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COMPREHENSIVE TREATMENT PROGRAM FOR BRONCHIAL ASTHMA IN CHILDREN WITH A HISTORY OF PERINATAL CENTRAL NERVOUS SYSTEM PATHOLOGY

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ABSTRACT

Bronchial asthma remains a pressing issue in pediatrics, with high prevalence and a continuous increase in morbidity among children. It has been found that most children with bronchial asthma have a history of perinatal central nervous system (CNS) damage. Despite progress in the diagnosis and treatment of bronchial asthma, the mechanisms by which perinatal CNS lesions influence asthma development are varied, and existing treatment regimens for such children are not always highly effective. This highlights the need for improved treatment methods for children with bronchial asthma who also suffer from the consequences of perinatal CNS injury.

KEYWORDS: *bronchial asthma, central nervous system, perinatal injury, neurostimulation, morphofunctional indicators, Semax.*

Bronchial asthma (BA) is one of the most common chronic respiratory diseases in children. Recently, significant progress has been made in studying the etiology, pathogenesis, clinical course, and diagnosis of BA. However, many treatment-related issues remain unresolved. It is known that bronchial asthma typically begins in the first five years of life, often manifesting with pronounced bronchial obstruction (BO), especially in children who have atopic dermatitis. It should be noted that BO is widespread among children in the first 5–6 years of life, with respiratory viral infections being the main trigger for its development. In many pathological conditions, recurrent BO symptoms are observed. Therefore, differentiating BA from other diseases presenting with BO is not straightforward. This is due to the presence of various BO symptoms and the difficulties in functional diagnostics during the early years of life [National Program "Bronchial Asthma in Children: Treatment Strategy and Prevention", 2017; Heppe N.A. et al., 2018].

It should be noted that the timing of the initiation of BA treatment affects its outcome. Therefore, once a BA diagnosis is confirmed, therapy should commence as early as possible [Selroos O., 2008]. Early administration of low-dose inhaled glucocorticosteroids (ICS) in patients with BA leads to stabilization and improvement in lung function compared to those whose treatment began 2–4 years after diagnosis. Delaying treatment may require higher doses of ICS. The impact of delayed ICS therapy is noticeable even after 5 years of treatment [Selroos O, Löfroos AB, Pietinalho A, Riska H., 2004].

The choice of treatment depends on the severity, degree of control, and period of BA. However, an individualized approach in selecting treatments and methods is essential. Recent studies indicate that most children with BA have a history of perinatal central nervous system (CNS) injury, which increases the risk of BA by 3.4 times in preschool-aged children. It has been proven that perinatal injuries contribute to frequent bronchial obstruction in children in the first years of life [Pavlenko V.A. et al., 2015].

According to recent literature, newborns who experienced hypoxia-ischemia during the perinatal period often have neurological deficits of varying severity in later childhood, such as delays in neuropsychological and motor development, minimal brain dysfunctions, difficulties in social adaptation, cerebral palsy, and epilepsy [Trepilets S.V. et al., 2018; Krasnorutskaya O.N., Ledneva V.S., 2018]. However, the impact of CNS injury sequelae on BA progression in children, depending on psychosomatic status, has not been studied, nor are there data on the specifics of BA progression and treatment in children with different clinical manifestations of CNS pathology.

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Thus, all of the above necessitates further development of new diagnostic and prognostic criteria for the progression and course of bronchial asthma in children with perinatal CNS injury consequences.

OBJECTIVE OF THE STUDY

To investigate the causative factors and potential treatment options for bronchial asthma in children with perinatal CNS injury sequelae, considering a range of neuropsychological, psychosomatic, immunological, and functional parameters.

MATERIALS AND METHODS

According to the protocol, the examination of children included a comprehensive set of anamnesis (epidemiological and disease history, questionnaires), clinical, laboratory (IL-4, IL-8, TNF-α, neuron-specific enolase (NSE), insulin-like growth factor-1), and clinical-instrumental research methods.

A clinical and neurological examination was conducted among 72 children aged 5-7 years with moderate BA (51 boys and 21 girls) who had sequelae of perinatal CNS injury. Based on the therapy received, the children were divided into two groups: the main group, which included 38 children (52.8%) who, in addition to standard treatment, received therapy targeting identified neurological impairments, and the comparison group, which included 34 patients (47.2%) who received only standard therapy.

