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MODERN TREATMENT OF HYPERKINETIC DISORDERS IN CHILDREN

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Abstract

The article is devoted to an important problem of pediatric neurology – hyperkinetic syndrome in children. It is widely known that hyperkinetic syndrome does not have nosological independence and is included in the structure of more than a hundred neurological diseases. The variety of these motor disorders includes a wide range of disorders from common motor tics to severe extrapyramidal disorders. In addition to the challenges of the diagnostic algorithm in verifying each clinical case, the most important task, to date, is the correction of these complex motor disorders.

During the treatment of these conditions, practical neurologists encounter polypharmacy, but even the simultaneous administration of several drugs does not lead to the desired effect. This fact has made it necessary to find new methods of treatment for these severe patients. Such a scientific and practical search has led to the use of botulinum toxin type A in the correction of hyperkinetic syndrome.

In our article, using specific clinical examples, namely, severe congenital muscular dystonia and Hallervorden-Spatz disease which is a rare degenerative condition, we made an attempt to give an appropriate reasoning to the use of the botulinum toxin A drug Xeomin (Merz). It has been demonstrated that botulinotherapy in these patients not only enables to increase the motor volume, but also helps significantly reduce the amplitude and frequency of hyperkinetic manifestations, which positively affects the life quality of both the patients themselves and their families. It is known that botulinum toxin type A is widely practiced in the treatment of spastic forms of cerebral palsy in children and is the best pathogenetic cure for leveling high muscle tone. However, the application of botulinum therapy for severe hyperkinetic disorders in a number of cases is also the only appropriate therapeutic solution. The choice of the Xeomin drug can be explained by its safety, since this botulinum toxin type A has a high specific biological activity and the lowest content of complexing proteins.

Keywords: *hyperkinetic disorders, muscular dystonia, children, Hallevorden-Spatz disease, botulinum therapy, xeomin.*

Introduction

Hyperkinetic disorders occupy a special place in the structure of motor disorders in children. The variety of hyperkinetic disorders includes various involuntary forced movements from tremor to myoclonus [*Golubev V, 1990; Belousova Y, 2006*; *Illarioshkin S, Ivanova-Smolenskaya I, 2011; Mikhailova S et al., 2011*]. Muscular dystonia is considered to be one of the most serious disorders of this group. It is characterized by irregular and irregularly repeating stereotypical changes in muscle tone in various muscle groups associated with the disbalance of excitatory neurotransmitters and characterized by constant or episodic muscle contraction with the formation of repeated stereotypic movements and/or postures, [*Oppenheim H, 1911; Belousova Y, 2006; Horstink M et al., 2007; Lu C et al., 2012*].

The term "dystonia" was first proposed by H. Oppenheim in 1911 to mean "a syndrome of constant muscle contractions that cause repeated twist-

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ing movements or pathological postures of the trunk, neck, arms, legs, and spasms of the facial muscles" [*Oppenheim H, 1911; Orlova O, 2008*].

According to the occurrence, dystonia takes the third place among all forms of movement disorders. According to the available estimates, the prevalence of dystonia can be 3-11 cases per 100,000 population for generalized forms (starting most often in the 1st-2nd decade of life and often having a hereditary nature) and 30-60 cases per 100,000 for focal (localized) forms that usually manifest at a later [*Horstink M et al., 2007; Lu C et al., 2012*] age.

There are several classifications of dystonia [*Zalyalova Z, 2005; Geyer L, 2006; Zalyalova Z, 2013*]. According to process diffusion, dystonia is divided into focal (one anatomical area is involved: blepharospasm, "writer" cramp, etc.), segmental (two neighboring areas are involved: blepharospasm + oromandibular dystonia), multifocal (unrelated regions: blepharospasm and "writer" cramp) hemidystonia (proximal and distal regions of limbs on one side of the body are involved) and generalized forms of dystonia.

The etiological classification of dystonia was proposed by S. Fahn, according to which dystonia is divided into four large heterogeneous groups: primary dystonia, dystonia plus (dystonia Parkinsonism, myoclonic dystonia), neurodegenerative diseases associated with dystonia, and secondary dystonia [*Fahn S, 1988*].

