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CLINICAL CHARACTERISTICS IN CORNELIA DE LANGE SYNDROME OF THE FIRST TYPE ON THE EXAMPLE OF A CLINICAL CASE

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ABSTRACT — Relevance: Cornelia de Lange syndrome is a rare congenital disorder associated with orphan diseases and is characterized by multiple stigmas of dysembryogenesis at birth. This syndrome occurs in newborns with a frequency of 1: 30,000 to 1: 10,000; there are no gender differences in the frequency of occurrence. Cornelia de Lange syndrome is a dominantly inherited disease, but most cases are sporadic de novo, therefore, mainly children with Cornelia de Lange syndrome are born from genetically healthy parents.
Purpose: Using the example of a clinical case, to demonstrate the characteristic features of the clinical picture, namely the phenotype and deviations of the neurological status in Cornelia de Lange syndrome.
Materials: Girl M., born in 2018, at the age of 1 year 11 months, together with her mother, was admitted to the Center for Pediatric Neurology and Medical Rehabilitation No. 2 in Tver, Russia. The girl had the following complaints (according to the mother): the child does not walk independently, stands with legs apart, and does not speak. She has obsessive movements ("crossed out" hand movement, waves her arms, puts his right hand behind the body, shakes objects in the mouth area), lags behind in development, does not differentiate significant adults, does not speak, there is no pointing gesture. Inpatient examination and treatment was carried out at the Center for Pediatric Neurology and Medical Rehabilitation.
Results: Based on the examinations, the following diagnosis was established: Cornellia de Lange syndrome, type 1. Delayed physical, static-motor and mental development. Short stature. Congenital kidney anomaly: horseshoe kidney. Sensorineural hearing loss I-II degree The priority areas in this case are: improving the patient's quality of life, stimulating the development of the mental and motor spheres, socialization with other children.
Conclusion: This clinical case demonstrates the need for early diagnosis of genetic disorders in order to build correct social and medical rehabilitation.

KEYWORDS — Orphan diseases, Cornelia de Lange syndrome, Brahman de Lange syndrome.

RELEVANCE

Cornelia de Lange syndrome is a rare congenital disorder associated with orphan diseases and is characterized by multiple stigmas of dysembryogenesis at birth.

The risk factors for the development of Cornelia de Lange syndrome in the fetus do not differ from those for other de nova mutations.

Etiologically, this disease is genetically determined. In the described syndrome, the normal karyotype is most often preserved. However, the genetic heterogeneity of the disease should be considered. Three different variants of genetic disorders have been identified: NIPBL (about 50%), SMCIA (5%), and SMC3. The SMC1A gene is located on the sex X chromosome — with its defects, inheritance is linked to the sex (men are more often sick, women are heterozygous carriers). This gene encodes a subunit of the cohesin protein complex. One case described is associated with a mutation in the SMC3 gene, which also encodes one of the cohesin subunits. In some cases, a cytogenetic study finds microduplication of the q25 — q29 loci of chromosome 3.

From the described violations of protein synthesis, it can be concluded that the pathogenesis of this disease is associated with disruption of the function of cohesin proteins. Cohesins play an important role in the process of cell division, DNA repair, and regulation of gene expression. Due to the dysregulation of these processes, organogenesis is impaired. Significant changes in the brain are revealed (aplasia of the cortex, underdevelopment of the Roland groove, impaired myelination, hypoplasia of the thymus).

Depending on the severity of the impairment of psychomotor development, there are two variants of the course of Cornelia de Lange's syndrome. The first type, classic, is accompanied by a significant delay in physical and intellectual development, with gross defects. The second type, benign, is characterized by facial and minor skeletal anomalies, but borderline retardation of psychomotor development and the absence of gross defects. The final diagnosis is made on the basis of the phenotype, karyotype research and methods of cytogenetic analysis.

Cornelia de Lange syndrome is characterized by features of the phenotype in the form of typical

stigmas of dysembryogenesis, skeletal anomalies (funnel chest, short neck, spina bifida, articular contractures, hypoplasia and deformity of the hands and feet, defects in the development of fingers, congenital dislocation of the hip). Also congenital dislocations of the hip (tetrad of Fallot, coarctation of the aorta, heart septal defects, pulmonary valve stenosis, pyloric stenosis, hydronephrosis, horseshoe kidney, polycystic, gastroesophageal reflux, incomplete bowel rotation, as well as hypospadias, scrotal hypoplasia, bicornuate uterus). Appearance features are common, such as thin fused eyebrows, long curled eyelashes, a thin upper lip, marbled skin, hypertrichosis, and short stature. Possible delay in sexual development. Due to imperfections in the airways, there is a high likelihood of frequent recurrent respiratory diseases.

