnosis between TS and chronic motor and vocal tics, in connection with which genetic, neurophysiological markers of the disease and neuroimaging data are studied . Tics are inherited in an autosomal dominant manner, there is a semi-dominant type with skipped generations, with an increase in symptoms when transmitting disease signs. Both an autosomal recessive type of inheritance and sporadic variants of the disease are assumed. The latest success in neurogenetics was the discovery of a special mutation of the RICTOR gene in sporadic cases of TS, which changes the regulation of intracellular signal transmission in neurons and myocytes regardless of the specific neurotransmitter models of the disease [5, 6]. In our studies, compiling pedigrees for familial forms of the disease showed the presence of tics in first- and second-degree relatives in up to 70% of cases. In ICD-10, as well as in the 11th version, a classification of tics is presented using adult patients as an example. It should be emphasized that age-dependent stages of the disease are observed only in children: the onset of tics is from 3 to 7 years, the stage of symptom expression is from 8 to 12 years, and the residual stage is after 15 years. Semiotics of tics and topography of hyperkinesis have the following feature of the transition of chronic tics to ST, namely, generalization of motor tics with the inclusion of the upper and lower limbs, back and abdominal extensor muscles.

Chronic tics differ from ST in the severity of hyperkinesis according to the Yale Tic Severity Scale YGTSS [7], the duration of exacerbation periods, and difficulties in social adaptation. In ICD-11 there is a nosology of "chronic motor and vocal tic", only for childhood there is a combination of chronic motor and vocal tics, but in terms of severity of manifestations they do not reach ST. In the semiotics of hyperkinesis, we distinguish clonic and dystonic tics.

Secondary tics

Secondary tics: post-infectious, as a consequence of streptococcal infection, pediatric autoimmune syndrome caused by streptococcus, and pediatric immune syndrome caused by any infection. According to our data, up to 17% of patients had antibodies to the caudate nucleus after respiratory infections. Clinical criteria for infectious tics are the onset of hyperkinesis and exacerbation after respiratory infections, an insignificant effect of antitic drugs - neuroleptics. According to the nosological classifier DSM-IV, tics are divided by duration into transient (duration less than 12 months and remission more than 3 months) and chronic (duration of at least 12 months, remission no more than 3 months) [8]. This division is rather arbitrary and depends on the quality of the anamnesis collection and the parents' memories of the manifestations of the symptoms of the disease. The most successful option is when the doctor observes the patient before making a diagnosis. Tics associated with developmental disorders are highlighted in a separate section, but it is not specified whether they are associated with the development of speech, memory, attention, coordination disorders, probably these are tics in autism or decreased intelligence.

In this case, hyperkinesis occurs without age-related exacerbation phases, the leading clinical significance is the child's developmental disorder and methods of its correction. The decisive factors for determining the nosological form are semiotics and the number of tic series in 20 minutes. As can be seen from Table 1, ST differs from chronic tics in the polymorphism of motor hyperkinesis, including tics of the upper and lower extremities, the presence of complex vocalisms. Exacerbations of the disease occur with a high frequency of tics

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in 20 minutes up to 100 or more and a high level of points on the Yale Tic Severity Scale. Hyperkinesis leads to a violation of adaptation and learning at school. D. Martino et al. (2015) [10] consider that attention deficit disorder, obsessive- compulsive disorder and sensory symptoms (premonition of tics) are the main criteria of TS.

Clinical observation

We examined 130 patients with tic disorders aged 6–14 years, the average age was 10±4 years. Table 1 presents the semiotics and topography of hyperkinesis, severity assessment by the 20-minute counting method and the YGSST tic severity scale.
It is noteworthy that the difference between TS and chronic motor-vocal tic disorders consisted in the generalization of hyperkinesis to the upper and lower extremities, the presence of 3 or more different types of motor tics, status vocalisms, and the appearance of echo- coprolalia . The results of counting tics for 20 minutes corresponded to the results of the score according to the YGTSS scale. The maximum number of motor and vocal tics when counting for 20 minutes was revealed in patients with TS, as well as the score assessment of the total and cumulative severity of tics. Reliable differences were observed only between the groups of patients with isolated motor symptoms and TS.
Electromyography (EMG) was performed to search for neurophysiological patterns for differential diagnosis of ST from chronic motor-vocal tics.
Our studies have shown the feasibility of dividing tics into clonic: rapid movements lasting up to 0.5 s and dystonic hyperkinesis lasting more than 0.5–1 s. According to surface EMG data, clonic tics are characterized by spindle-shaped burst activity (SVA), and dystonic tics are characterized by rhomboid.