Primary dystonia is characterized as monosymptomatic in the clinical picture of the disease. According to the clinical genetic classification, DYT types 1,2, 4, 6, 7, 13, 14, 17 are assigned to primary dystonia. Hereditary neurodegenerative diseases associated with dystonia include five groups depending on the nature of inheritance: autosomal dominant, autosomal recessive, X-linked, mitochondrial and multiple forms [*Zalyalova Z, 2005; Ozelius L et al., 2011; Zalyalova Z, 2013*].

Secondary dystonia is the result of neurological or somatic diseases such as perinatal anoxia, bilirubin encephalopathy, head injuries, tumors, encephalitis, intoxication etc.

One of the most challenging and important issues is the approach to the treatment of dystonia. The main methods in the treatment of muscular dystonia include drug therapy (anticholinergics, muscle relaxants, benzodiazepines); chemical denervation (botulinum toxin injections); intrathecal administration of baclofen; chronic deep brain stimulation. As a rule, various combinations of medications, injections of botulinum toxin type A and neurosurgical correcting methods are used, which significantly improves the life quality of patients.

However, today, the botulism toxin injection method is becoming more and more common in the treatment of local dystonia throughout the world.

It is known that botulinum toxin was introduced in 1793 by the German doctor Justin Kerner. Later in 1895 another discovery was made by Dr. Emil Van Ermengem who revealed a bacterium that is responsible for botulism, thus proving the bacterial nature of this disease. In 1949 it was proved that botulinum toxin had a paralyzing effect on neuromuscular connection and it quickly found its application for medical purposes. In the 1970s, the American doctor Alan Scott began administering botulinum toxin to his patients with blepharospasm and had a positive effect. The first official drug containing botulinum toxin type A was "Oculinum" ("Botox") produced by the American company "Ocutinum, Inc", which was approved in the United States in 1989 and was intended to treat strabismus, blepharospasm and hemifascial spasm.

The first European analogue of Botox was Dysport launched in 1991 by the French company Beaufour Ipsen Ltd.

Preparations containing botulinum toxin type A.

Currently, the following drugs containing botulinum toxin type A are approved for injection in different countries:

1. **Botox** (Botox – USA), manufacturer – Allergan Pharmaceuticals Ireland,
2. **Dysport** (Dysport – France), manufacturer – Ipsen Biopharm Ltd,
3. **Xeomin** (Xeomin – Germany), manufacturer – Merz Pharma GmbH & Co. KGaA,
4. **Lantox** (Lantox – China), manufacturer – Lanzhou Institute of Biological Products.

Xeomin is approved for the use in the treatment of blepharospasm, cervical dystonia, arm spasticity after a stroke, facial wrinkles. In pediatric practice, there is only one currently registered official indication for the use of BTA (Xeomin), namely, spastic equinovarus and equinus foot deformity in cerebral palsy in children aged 2 to 18 years. The drug is a leophilisate, which is used to prepare a solution for intramuscular toxin injection

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

produced by Clostridium botulinum type A bacterium strain, freed from complexing proteins, and therefore has the lowest potential for the formation of neutralizing antibodies and, thus, does not cause allergic reactions), which is extremely important in pediatric practice. The indisputable advantages of Xeomin in comparison with other BTA drugs is its convenience for transportation (the drug is a lyophilisate and does not require cooling), its availability in bottles (for making a solution), as well as its packaging in 50 and 100 *units*, which makes it convenient for dose selection for children. However, the use of xeomin in children with hyperkinetic disorders can significantly neutralize motor impairment and not only improve the life quality of patients, but also of the whole family.

Two children with muscle dystonia syndrome of different genesis, were under observation at the Department of Neurology of I.M. Sechenov First Moscow State Medical University Children's Hospital. With the approval of board of doctors and the official consent of the child representatives, BTA (Xeomin) was administered to the children.

Clinical case No 1

Patient M., born on 10.12.2003

He first contacted the Sechenov First Moscow State Medical University Children's Clinical Hospital with complaints of a forced head position (tilting to the right shoulder and turning to the left), the body turned to the right, with apparent curvature and muscle tension.

