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Article

Combined Neurometabolic Therapy in Various Clinical Forms of Tic Hyperkinesis in Children: Effects on Motor and Non-Motor Symptoms

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Abstract: Tic hyperkinesis is one of the most common forms of extrapyramidal pathology in childhood. Recently, interest in non-motor manifestations of tic hyperkinesis in children has increased, as they include ADHD, OCD and anxiety disorder. It is assumed that all these neuropsychiatric diseases have a single pathophysiological basis. However, the question of effective therapy of these comorbid disorders accompanying tic hyperkinesis in children still remains. **Aim:** to im-prove the quality of inpatient medical care in military hospitals and increase patient satisfaction with medical services**. Materials and methods:** the study involved 167 patients (193 boys and 74 girls) with tic hyperkinesis aged 6 to 12 years (mean age 8.2 ± 2.3 years). All patients were divided into four groups depending on the clinical course of the disease: Group I: 32 patients with transient tics; Group II: 120 patients with chronic tics. Group III: 15 patients with Gilles de la Tourette syndrome. Motor symptoms were assessed using the YGTSS scale, and non-motor symptoms were assessed using standardized scales: Y-BOCS, SNAP-IV and STAI. The severity of symptoms was assessed before and after treatment. **Results:** combination neuropharmacotherapy was effective in reducing the severity of tics, ADHD, OCD, and anxiety disorder symptoms in all clinical forms of tic hyperkinesis in children. In addition, combination therapy statistically significantly reduced the severity of tics in patients with Gilles de la Tourette syndrome, ADHD symptoms in patients with transient tics and Gilles de la Tourette syndrome, and OCD symptoms in patients with Gilles de la Tourette syndrome compared to monotherapy. **Conclusion:** the results of this study showed that combination therapy with hopantenic acid in combination with the main line of therapy in children with tic hyperkinesis is effective in treating both tics themselves and symptoms of ADHD, OCD, and anxiety disorder.

Keywords: *tics, Gilles de la Tourette syndrome, hopantenic acid, OCD, ADHD, anxiety disorder.*

1. INTRODUCTION

Today, tic hyperkinesis remains one of the most pressing problems in neurology and psychiatry [1, 8, 11, 17]. In the child population, according to B. Kadesjö and C. Gillberg (2000), the prevalence of tics varies from 0.5% to 1.1% [1]. According to a 2018 epidemiological study among children aged 6 to 16 years in China, the prevalence of tic disorder was 2.5% [2]. The prevalence of Gilles de la Tourette syndrome in children in Brazil is 0.43%, reaching a maximum of 1% by the age of 9 [3]. N. Khalifa and A. von Knorring (2007) [4] identified Gilles de la Tourette syndrome in 0.6% of schoolchildren, which causes social and psychological problems of integrating schoolchildren with tic hyperkinesis into the general educational process and productive interaction of patients with normotypical children. In Scandinavian countries, according to research data for 2008-2016, the prevalence of Gilles de la Tourette syndrome varied from 0.15% to 1.23%, and on average

by the age of 12, the diagnosis of Gilles de la Tourette syndrome was established in 0.43% of children, it is noteworthy that the incidence among boys is 4 times higher than among girls [5]. In the adult population, Tourette syndrome occurs 5-10 times less frequently than in children, according to various estimates, from 50 to 659 cases per 1,000,000 adults [3]. The results of M. Bloch et al. (2006) indicate that 25% of tics that once existed in children persist in the adult population [3]. A significant factor in maladaptation in most patients with Gilles de la Tourette syndrome are comorbid disorders: obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), epilepsy, anxiety disorder, affective disorder, learning difficulties [6, 7]. Comorbid disorders are present in 88% of patients with Gilles de la Tourette syndrome [8].