All patients in the main group received the following treatment: a hypoallergenic regimen; a hypoallergenic diet (an elimination diet excluding or limiting allergens depending on sensitization level); baseline anti-inflammatory therapy in the form of combination medications (salmeterol + fluticasone) at a dose of 25/125 mg. During remission periods, respiratory muscle training was prescribed, including therapeutic exercise, chest massage, and breathing exercises with forced exhalation.

In addition to the baseline therapy, main group patients received methionyl-glutamyl-histidyl-phenylalanine-prolyl-glycyl-proline (Semax nasal drops 0.1%) to correct the consequences of perinatal CNS injury. The drops were administered daily in each nostril, 1 drop twice a day (morning and afternoon) at a dose of 5-6 mcg/kg. The average daily dose was 300–400 mcg/day. The treatment course lasted 2 months, split into two 30-day courses with a 3-month break in between.

To enhance neuroplasticity, interhemispheric relationships, and cortical-subcortical interactions, the children in the main group also underwent translanguage neurostimulation using the “Neuroport” device (Figure 1). The procedure lasted 30 minutes, twice a day, with a total of 10 sessions per course. A second neurorehabilitation course was conducted for all patients after 3 months.



Figure 1. Translanguial Neurostimulation Device

Numerous studies have shown that physical factors significantly contribute to the treatment and rehabilitation of children with BA. This is partly due to their comprehensive effects and physical properties, as well as their alignment with physical processes within the body and their ability to influence regulatory systems. Since the multifactorial nature of allergic inflammation in BA involves many bodily systems, 15 sessions of Nordic walking (NW) were included in the BA therapy program for children in subgroup A, with each session lasting 30 minutes twice a week.

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RESULTS AND DISCUSSION

In the main group, the majority of children (84.2%, n=32) achieved disease control within three months of starting the comprehensive therapy. Only 15.8% (n=6) required an increase in baseline anti-inflammatory therapy up to 375 mcg/day. With this dosage, disease control was achieved in all children within four weeks. In the comparison group, fewer than half (44.1%, n=15) achieved disease control within three months (p=0.0078). The remaining 55.9% (n=19) required an increase (step-up) in therapy, raising the baseline dose to 375 mcg/day of fluticasone. Of these, 23.5% (n=8) achieved control, but 32.4% (n=11) (p=0.011) continued to show exercise intolerance over six weeks. For these children, baseline therapy was increased to 500 mcg/day, resulting in disease control. Two children (5.9%) did not achieve control even at 500 mcg/day due to unfavorable living conditions; their BA severity was reclassified as severe, and therapy was adjusted accordingly.

It was also found that among the main group children who needed higher doses of inhaled glucocorticosteroids (ICS) (25 children; 34.7%), 48% (n=12) had autonomic dysfunction, 40% (n=10) had attention deficit hyperactivity disorder (ADHD), and only 12% (n=3) had speech disorders. This indicates that children with ADHD and autonomic dysfunction more frequently required higher doses of ICS.

To evaluate the effectiveness of the proposed BA therapy program, a follow-up assessment of disease control (complete, partial, or absent) was conducted six months later using the ACT test, peak flowmetry, and spirometry with forced expiratory volume (FEV1). Special attention was paid to the frequency of daytime symptoms and nighttime awakenings (Table 1). Spirometry and peak flowmetry parameters analyzed included vital capacity (VC), vital index, peak expiratory flow rate, breath-hold duration on inhalation (Stange test), and chest excursion. Abdominal muscle strength was assessed with the child lying on their back, measuring the time they could hold their legs straight at the knees and bent at a 45º angle at the hips. Back muscle strength was measured in seconds, with the child in a "swallow" position lying on their stomach, noting the duration of torso hold until the child stopped the test. Physical performance was also evaluated using a two-step step test. The Robinson index (double product=heart rate (HR) in bpm x systolic blood pressure in mmHg; normal Robinson index is 70-94 units) and Ruffier index (where RI=Ruffier index, P1= resting pulse rate, P2=pulse rate after the first 15 seconds of the first recovery minute, P3=pulse rate in the last 15 seconds of the first recovery minute) were calculated. If RI ≤ 3, performance was rated excellent; from 4 to 6, good; from 7 to 9, average; from 10 to 14, satisfactory; and 15 or more, poor.