According to the anamnesis: born from the 3rd pregnancy without special features, 1st natural labor and delivery at 40 weeks of gestation in the head presentation. According to the parents, early psychomotor and speech development was without features

The onset was in May 2016, when he got an injury to the cervical spine (asphyxiation) during a training session (wrestling section), followed by pains in the neck and, the next morning, a forced position of the head with a tilt to the right shoulder and a turn to the left. The diagnosis at the examination of traumatologists: the consequences of trauma to the cervical and thoracic spine, hypoxic-ischemic damage to the brain, hypoplasia of the right vertebral artery. The performed brain MRI revealed multiple foci of increased MR signal of various shapes and sizes, without focal edema and signs of volumetric effects on surrounding tissues, located subcortically in the cortex of the temporal and frontoparietal parts of both hemispheres. These changes were considered as gliotic posthypoxic foci of perinatal genesis. According to MR-angiography, narrowing of the vertebral artery was revealed. Shantz collar immobilization was performed, but the treatment had no effect.

Further, the boy was hospitalized at the Research Institute of Traumatology and Orthopedics (Moscow). Underwent examination: ultrasound examination of the neck muscles showed no data of traumatic injury. According to needle electromyography: no signs of volley activity of motor units in the neck muscles. During the repeated stimulation electromyography, normal indicators of M-responses on both sides were obtained. No changes in nerve conduction rates were noted. Examined by a neurologist on 11/03/17 with the conclusion: "Taking into consideration the dynamic observation and examination results, the clinical picture can be classified as consistent with spastic muscle torticollis provoked by an injury to the cervical spine". Diagnosis: Focal cervical dystonia? An additional examination and consultation of a geneticist was recommended and baclofen symptomatic therapy was prescribed.

In order to verify, a diagnostic anesthesia was carried out in which the head was brought to a central position without effort and the diagnosis of torticollis of muscle origin was substantiated.

Gradually (during 2-3 months) there was an increase in the tone of the back muscles and a pathological tilt of the body with rotation, scoliosis, muscle defense and pain (Fig. 1a). An MRI of the thoracic spine revealed lumbar scoliosis. CT of the cervical spine revealed rotational subluxation of C1 vertebra to the left. Bilateral Kimmerle's anomaly. According to the repeated MRI of the brain under anesthesia with contrast enhancement, there was no pathological accumulation of contrast. A comprehensive examination carried out at University Clinical Children's Hospital allowed to rule out the Wilson-Konovalov disease, dopa-responsive dystonia, as well as genetic forms DYT1 (TORSIN1) and DYT6 (late torsion dystonia). In connection with the above-stated, the patient was diagnosed with torsion dystonia. He was prescribed finlepsin and clonazepam at age dosages. The child's parents refused further genetic research. A follow-up examination after 1.5 months revealed slight positive dynamics in the reduction of dystonia.

Four months later, the boy's parents contacted

the University Hospital with complaints of a tone increase in the legs, marked twisting movements in the body, regular dystonic posturing in the wrist according to the type of "writer's" cramp. On examination: cooperative, emotional - behavioral sphere is adequate. A pathological tilt of the head to the right shoulder with a turn in the opposite direction, the body tilts forward, twisting movements in the fingers of the right hand were noted during the examination. The child uses corrective gestures such as a hand touch to the back of the head, after which the pathological position of the head is temporarily leveled, squeezes his right hand into a fist to eliminate the writing spasm. As for the motor sphere: gait on a wide base with the body tilted forward. Muscle tone is not changed, D = S. The volume of active and passive movements is limited in all parts of the spine, in the right hand, in the knee joints on both sides. Muscle strength on a five-point scale: 5 points in all muscle groups. The pace of movement is reduced. Periosteal and tendon reflexes are responsive, D = S. There are no pathological signs. Stable in the Romberg test, satisfactorily performs the finger-bearing test on both sides, the heel-knee test, with dysmetria, on both sides. Surface sensitivity is not impaired. No pelvic abnormalities.