Approximately 40-60% of patients with Gilles de la Tourette syndrome have OCD [7]. According to epidemiological studies, OCD is observed in 2-3% of the population, so such a high incidence of OCD among people with Gilles de la Tourette syndrome cannot be explained by a random combination of these two diseases. OCD symptoms in patients with Gilles de la Tourette syndrome usually begin within a few years after the onset of tics [9, 10]. OCD in Gilles de la Tourette syndrome is an age-dependent phenomenon: symptoms intensify in adolescence and young adulthood, a period when tics begin to weaken [7]. Common compulsions (obsessive actions) in Gilles de la Tourette syndrome include echophenomena, tidying up or arranging objects in a certain sequence, rubbing hands, touching and sniffing objects, trying to achieve absolute symmetry, obsessions (fixated ideas) - obsessive counting, repetitive thinking of various thoughts, unfounded fears about the health of family members, fear of contamination or infection, thoughts of guilt for the misfortunes that happen to others [7]. In general, patients with Gilles de la Tourette syndrome often commit impulsive acts and are prone to ill-considered ideas that are not a consequence of anxiety and do not arise to reduce it. Symptoms of ADHD (age-inappropriate hyperactivity, impulsivity, inattention) are observed in 50-60% of patients with Gilles de la Tourette syndrome, as opposed to 3-7% of the child population. The onset of ADHD symptoms usually precedes the appearance of motor and vocal tics by an average of 2.4 years [11]. As for the severity of tics, the presence of ADHD is not accompanied by an in-crease in their intensity, while concomitant OCD usually leads to an increase in the severi-ty of tics [12]. In a comparative examination of two groups of children - with Gilles de la Tourette syndrome and Gilles de la Tourette syndrome combined with ADHD - the second group more often showed emotional and behavioral disorders, as well as more pronounced disorders of social adaptation [12].

Many children and adolescents with Gilles de la Tourette syndrome have anxiety disorders. These include generalized anxiety disorder, social and other phobias, and separation anxiety. Anxiety and depression occur in approximately 30% of patients with Gilles de la Tourette syndrome [11]. The high-risk period for anxiety disorders begins at approximately 4 years of age, and for mood disorders, at approximately 7 years of age [11]. Comorbid depression is positively correlated with tic severity [13]. Patients with Gilles de la Tourette syndrome and depression often have a family history of depression [13]. About 10% of young people with tic disorders experience suicidal thoughts and attempts, which often occur in the context of anger and frustration [14, 15]. Although there is no correlation between suicidal thoughts and tic severity, the presence of anxiety and depression in-creases the risk of suicide in patients with tic disorders [14]. In a large epidemiological cohort study from the Swedish National Registry, patients with Gilles de la Tourette syn-drome had an approximately four-fold increased risk of attempted suicide [16]. It is there-fore important to assess symptoms of depression and anxiety, especially in patients with a positive family history of depression in tic disorders.

Aim of the study: to study the effectiveness of combination pharmacotherapy in the treatment of motor and non-motor symptoms of various clinical forms of tic hyperkinesis in children.

2. MATERIALS AND METHODS

The study involved 167 patients (193 boys and 74 girls) with tic hyperkinesis aged 6 to 12 years (mean age 8.2 ± 2.3 years). All patients were divided into four groups depending on the clinical course of the disease: Group I: 32 patients (20 boys and 12 girls) with transient tics. Group II: 120 patients (92 boys and 28 girls) with chronic tics. Group III: 15 patients (11 boys and 4 girls) with Gilles de la Tourette syndrome. Each group of patients was di-vided into 2 subgroups (equal in clinical form of tics, age and gender): the first subgroup received first-line drugs (neuroleptics or anticonvulsants) - monotherapy; The second subgroup received first-line drugs (neuroleptics or anticonvulsants) + hopantenic acid 250 mg, 2 tablets 3 times a day - combination therapy. Motor symptoms were assessed using the YGTSS (Yale Global Tic Severity Scale), and non-motor symptoms were assessed using standardized scales: Y-BOCS (Yale-Brown Obsessive-Compulsive Scale), SNAP-IV (Swanson ADHD Rating Scale), STAI (Spielberger-Hanin Anxiety Scale). The severity of symptoms was assessed before and after treatment.

Statistical data processing was per-formed using the STATISTICA version 13 program, while values at p-value < 0.05 were considered statistically significant. The study was approved by the Ethics Committee of the Siberian State Medical University No. 10005 dated 02.24.2025.