Table 1
Dynamics of Morphofunctional Indicators After the Therapy Course

Indicator	Patient Group	
	Comparison Group (n=34)	Main Group (n=38)
Chest excursion, cm	3,8±3,9	8,5±5,3*
Vital lung capacity, L	1,3±1,5	3,3±1,8*
Vital index, mL/kg	44,3±2,4	56,2±2,3*
FEV1, % of formed VC	1,3±0,6	3,8±1,8*
Peak expiratory flow rate, L/min	316,1±6,8	393,3±3,3*
Stange test (breath-hold on inhalation), sec	23,8±2,3	37,1±2,7*
Abdominal muscle strength, sec	13,8±6,5	39,4±6,3*
Back muscle strength, sec	12,9±5,8	28,5±8,6*
Ruffier index, units	19,8±6,3	12,1±5,2
Robinson index, units	112,4±3,7	84,8±4,5
General physical performance, kgm/min·kg	41,7±2,2	54,6±2,5*

Note: * – p<0.05, indicating significant differences between the main group and the comparison group

Since there were no significant differences in the evaluated parameters between groups at the beginning of the study, it was reasonable to conduct a comparative analysis after six months of observation. The results showed that in the main group, the comprehensive therapy course significantly improved respiratory function indicators. Chest excursion was 2.2 times greater in the main group compared to the comparison group receiving only baseline therapy (3.8±3.9 cm vs. 8.5±5.3 cm, respectively). The main group also showed increases in vital lung capacity and vital index to 3.3±1.8 L and 56.2±2.3 mL/kg, exceeding the comparison group values by 2.5 and 1.3 times, respectively. Comprehensive therapy led to an increase in forced expiratory volume (3.8±1.8 L) and peak expiratory flow rate (393.3±3.3 L/min) compared to those in the comparison group receiving standard therapy (1.3±0.6 L and 316.1±6.8 L/min, respectively). Breath-hold time on inhalation in the main group was 1.6 times higher than in the comparison group, reaching 37.1±2.7 seconds. Similar improvements were seen in back muscle strength (2.2 times), abdominal muscle strength (2.9 times), and general physical performance (1.3 times).

Significant improvements were also observed in the psychoneurological status of the main group (Figure 2).

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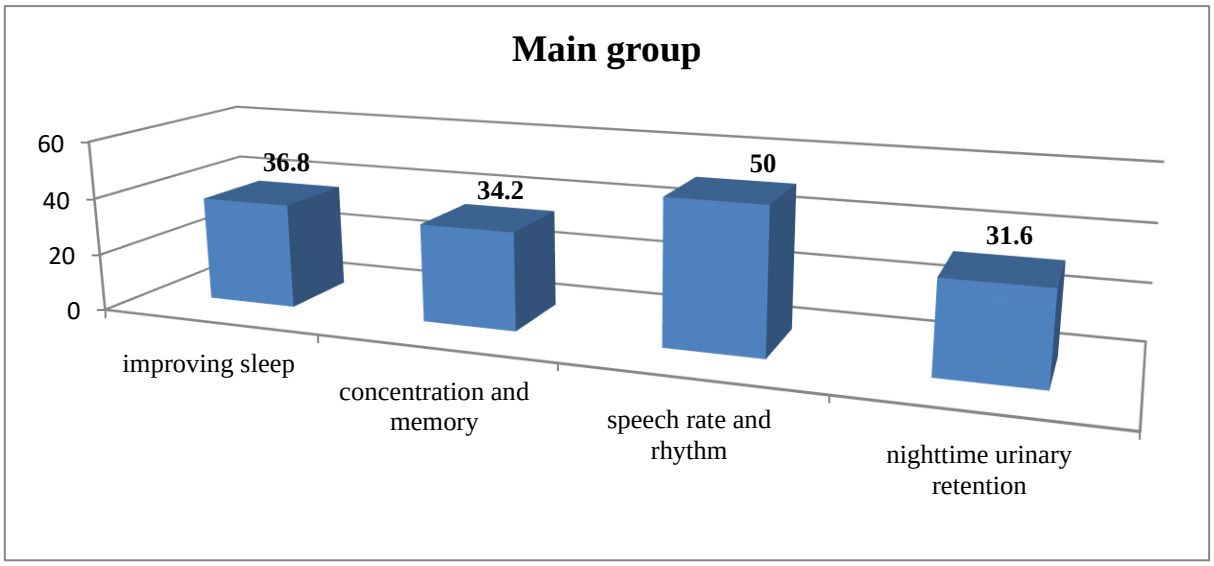