Botulinum toxin type A (XEOMIN drug) was administered for a total of *265 units* under the ENMG control with a Bo-Jekt needle according to the scheme:

- Pectoralis major sinistra – *20 units*,
- Latissimus dorsi sinistra – *15 units*,
- Ectopectoralis – *20 units*,
- sternocleidomastoideus – *20 units*,
- m.splenius capitis dextra – *20 units*, sinistra *40 units*,
- levator scapulae sinistra – *30 units*,
- m. Rhomboideus dextra – *30 units*,
- m. Trapezius dextra – *20 units*, sinistra *20 units*,
- m. semispinslis capitis dextra – *10 units*,
- m. Extensor indicicis – *20 units*.

The procedure was well tolerated, discharged on the 3rd day. According to the boy, at the time of

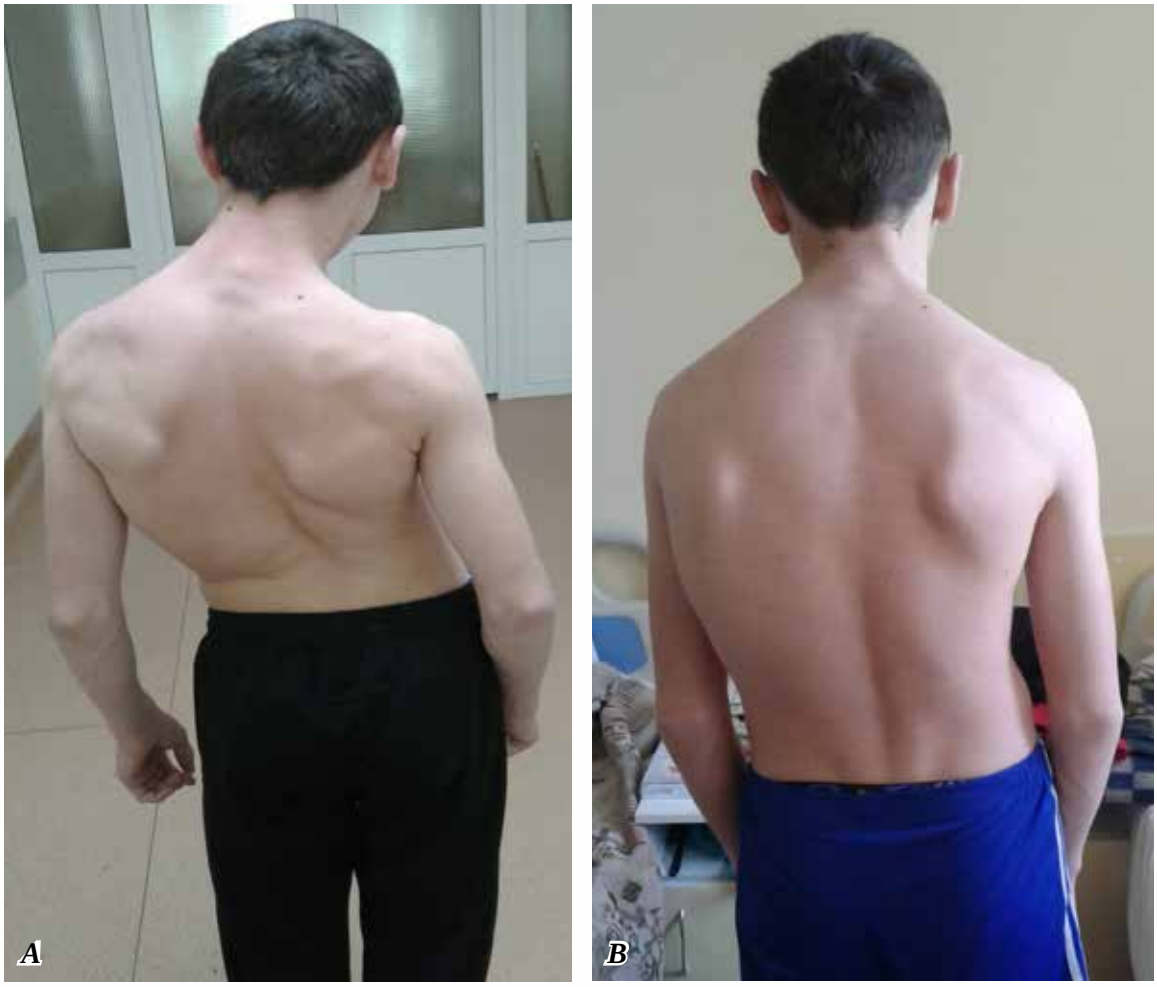

***Figure** 1. The patient before (A) and 3 weeks after (B) Xeomin therapy.*

discharge from hospital there was a decrease in painful twisting sensation in the thoracic spine.