Clinical and electromyographic verification of hyperkinesis is presented. In patients of the 1st group, cluster burst activity (CVA) was not detected during the study in the interference mode of EMG. In patients of the 2nd group, CVA was most often detected in the facial muscles (orbicularis oculi muscle), in patients of the 3rd group — in the facial and shoulder girdle muscles. In patients of all three groups, volleys without a tic were detected in the muscles of the face, shoulder girdle, and upper limbs. The duration of a volley without a tic was no more than 12 ms . In patients of group 3, subclinical volleys were recorded significantly more often than in patients of groups 1 and 2 ($p < 0.001$ and $p < 0.05$, respectively).
According to our observations, KZA was recorded mainly during an exacerbation of the disease or during its severe course.

The amplitude of bioelectrical activity (BEA) of the frontal muscle (when recording on the left), shoulder girdle muscles (trapezius, supraspinatus muscles when recording on the right) in patients with motor tics (group 1) did not differ from that in the control group. A significant increase in the amplitude of BEA of the facial muscles (frontal muscle when recording on the right, orbicularis oculi muscle, orbicularis oris muscle), shoulder girdle (trapezius muscle, supraspinatus muscle when recording on the left), upper limb muscles without recording KZA was found;
these parameters significantly exceeded the corresponding indicators in the control group ($p < 0.01$.

In patients of the 2nd group, the amplitude of the frontal muscle BEA (when recording from the

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right) did not differ from that in the control group (Table 2). A reliable increase in the amplitude of the frontal muscle BEA was found when recording from the left compared to that in the control group ($p<0.01$), the orbicularis oris muscle ($p<0.01$), and the supraspinatus muscle when recording from the right ($p<0.01$). KZA was recorded in the facial muscles - in the orbicularis oculi muscle, in the shoulder girdle muscles - the trapezius muscles, the supraspinatus muscle when recording from the left, and the muscles of the upper limbs with a burst amplitude of 350.33+356.63 μV with a duration of up to 100 ms .

In patients with ST (group 3), the frontal muscle BEA was significantly higher than in the control group ($p<0.01$). The CAA was detected in all the muscles studied - the face (orbicularis oculi, orbicularis oris), shoulder girdle, upper limbs with an AO amplitude of 380.24+512.55 μV and an oscillation duration of 100 ms . In patients of the 3rd group, a significant predominance of the frontal muscle BEA was noted when recording on the left compared to patients of the 1st ($p<0.01$) and 2nd groups ($p<0.05$). There was a significant increase in the duration of the CAA of the shoulder girdle muscles (trapezius and supraspinatus muscles on the left), upper limb muscles (superficial flexor of the fingers on the left) in patients of the 3rd group compared to the 2nd group ($p<0.05$).

Thus, only EMG data revealed clear differences between groups of patients with motor, motor-vocal tics and TS in the parameters of the initial background of the BEA muscles, the number of serial (cluster) volleys and their amplitude, a direct correlation with the severity of hyperkinesis according to the YGSST scale was obtained.
Pathogenetic concepts that are considered in modern literature concern dysfunction of the neurotransmitter systems of dopamine, norepinephrine, GABA, serotonin and glutamate in the cortico - striato - amygdalothalamo - cortical system [10-12]. Recent studies using functional MRI have shown a connection between emotional factors and the visual cortex, insular region and striatal system in patients with TS compared to healthy subjects [13]. This study made it possible to explain the role of the psychoemotional factor provoking a tic, and to consider the zone of hyperkinesis debut as an additional motor cortex. MRI with anisotropy mode determined the relationship between the severity of tics, disturbances in the density of connections and neurons in the cortical regions of the sensorimotor cortex of the left hemisphere, which were assessed as congenital or acquired changes that explain the long-term course of the disease and its continuation in adults [14].

