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EVALUATION OF THE RESULTS OF COMBINED NEUROMETABOLIC THERAPY IN CHILDREN WITH TICS: DYNAMICS OF MOTOR AND PSYCHOPATHOLOGICAL SYMPTOMS

Abstract: *tic hyperkinesis represents one of the most prevalent forms of extrapyramidal pathology in the pediatric population. In recent years, there has been growing clinical and research interest in the non-motor manifestations of tic disorders, which frequently include comorbid attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and anxiety disorders. A prevailing hypothesis suggests these neuropsychiatric conditions may share a common underlying pathophysiology. Nevertheless, establishing effective therapeutic strategies for these complex comorbid presentations in children with tic hyperkinesis remains a significant clinical challenge. The aim of this study was to evaluate the efficacy of combination pharmacotherapy in improving the core and comorbid symptoms of tic disorders in children, thereby contributing to enhanced therapeutic outcomes. The results of this study indicate that adjunctive therapy with hopantenic acid, in combination with first-line treatment, is effective for the comprehensive management of both motor tics and the common comorbid symptoms of ADHD, OCD, and anxiety in children with tic hyperkinesis. These findings support the utility of a targeted, multi-symptom treatment approach for this patient population.*

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

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ОЦЕНКА РЕЗУЛЬТАТОВ КОМБИНИРОВАННОЙ НЕЙРОМЕТАБОЛИЧЕСКОЙ ТЕРАПИИ У ДЕТЕЙ С ТИКАМИ: ДИНАМИКА ДВИГАТЕЛЬНЫХ И ПСИХОПАТОЛОГИЧЕСКИХ СИМПТОМОВ

Аннотация. *Тикозные гиперкинезы являются одной из наиболее распространенных форм экстрапирамидной патологии в детской популяции. В последние годы наблюдается растущий клинический и научный интерес к немоторным проявлениям тикозных расстройств, которые часто включают коморбидные синдром дефицита внимания и гиперактивности (СДВГ), обсессивно-компульсивное расстройство (ОКР) и тревожные расстройства. Существует гипотеза, что эти нейропсихиатрические состояния могут иметь общую патофизиологическую основу. Тем не менее, разработка эффективных терапевтических стратегий для этих сложных коморбидных состояний у детей с тикозными гиперкинезами остается серьезной клинической задачей. Целью данного исследования была оценка эффективности комбинированной фармакотерапии в улучшении основных и сопутствующих симптомов тикозных расстройств у детей, способствуя тем самым повышению эффективности лечения. Результаты данного исследования показывают, что адъювантная терапия гопантеновой кислотой в сочетании с терапией первой линии эффективна для комплексного лечения как моторных тиков, так и распространенных коморбидных симптомов СДВГ, ОКР и тревоги у детей с тикозными гиперкинезами. Эти данные подтверждают целесообразность применения целенаправленного подхода, ориентированного на одновременное купирование нескольких симптомов у данной группы пациентов.*

Ключевые слова: *тики, синдром Жиля де ла Туретта, гопантеновая кислота, ОКР, СДВГ, тревожное расстройство.*

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BOLALARDA TIKLARNI KOMBINALASHGAN NEYROMETABOLIK TERAPIYA BILAN DAVOLASH NATIJALARINI BAHOLASH: HARAKAT VA PSIXOPATOLOGIK SIMPTOMLARNING DINAMIKASI

Annotatsiya. *Tik giperkinezi bolalar populyatsiyasida ekstrapiramidal patologiyaning eng keng tarqalgan shakllaridan biridir. So'nggi yillarda tik buzilishlarining nomotor ko'rinishlariga, ularga tez-tez komorbid e'tibor yetishmovchiligi va giperaktivlik sindromi (SDBG), majburiy-majburlı buzilish (MMB) va tashvish buzilishlari kiradi, katta klinik va ilmiy qiziqish mavjud. Bu neyropsixiatrik holatlar umumiy patofiziologik asosga ega bo'lishi mumkin degan taxmin mavjud. Shu bilan birga, bolalarda tik giperkinezi bilan murakkab komorbid ko'rinishlar uchun*

samarali terapevtik strategiyalarni ishlab chiqish jiddiy klinik muammo bo'lib qolmoqda. Ushbu tadqiqotning maqsadi bolalarda tik buzilishlarining asosiy va hamroh simptomlarini yaxshilashda kombinatsiyalangan farmakoterapiyaning samaradorligini baholash, shu bilan davolash natijalarini yaxshilashga hissa qo'shish edi. Ushbu tadqiqot natijalari shuni ko'rsatadiki, birinchi navbatdagi terapiya bilan birgalikda gopantenik kislota bilan qo'shimcha terapiya bolalarda tik giperkinezi bilan ham motor tiklarni, ham SDBG, MMB va tashvishning keng tarqalgan komorbid simptomlarini kompleks boshqarish uchun samaralidir. Ushbu topilmalar ushbu bemorlar populyatsiyasida bir nechta simptomlarni bir vaqtning o'zida yo'q qilishga qaratilgan maqsadli yondashuvdan foydalanishning maqsadga muvofiqligini tasdiqlaydi.