3. RESULTS

The results of the study of the severity of tics showed that tics have the highest severity according to the YGTSS scale in group III and the least in group I (Table 1). Such distribution of the severity of motor manifestations of tic hyperkinesis was expected, since it is known that the most severe clinical form of tic hyperkinesis is Gilles de la Tourette syn-drome (group III), and the mildest are transient tics (group I). As a result of monotherapy, tics were statistically significantly relieved in all 3 clinical groups, the greatest effect was observed in group I, and the least in group III. After combination therapy, it was possible to achieve the maximum therapeutic response in relation to the severity of tics in all groups of patients. Thus, in group I, the severity of tics decreased from 29.8 ± 15.9 to 8.3 ± 2.1; in group II from 48.35 ± 16.17 to 22.2 ± 6.3 and in group III from 69.27 ± 13.65 to 30.3 ± 5.9. Interestingly, in group III (Gilles de la Tourette syndrome), the effectiveness of combination therapy compared to monotherapy was statistically significantly lower: 30.3 ± 5.9 to 48.9 ± 10.2, respectively.

Table 1. Pre- and post-treatment tic severity scores using the YGTSS

Group	Before treatment **M** ± SE	Monotherapy **M** ± SE	Combination therapy **M** ± SE
I group	29.8 ± 15.9	9.2 ± 3.5*	8.3 ± 2.1*
II group	48.35 ± 16.17	29.3 ± 9.2*	22.2 ± 6.3*
III group	69.27 ± 13.65	48.9 ± 10.2*	30.3 ± 5.9*#

Note: *– p-value < 0.05 compared to before treatment; # - p-value < 0.05 compared to monotherapy; YGTSS – Yale Global Tic Severity Scale).

The results of the study of the prevalence of ADHD symptoms according to the SNAP-IV scale showed ambiguous results (Table 2). Thus, the prevalence in all clinical groups did not differ, although it was assumed that there should be significant differences

among different forms of tic hyperkinesis in children. As a result of monotherapy, ADHD symptoms were statistically significantly relieved in all 3 clinical groups, the greatest effect was observed in group II, and the least in group III. After combination therapy, it was possible to achieve the maximum therapeutic response in relation to ADHD symptoms in all groups of patients.

Table 2. Prevalence of attention deficit hyperactivity disorder symptoms according to SNAP-IV scale before and after treatment

Group	Before treatment **M** ± SE	Monotherapy **M** ± SE	Combination therapy **M** ± SE
I group	81.25%	30.89*	21.80%*#
II group	76.6%	25.2%*	23.20%*
III group	80.00%	39.26%*	20.00%*#

Note: *– p-value < 0.05 compared to before treatment; # - p-value < 0.05 compared to monotherapy; ADHD – attention deficit hyperactivity disorder; SNAP - Swanson ADHD Rating Scale.

Thus, in group I, the prevalence of ADHD symptoms decreased from 81.25% to 21.8%; in group II from 76.6% to 23.2% and in group III 80% to 20%. Despite the fact that in Group III (Gilles de la Tourette syndrome) the prevalence of ADHD symptoms was one of the highest, after combination therapy it was possible to achieve the maximum reduction in prevalence compared to other clinical groups. In addition, combination therapy was statistically significantly more effective than monotherapy in terms of relieving ADHD symptoms in Groups I and III.

The prevalence of OCD symptoms according to the Y-BOCS scale was the highest in group III and the lowest in groups II and I (Table 3). These data are consistent with the da-ta of foreign colleagues who studied comorbid OCD among children with tic hyperkinesis. As a result of monotherapy, OCD symptoms were statistically significantly relieved in all three clinical groups, the greatest effect was observed in group I, and the least in group III. After combination therapy, it was possible to achieve the maximum therapeutic response in relation to OCD symptoms in all groups of patients. Thus, in group I, the prevalence of OCD symptoms decreased from 46.6% to 9.04%; in group II from 51.6% to 10% and in group III 60% to 6.6%. Despite the fact that in group III (Gilles de la Tourette syndrome) the prevalence of OCD symptoms was one of the highest, after combination therapy it was possible to achieve the maximum reduction in prevalence compared to other clinical groups, and it was in this group of patients that combination therapy was statistically significantly more effective in relieving OCD symptoms compared to monotherapy.