Figure 2. Neurological status of children in the main group under comprehensive therapy

In 36.8% of children (n=14), improvements in sleep and its quality were observed, while attention span and memory were restored in 34.2% (n=14) of cases. The children were more engaged, their attention span increased significantly, and fatigue decreased. Due to the activation of the brain's speech areas, including both expressive (motor) and receptive (sensory) speech, improvements in speech rate and rhythm were noted (n=19; 50%). Additionally, the activation of the Barrington center, responsible for regulating urination, led to the development of circadian rhythms and the habit of bladder control at night in 31.6% (n=14) of children.

Upon enrolling children with BA in the study, it was found that high levels of TNF-α, IL-4, and IL-8 correlated with the extent of CNS damage, as confirmed by elevated NSE levels. This further illustrates the systemic and profound interconnection between immune and neurological processes. Meanwhile, low levels of physical development and its disharmony were associated with decreased serum insulin-like growth factor-1. Overall, the synergistic integration of data on inflammation and neurological conditions may lead to a deeper understanding of the pathogenesis of BA and perinatal CNS injuries in children.

One key aspect of a multimodal therapeutic approach may be combining anti-inflammatory therapy with neuroprotective drugs. For instance, TNF-α antagonists could help reduce systemic inflammation, potentially decreasing tissue damage not only in the respiratory tract but also in the CNS. The use of neuroprotectors (specifically, 0.1% nasal solution of Semax) aims to lower neuron-specific enolase levels (44.7±4.4 ng/mL at the start of therapy to 26.2±1.4 ng/mL at the six-month follow-up) and protect neurons, enhancing the therapeutic effect and improving disease prognosis. Nordic walking (NW) contributed to a 1.2-fold increase in insulin-like growth factor-1 levels, rising from 153.2±2.2 µg/L before treatment to 183.2±1.2 µg/L by the end, which should positively affect the physical development of children with BA against the background of long-term CNS effects (Table 2).

Table 2
Laboratory indicators in children with BA in the main group during therapy

Indicator	Main Group (1 Month of Observation)	Main Group (6 Months of Observation)	Reference Values
IL-4, pg/mL	8,98±0,33*^	4,9±0,15*	2,23±0,08
IL-8, pg/mL	58,13±1,38*^	29,24±0,68*	4,43±0,06
TNF-α, pg/mL	92,6±4,5*^	58,9±3,1*	9,87±1,9
NSE, ng/mL	44,7±4,4*^	26,2±1,4	15,9±1,4
Insulin-like Growth Factor-1, µg/L	153,2±2,2*^	183,2±1,2	213,2±1,7
**Note: * - significance compared to reference values ($p<0.05$)* *^ - differences between the main group's indicators at the start and end of therapy ($p<0.05$)*			

Therefore, when developing personalized therapy for BA in children, a comprehensive clinical-neurological examination that includes a range of functional parameters is necessary. The inclusion of the developed comprehensive therapy program for children with BA against the background of long-term CNS damage contributes to improved neurological status, leading to positive dynamics in the functioning of the respiratory and cardiovascular systems.

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The proposed comprehensive treatment program for BA in children with long-term CNS damage is a cyclical process and includes patient assessment, therapy adjustment (both pharmacological and non-pharmacological), and monitoring of treatment response with correction of identified neurological syndromes. The primary goal of the presented algorithm and a parameter of therapeutic efficacy is to achieve control with prolonged remission and to prevent exacerbations.

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