Treatment of tics

Treatment of tics is a long-term program — from 4-6 months to several years. During an exacerbation, it is recommended to limit watching TV programs and using a personal computer. Introduce long walks into the regime. Treatment of comorbid syndromes is recommended after stabilization of tic hyperkinesis. At the debut stage in preschool and primary school age, it is recommended to prescribe hopantenic or aminophenylbutyric acid (Anvifen®).

Aminophenylbutyric acid is a phenyl derivative of gamma-aminobutyric acid (GABA). Pharmacological properties, including the effect on GABA, dopaminergic and benzodiazepine receptors, were comparable to those of diazepam and piracetam . Aminophenylbutyric acid and GABA have the same effect on ion channels, which was proven in a study on isolated neurons of invertebrates [15]. In addition, the drug has a neurochemical effect on the subcortical nuclei

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similar to benzodiazepines [16, 17]. It has been shown that the introduction of phenibut before exposure to a stress factor increases the sensitivity of benzodiazepine receptors [16, 17]. L.S. Mekhilane et al . conducted a double-blind, placebo-controlled study of the efficacy of aminophenylbutyric acid in patients with neurotic and psychotic disorders [18]. This study showed that administration of the drug in a dose of 0.25-0.5 g three times a day leads to activation of intellectual functions, increase in physical endurance, motivational activity, reduces symptoms of asthenia and irritability.

In childhood, aminophenylbutyric acid is used mainly to correct mild tic disorders and stuttering [19, 20]. Until recently, the drug was available only in a dose of 0.25 g (Phenibut), which, when treating preschool children, required dividing the tablets and was inconvenient. In addition, there was a possibility of a negative irritant effect on the gastrointestinal tract. In recent years, a new drug, Anvifen ® , has appeared , the advantages of which are the encapsulated form and the availability of a pediatric dosage (50 mg). This made it possible to use the drug from the age of 3. We used aminophenylbutyric acid to treat 25 patients with tics at the debut stage at the age of 5-10 years in order to act on the inhibitory GABAergic systems of the brain. The doses were calculated based on the instructions for the drug: for children aged 5–8 years 50–100 mg 3 times a day, for children aged 8–10 years 250 mg 3 times a day [21], the course of treatment was 3–6 months. Along with a decrease in the symptoms of tics (increased blinking) and movements of the wings of the nose, stuttering manifestations decreased, speech improved. After 10–12 months, all patients were without therapy, and 3 of them experienced an exacerbation of tic symptoms with an increase in hyperkinesis from the initial indicators by 2 times, in connection with which clonazepam was prescribed. The use of aminophenylbutyric acid leads to the complete disappearance of isolated local tics during the period of its administration, while the drug simultaneously has a positive effect on clonic stuttering. If there is no effect from treatment with the drug, the dosage can be increased to the maximum tolerated dose and the course of treatment can be extended to 12 months.

The criterion for the expression stage — the peak of clinical manifestations of tics — is more than 50 tics in 20 minutes of counting (tic status). At the stage of expression of symptoms, we recommend starting treatment with Anvifen for children aged 8–12 years ; if there is no dynamics of symptoms after 3–4 weeks , switch to treatment with anticonvulsants and neuroleptics:
anticonvulsants: clonazepam, topiramate , levetiracetam ; neuroleptics: tiapride 100–300 mg, haloperidol 1.5–3 mg (level of evidence A), risperidone 2–4 mg, aripiprazole (level of evidence C), olanzapine (level of evidence B) [22, 23]. It is promising to use behavioral therapy in children starting from 9-10 years old as an additional or alternative treatment, training in symptom relief, prevention of habitual tics or replacement of some movements with others (in the English version - Habit reversal training), the purpose of which is to teach the child the skills to prevent a tic before it appears [24] . The EMG criteria for tics proposed in our work will allow monitoring drug treatment, as well as displaying burst and background muscle activity on the screen in front of the patient during a behavioral therapy session.

It is advisable to cancel antitic therapy during the period of remission of the disease, preferably during school holidays.

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