Kalit so'zlar: *tiklar, Jil de la Ture sindromi, gopanten kislotasi, tashvish buzilishi.*

Introduction. Tic hyperkinesis continues to be one of the most significant challenges in the fields of neurology and psychiatry [1, 8, 11, 17]. Epidemiological data indicate a notable prevalence of tic disorders within the pediatric population. Studies by researchers such as B. Kadesjö and C. Gillberg (2000) report rates ranging from 0.5% to 1.1% [1]. More recent investigations reveal geographical variations; for instance, a 2018 study of Chinese children aged 6–16 years found a prevalence of 2.5% for tic disorders [2]. The occurrence of Gilles de la Tourette Syndrome (GTS) specifically is estimated at 0.43% among children in Brazil, peaking at approximately 1% by age 9 [3]. Research by N. Khalifa and A. von Knorring (2007) identified GTS in 0.6% of schoolchildren, highlighting the social and psychological integration challenges these individuals may face within mainstream educational settings [4]. Data from Scandinavian countries (2008–2016) show a GTS prevalence range of 0.15% to 1.23%, with an average diagnosis rate of 0.43% by age 12 and a marked male predominance, as boys are affected about four times more frequently than girls [5].

In adulthood, GTS is observed 5–10 times less commonly than in children, with estimates varying from 50 to 659 cases per 1,000,000 adults [3]. Longitudinal studies, including one by M. Bloch et al. (2006), suggest that approximately 25% of childhood tics persist into adulthood [3]. A critical factor contributing to functional impairment in GTS is the high rate of comorbid conditions, including obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), epilepsy, and various anxiety and affective disorders [6, 7]. Comorbidities are present in up to 88% of GTS patients [8].

The co-occurrence of OCD with GTS is particularly prominent, observed in 40–60% of cases [7]. Given that the general population prevalence of OCD is only 2–3%, this high frequency suggests a non-random, pathophysiological link between the two disorders. Typically, OCD symptoms in GTS emerge several years after tic onset [9, 10]. This comorbidity exhibits an age-dependent pattern, often intensifying during adolescence and early adulthood—a period when tic severity commonly begins to diminish [7]. Characteristic compulsions in GTS include echophenomena, ordering or arranging objects, repetitive touching or sniffing, and a need for symmetry. Common obsessions involve counting, intrusive thoughts, health-related anxieties about family members, contamination fears, and guilt [7]. Patients with GTS also frequently exhibit impulsive behaviors and non-anxiety-driven, poorly conceived actions.

Symptoms of ADHD are present in 50–60% of individuals with GTS, a rate substantially higher than the 3–7% found in the general pediatric population. Notably, ADHD symptoms usually precede the onset of motor and vocal tics by an average of 2.4 years [11]. While the presence of ADHD does not appear to correlate with increased tic severity, comorbid OCD is often associated with more pronounced tics [12]. Comparative studies indicate that children with GTS and comorbid ADHD experience greater emotional, behavioral, and social adaptation difficulties than those with GTS alone [12].

Anxiety disorders, including generalized anxiety, social phobia, and separation anxiety, are also prevalent among children and adolescents with GTS. Approximately 30% of patients experience significant anxiety or depressive symptoms [11]. The high-risk period for anxiety disorders begins around age 4, while mood disorders often emerge around age 7 [11]. The severity of comorbid depression shows a positive correlation with tic severity [13], and a family history of depression is common in such cases [13]. Suicidal ideation and attempts affect about 10% of youth with tic disorders, frequently in contexts of anger and frustration [14, 15]. Although tic severity itself is not directly linked to suicidality, the co-presence of anxiety and depression significantly elevates the risk [14]. A large-scale Swedish national registry cohort study found a nearly four-fold increased risk of suicide attempts in patients with GTS [16]. Consequently, systematic assessment for symptoms of depression and anxiety is essential, particularly for patients with a positive family history.

Aim of the Study: To evaluate the efficacy of combination pharmacotherapy in treating both motor and non-motor symptoms across various clinical forms of tic hyperkinesis in children.

Materials and Methods. The study included 167 patients (93 boys and 74 girls) aged 6 to 12 years (mean age 8.2 ± 2.3 years) diagnosed with tic hyperkinesis. Participants were categorized into three groups based on clinical diagnosis:

Group I: 32 patients (20 boys, 12 girls) with transient tic disorder.

Group II: 120 patients (92 boys, 28 girls) with chronic tic disorder.

Group III: 15 patients (11 boys, 4 girls) with Gilles de la Tourette Syndrome.

Each diagnostic group was subsequently divided into two matched subgroups (balanced for clinical form, age, and sex):

Monotherapy Subgroup: Received first-line treatment (antipsychotics or anticonvulsants) only.

Combination Therapy Subgroup: Received first-line treatment plus hopantenic acid (250 mg tablets, 2 tablets three times daily).