On examination 3 weeks later, a decrease in muscle tone is noted, a slight pathological tilt of the head persists, but is much less troublesome (mainly with prolonged vertical load). Does not use corrective poses and gestures, there is no turn in the opposite direction. According to the patient, there is no pain in the thoracic and cervical spine (Fig. 1b).

On examination 9 weeks later: the pathological tilt of the head is minimal, the child maintains an upright posture with centralization of the head for a long time, the "writing cramp" does not bother. In the clinical picture, there is a pronounced kyphoscoliotic posture, neck muscle weakness during physical exertion remains. Swallowing and phonation are not disturbed.

This clinical case demonstrates the advisability of using BTA drugs in the first line of torsion dystonia therapy at any age, including in children. Taking into consideration the botulinum therapy carried out by Xeomin and the lack of effect of drug treatment, Clonazepam and Finlepsin were gradually canceled in therapy. The child was re-invited to hospitalization after 3 months for routine BT. During this period, he was consulted by neurosurgeons N.N. Scientific Research Institute of Neurosurgey to evaluate the feasibility of surgical intervention, and it was agreed to abstain from surgery until the age of 18. Thus, botulinum therapy can be considered the only effective therapy for this patient until the age of majority, possibly even later, in case of a refusal from neurosurgical correction.

Clinical case No 2

Boy A., born on March 18, 2007

The boy is under observation with a diagnosis of pantothenate kinase deficiency (Hallervorden Spatz syndrome). Cerebral palsy syndrome: spastic-hyperkinetic form. GMFCS 5 functional class. Oromandibular dystonia. Symptomatic torsion deforming dystonia. Dislocations of the ankle joints on both sides. Severe osteoporosis. Concomitant diagnosis: Protein-energy deficiency (-5.4 SD by weight, -3SD by BMI) Functional constipation. Biliary tract dysfunction. Secondary pancreatic changes.

The parents brought the child to the Children's Psycho-Neurological Department of Sechenov University Children's Clinical Hospital with complaints of severe involuntary forced torsional movements in the muscles of the trunk and limbs; forced position due to constant, sequential serial torsion spasms; pronounced oromandibular hyperkinesis, tongue hyperkinesis (The child's mother holds the lower jaw to help him avoid biting the tongue); difficulty feeding; chronic constipation. The weight at the time of hospitalization: 12.400 *kg*. Age: 11 years old.

According to the anamnesis: the child is from the 2nd pregnancy, 2nd urgent on time delivery. Pregnancy and delivery, according to the mother, were without features. Birth weight 3650 *g*, length 52 *cm*, Apgar score 8/9 points. The condition after birth was evaluated as satisfactory. Early motor development: keeping the head from 2 months old, turning over from 4 months old, sitting from 6 months old, standing with the support from 9 months, crawling on all fours from 2 years old, unstable, walking with one hand from 3 years old, independently - from 5 years old. Speech developed with a delay: individual syllables from about 2 years, no phrasal speech. Diagnosed with cerebral palsy, spastic diplegia at the age of 3 years. Received habilitation therapy.

From September 2012, muscle tone began to increase gradually, baclosan and cortexin were prescribed by the local doctor, underwent rehabilitation courses in Yevpatoria without positive dynamics, and in the spring of 2013 the boy's condition worsened sharply. On the consultation at the Genetic Center: Niman-Peak disease was ruled out. On brain MRI in 2008, 2009, 2013: without structural pathology. Examined at the "Psychoneurological hospital for children with central nervous system damage and mental disorders" State Clinical Healthcare Institution of Moscow Region with a diagnosis of cerebral palsy: spastic-hyperkinetic-atactic form, level 3 according to GMFCS. Equinovarus fixed contracture of the ankles on both sides. General speech underdevelopment of level 1. Visual impairment. Delay in psycho-speech development. Digestive tract functional disorders.