The results of the anxiety disorder symptoms assessment showed that the prevalence remains at the same level in all 3 groups and in the case of group III (Gilles de la Tourette syndrome) it is slightly higher than the others (Table 4). Such prevalence of anxiety among patients, which does not depend on the clinical form of tic hyperkinesis and the severity of tics, suggests that anxiety is most likely a result of the child's internal empathy and occurs as a consequence of an intrapersonal conflict. After a course of treatment in the form of monotherapy, anxiety symptoms were reduced almost 2 times in all 3 groups of patients. However, the maximum effect of neuropharmacotherapy was achieved with the combination regimen. Thus, combination therapy turned out to be statistically significantly more effective in relieving anxiety symptoms in patients in groups II (chronic tics) and III (Gilles de la Tourette syndrome) from 63.3% to 26.6 and from 66.6% to 13.3%, respectively.

Table 3. Prevalence of obsessive-compulsive disorder symptoms according to the Y-BOCS scale before and after treatment

Group	Before treatment **M** ± SE	Monotherapy **M** ± SE	Combination therapy **M** ± SE
I group	46.6%	11.5%*	9.04%*
II group	51.6%	13.6%*	10.0%*
III group	60.0%	35.6%*	6.6%*#

Note: *– p-value < 0.05 compared to before treatment; # - p-value < 0.05 compared to monotherapy; OCD - obsessive-compulsive disorder; Y-BOCS - Yale-Brown Obsessive-Compulsive Scale.

Table 4. Prevalence of anxiety symptoms according to the STAI scale before and after treatment

Group	Before treatment **M** ± SE	Monotherapy **M** ± SE	Combination therapy **M** ± SE
I group	65.6%	30.9%*	21.8%*
II group	63.3%	36.2%*	26.6%*#
III group	66.9%	26.6%*	13.3%*#

Note: *– p-value < 0.05 compared to before treatment; # - p-value < 0.05 compared to monotherapy; STAI - Spielberger-Hanin Anxiety Scale.

Clinically and statistically significant improvement of ADHD, OCD and anxiety disorder symptoms in groups I (transient tics) and II (chronic tics) compared to group III (Gilles de la Tourette syndrome), in our opinion, is due to the fact that Gilles de la Tourette syndrome is characterized by greater involvement of the basal ganglia and mesocortical dopamine pathways in the pathological process compared to patients suffering from transient and chronic forms of tics. Children with Gilles de la Tourette syndrome require a more comprehensive approach to therapy, including neuropharmacotherapy and cognitive behavioral therapy to relieve both motor and non-motor symptoms.

4. DISCUSSION

Our study revealed clinically and statistically significant improvements in ADHD, OCD and anxiety disorder symptoms in patients with transient (group I) and chronic tics (group II) compared to patients with Gilles de la Tourette syndrome (group III). These results highlight important differences in the pathophysiology and clinical course of different tic spectrum disorders.

Gilles de la Tourette syndrome is known to be associated with more pronounced involvement of the basal ganglia and mesocortical dopamine pathways. This may explain the more complex and stable nature of symptoms in this group of patients. Unlike transient and chronic tics, which may be more susceptible to change in response to therapy, Gilles de la Tourette syndrome requires a deeper understanding of the neurobiological mechanisms underlying its manifestations.

Children with Gilles de la Tourette syndrome indeed require a more comprehensive approach to treatment. Neuropharmacotherapy aimed at correcting dopaminergic dysfunctions may be necessary to manage both motor and non-motor symptoms. Cognitive

behavioral therapy also plays an important role in the treatment of this syndrome, helping children cope with anxiety and other comorbid disorders.

These results highlight the need for an individualized approach to the treatment of children with tic disorders. It is important to take into account not only the type of tic disorder, but also comorbid psychiatric conditions such as ADHD and OCD. This will allow for the development of more effective intervention strategies and improve the quality of life of patients.

To further understand the differences between these groups of patients, additional studies are needed to deepen our understanding of the neurobiological basis of Tourette syndrome. It is also worth considering the possibility of studying the long-term effects of different therapeutic approaches on symptoms of both motor and non-motor nature.

5. CONCLUSIONS

The results of this study showed that combination therapy with haponтenic acid in combination with the main line of therapy in children with tic hyperkinesis is effective for the treatment of both tics themselves and symptoms of anxiety, ADHD and OCD. These data highlight the importance of a comprehensive approach to the treatment of tic hyperkinesis in children to achieve optimal treatment results.

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