Motor symptom severity was assessed using the Yale Global Tic Severity Scale (YGTSS). Non-motor symptoms were evaluated with standardized instruments: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for OCD, the Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) for ADHD, and the Spielberger State-Trait Anxiety Inventory (STAI) for anxiety. Assessments were conducted before and after the treatment course.

Statistical analysis was performed using STATISTICA software, version 13. A p-value of less than 0.05 was considered statistically significant. The study protocol received approval from the Ethics Committee of the Siberian State Medical University (Protocol No. 10005, dated February 24, 2025).

Results and Discussion. Analysis of tic severity using the YGTSS scale revealed the expected gradient across clinical groups. The highest scores were recorded in Group III (Gilles de la Tourette Syndrome), while the lowest were in Group I (transient tic disorder), consistent with the known clinical spectrum of tic hyperkinesis (Table 1).

Monotherapy with first-line agents yielded a statistically significant reduction in tic severity across all three groups. The therapeutic response was most pronounced in Group I and least pronounced in Group III.

Combination therapy (first-line treatment plus hopantenic acid) produced a maximal therapeutic response, further reducing tic severity in all patient groups. The post-treatment YGTSS scores decreased as follows:

- Group I: from 29.8 ± 15.9 to 8.3 ± 2.1
- Group II: from 48.35 ± 16.17 to 22.2 ± 6.3
- Group III: from 69.27 ± 13.65 to 30.3 ± 5.9

A notable finding was the comparative efficacy in Group III. The final tic severity score following combination therapy (30.3 ± 5.9) was statistically significantly lower than that achieved with monotherapy alone (48.9 ± 10.2).

Table 1.

Pre- and post-treatment tic severity scores using the YGTSS scale

	Before treatment	Monotherapy	Combination therapy
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<0.05 compared to before treatment; # - p<0.05 compared to monotherapy*

Assessment of ADHD symptoms via the SNAP-IV scale yielded results that did not align with initial expectations (Table 2). The prevalence of significant ADHD symptoms did not show statistically significant differences across the three clinical groups, despite the hypothesis that varying forms of tic hyperkinesis might present distinct comorbid profiles.

Monotherapy led to a statistically significant reduction in ADHD symptom severity in all groups. The magnitude of this effect was greatest in Group II (chronic tics) and most modest in Group III (Gilles de la Tourette Syndrome).

The introduction of combination therapy resulted in a maximal therapeutic response for ADHD symptoms across all patient cohorts. The adjunctive use of hopantenic acid provided a greater reduction in SNAP-IV scores compared to monotherapy alone in each group.

Table 2.

Prevalence of ADHD symptoms according to SNAP-IV scale before and after treatment

	Before treatment	Monotherapy	Combination therapy
I group	81,25%	30,89*	21,8%*#
II group	76,6%	25,2%*	23,2%*
III group	80%	39,26%*	20,0%*#

***Note: *–** p<0.05 compared to before treatment; # - p<0.05 compared to monotherapy*

The application of combination therapy resulted in a pronounced decrease in the prevalence of clinically significant ADHD symptoms across all cohorts. The post-treatment prevalence rates were as follows:

- Group I: Decreased from 81.25% to 21.8%.
- Group II: Decreased from 76.6% to 23.2%.
- Group III: Decreased from 80% to 20%.

Notably, while Group III (Gilles de la Tourette Syndrome) exhibited one of the highest baseline prevalences, it demonstrated the greatest relative reduction following combination therapy. Statistical analysis confirmed that the combination regimen was significantly more effective than monotherapy in alleviating ADHD symptoms in Groups I and III.

The assessment of obsessive-compulsive symptoms using the Y-BOCS scale revealed the highest baseline prevalence in Group III, with lower rates in Groups II and I (Table 3). This distribution aligns with existing international research on comorbid OCD in pediatric tic disorders.

Table 3.

Prevalence of OCD symptoms according to the Y-BOCS scale before and after treatment

	Before treatment	Monotherapy	Combination therapy
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<0.05 compared to before treatment; # - p<0.05 compared to monotherapy*

Monotherapy led to a statistically significant alleviation of OCD symptoms in all three groups, with the most substantial effect observed in Group I and the most modest in Group III.

Combination therapy yielded a maximal therapeutic response for OCD symptoms. The prevalence of significant OCD symptoms post-treatment was markedly reduced:

- Group I: Decreased from 46.6% to 9.04%.
- Group II: Decreased from 51.6% to 10%.
- Group III: Decreased from 60% to 6.6%.

A key finding is that Group III, despite its high baseline severity, achieved the greatest reduction in OCD symptom prevalence. Furthermore, it was in this group that combination therapy proved statistically significantly superior to monotherapy in relieving OCD symptoms.

Conclusions. The findings of this study demonstrate that combination therapy utilizing hopantenic acid as an adjunct to first-line treatment is effective in managing both the core motor symptoms and key comorbid conditions—namely anxiety, ADHD, and OCD—in children with tic hyperkinesis. These results underscore the critical importance of adopting a comprehensive, multi-targeted treatment strategy to achieve optimal clinical outcomes in this patient population.

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