From 2013 to 2015, the boy's condition began to deteriorate significantly: muscle tone began to grow rapidly, hyperkinesis of the tongue and oromandibular zone (smacking) appeared. The boy began to "throw back", but retained the ability to maintain an upright posture, sat, walked with support. The therapy was prescribed: PK-Merz (without significant dynamics), Nakom (decrease in "throwing back"), Baklosan (decrease in muscle tone), Akineton (some decrease in hyperkinesis). After a single replacement of the full dose of PK-Merz with Nakom, an increase in hyperkinesis and a worsening of the condition were noted. Clonazepam was prescribed with a gradual increase in dose with slight positive dy-

namics. The repeated MRI of the brain on 05/17/15 revealed bilateral lesion of pale balls of both hemispheres for the first time. According to re-consultation by a geneticist: karyotype 46 XY; Fahr disease, Martin-Bell, Lesch-Nyhen syndromes were ruled out; 2 mutations in the PANK2 gene (pantothenate kinase 2) responsible for the development of Hallerwarden-Spatz disease were revealed.

Hallervorden Spatz is a rare neurodegenerative disease, accompanied by the deposits of iron in the basal ganglia (in a pale ball and in the substantia nigra). The occurrence of the disease is an average of 1-3 people per 1 million of the population [*Deschauer M. et al., 2012; Dezfouli M et al., 2013; Zakharova Y, Rudenskaya G, 2014; Pshikhacheva L, Rabadanova A, 2018*].

At the time of hospitalization, the child is in serious condition due to hyperkinetic syndrome, severe torsion and oromandibular dystonia, spastic contractures of ankle, knee, and hip joints; tetraparesis with a complete loss of motor functions; dysphagia. The boy is constantly in a forced position, due to constant torsion attacks; severe pain syndrome (Fig. 2a). The child's mother constantly has to keep his lower jaw when he is awake, in order to help him prevent biting his tongue and lips, periodically the boy tries to hold the lower jaw himself with his hand.

The neurological status at the time of admission to the department: general condition is serious due to the underlying disease, accompanied by gross hyperkinetic syndrome, tetraparesis, oromandibular dystonia. Visually significant deficit of body weight, diffuse atrophy of the muscles of the arms and legs. Emotionally instable, sensitive, acutely anxious. Intellect by age is reduced. The child reacts to the examination with a motor reaction, smiles, differentiates people, has expressive speech in the form of separate sounds, there are attempts of sign language. Self-care skills are absent, completely dependent on the mother. Performs simple commands (squeeze a hand, take an item, look at an item, etc.)

There are no meningeal symptoms. CBN (cranio-brain nerves): no ptosis, convergent strabismus, insufficient convergence, average pupil size D = S, nasolabial folds are symmetrical, tongue deviation to the right, permanent tongue hyperkinesis, gross oromandibular dystonia, dysphagia. Hearing is not reduced. In the motor sphere: spastic tetraparesis. In the motor sphere: spastic tetraparesis. Rough deforming torsion dystonia, dystonic deformity of the feet with the formation of persistent contractures in the ankle joints, "extensor position" in the knee joints, constant twisting dystonic attacks in the hands, constant torsion cramps. Independently keeps his head briefly in a position on his stomach. Muscular hypertonicity in all limbs, more apparent in the legs, D = S. Muscle strength reduced to 3 points. Tendon reflexes are high, symmetrical, reflexogenic zones are expanded, no feet clonuses. Coordination tests and sensitivity cannot be evaluated due to the patient's motor and mental status. The functions of the pelvic organs are not controlled, spastic constipation. Pronounced generalized hyperhidrosis, marbling of the skin. Red persistent dermographism. Kyphoscoliotic posture.

In the department, the boy was consulted by a gastroenterologist. Diagnosed with protein-energy malnutrition (-5.4 SD by weight, -3SD by BMI), functional constipation, biliary tract dysfunction, secondary reactive changes in the pancreas. Recommended: enteral nutrition based on the actual body weight of 1300 *kcal*/*day* - fractional nutrition

Figure 2. *"Dystonic torsion attacks". A) The boy is trying to hold his lower jaw to prevent "biting" of the tongue and lips; B) One month after Xeomin therapy.*

6 times/day with the predominance of the enteral mixture. Therapy: Creon 10 thousand units - 1 capsule 3 times per day at the beginning of the meal - for 1 month, Forlax - 4 *g* in the morning on an empty stomach for a long time + rectal suppositories to stimulate bowel movements. Bifiform - 1 capsule 1 time a day- for 1 month, Flamin 1 t 3 times per day 30 minutes before meals with warm water – for 21 days (courses 2-3 times a year).

Consulted by a neurosurgeon: it is recommended to continue conservative treatment. Repeated consultation in 4-6 months.

At the time of admission, the boy received 7 drugs: Phenobarbital 100 *mg* 1/8 tab in the afternoon, 1/4 at night;

- Akineton 2*mg* 1/2 t 3 times a day;
- PK-Merz 100 *mg* 1/4t 3 times a day;
- Sirdalud 4 *mg* 1/2t 3 times a day;
- Baclofen 10 *mg*, 1/4t morning/day, 1/2 t evening;
- Clonazepam 2 *mg* - 1/2 morning/evening;
- Neuleptil – 2 drops in the evening

Any attempt (during the entire period of hospitalization) to reduce or adjust therapy in order to increase its effectiveness, the child "responded" with a sharp deterioration, and increasing the doses didn't result in a significant positive reaction. It was agreed to use botulinum therapy with Xeomin.

Xeomin was administered according to the scheme:

- m.temporalis *10 units* right/left
- m.masseter *15 units* right/left
- m.spltniuscapitis *20 units* right/30 units left.
- A total of *100 units*.

The procedure was well tolerated.

After 4 weeks, a significant improvement was noted. The child can lie on his back for a long time, oromandibular dystonia does not bother (Fig. 2b). However, apparent weakness was observed in the oral and pharyngeal muscles. Mother noted difficulties in feeding, the child began to choke, cough when drinking liquid and semi-liquid food. In drug therapy with BT, it was possible to reduce the doses of Sirdalud, Baclofen, Phenazepam.

At the control examination 9 weeks later, the child sits in a stroller without additional fixation of the head and the support of lower jaw by the parents. He turns his head in both directions freely in the supine position and sits with support on the head holder of the stroller. Swallows well, does not choke. The phonation is not disturbed. There is an improvement in the digestive tract, absence of pronounced tension in the muscles of the abdominal press and the back. In a supine position, the boy can lie for a long time, dystonic attacks are practically not disturbing and appear only when the boy tries active movements (upheaval, leg movements) or an emotional reaction.

Taking into consideration the positive result and a decrease in muscle tone in a child with critical motor deficiency and dysphagia due to severe hyperkineses, as well as the presence of protein-energy insufficiency, the issue of gastrostomy installation is being considered. And this has become possible only after the torsion dystonic attacks were leveled and muscle tone decreased.

At the time of examination, 9 weeks after the BT procedure, the continuous use of neuleptil was canceled in drug therapy, the doses of phenobarbital and baclosan were reduced. These changes in drug therapy were well tolerated.

Conclusion

The syndrome of muscular dystonia does not have nosological independence and is included in the structure of more than one hundred neurological diseases. According to diffusion, dystonia can be focal, multifocal, hemidistonic and generalized. At present, the best standard for the treatment of focal and multifocal forms of dystonia in adults is the chemical denervation of the muscles of the affected area with botulinum toxin type A [*Timerbaeva S et al., 1998; Orlova O et al., 2008; Likhachev S. et al., 2009; Belova A, Prokopenko S, 2010; Karabanov A, Illarioshkin S., 2012; Akhmadeeva L. et al., 2017*]. This technique allows to achieve good results up to persistent long-term leveling of motor impairment. In cases of generalized dystonia, the use of BTA helps the patient to improve the quality of life, increase efficiency, as well as to facilitate the care of a patient. For generalized forms, along with BTA, it is necessary to conduct an appropriate accompanying constant drug therapy to prevent deterioration.

By analogy with adults, the use of botulinum therapy in children is the most effective and affordable method for the treatment of muscular dystonia, and the safety and low allergenicity of Xeomin allows to recommend it for widespread use in a pediatric neurological therapy.

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