In the clinical picture of the syndrome, various disorders of the neurological status are revealed, manifested by a delay in neuropsychic development and pathologies of the sensory organs. Visual impairment in the form of myopia, strabismus, astigmatism, atrophy of the optic nerves, coloboma of the optic nerve, as well as hearing impairment — bilateral sensorineural hearing loss, conductive hearing loss, or their combination are likely. Such children are characterized by episodic convulsive readiness, muscle dystonia, and stereotypic hand movements. Higher nervous activity also suffers, auto-aggression is possible, mental retardation of varying degrees, up to imbecility;

In addition to the systemic examination, full genome sequencing of the proband is required to make a diagnosis.

No specific treatment has been developed. Neurometabolic, nootropic drugs, vitamins, speech therapy and psychological correction are used symptomatically.

Life expectancy depends on the severity of the defects of vital organs, on the quality of medical care, as well as the care of a sick child.

PURPOSE OF THE STUDY

Using the example of a clinical case, demonstrate the characteristic features of the clinical picture, namely the phenotype and deviations of the neurological status, in Cornelia de Lange syndrome.

MATERIALS AND METHODS

Girl M., born in 2018, at the age of 1 year 11 months turned to the Center for Pediatric Neurology and Medical Rehabilitation of GBUZ KDB № 2 in Tver. Her mother complained, the child does not walk independently, stands with legs, does not speak, obsessive movements (*crossed out* hand movement, waves his arms, puts his right hand behind the body, shakes objects in the mouth area), lags behind in development, does not differentiate significant adults, does not speak, there is no pointing gesture.

Inpatient examination and treatment was carried out at the Center for Pediatric Neurology and Medical Rehabilitation.

RESULTS AND DISCUSSIONS

From the history of the patient's life, it is known that the girl was born from the 7th pregnancy, proceeding with the threat of termination of pregnancy, edema, high blood pressure, toxicosis, weight loss by 20 kg. Childbirth 3rd, at 37 weeks, urgent in breech presentation, by cesarean section, with an umbilical cord entwined around the neck and intrauterine fetal hypoxia. Body weight at birth 3480 g. Length 52 cm. Score on the Apgar scale 7/9 points. Discharged home on the 5th day.

Delayed neuropsychic and motor development was noted throughout life. Problems with humming, babbling, emotions from 6 months (according to the mother), motor development with a delay: he holds his head from 4 months, turns over from 6–8 months. Was observed by a neurologist irregularly from 3 months: PGIP of the central nervous system, syndrome of motor disorders (at 3 months — adductor spasm, delayed motor development). A course of exercise therapy and massage was carried out. Consultation with a neurologist at 11.5 months: PHIP of the central nervous system, grade 2, movement disorders syndrome, they refused inpatient treatment and examination, underwent an outpatient course of treatment. At the age of 1, the diagnosis was made: delayed motor development, syndrome of motor disorders. The treatment took place on an outpatient basis. According to neurosonography data: MPSH 4 mm, PRBZH 6 mm each, III ventricle 3.7 mm. Abdominal ultrasound was without pathology.

At 1 year 3 months, the child was again consulted by a neurologist about the delay in physical development, in the neurological status, muscle hypotonia, NRD: sits for a short time, staggering with a fall on his back, moves by jumping *like a frog*. Recommended examination — MRI of the brain, ENGM to exclude muscular dystrophy.

At 1 year 11 months, the diagnosis was made: Organic lesion of the central nervous system, delayed psychoverbal and motor development (genetically unverified form). Sent for inpatient examination and treatment at the Center for Pediatric Neurology and Medical Rehabilitation.

On admission to the hospital, somatically — a phenotype characteristic of Cornelia de Lange's syndrome. Height 76 cm (<5 percentile), weight 10.3

kg (<5 percentile), MG 47 cm. BMI = 17.8. Multiple stigmas of dysembryogenesis: microcephaly, deformity of the hands of both hands (flat scapular hands with clinodactyly of the little fingers, thumbs located proximally), varus-valgus deformity of the right and left foot, high palate, conical teeth, short neck, hypertrichosis of the whole body. The skin is clean, pale with a marble tint. The mucous membranes are pale pink, clean, moist, the tongue is coated with a white coating. Breathing is puerile. BH 30 times per minute. Heart sounds are sonorous, rhythmic. HELL 100/65 mm Hg Heart rate 140 beats per minute. The abdomen is soft and painless. The liver and spleen are not enlarged. The defecation is mushy, up to 3 times a day. Diuresis is not impaired.

From the side of the neurological status, there was a significant delay in CPR. Consciousness is clear. There are no general cerebral, meningeal symptoms. Partially accessible to verbal contact. Does not follow instructions. The head is microcephalic, in the sphere of cranial innervation: the sense of smell is preserved, the palpebral fissures are D = S, the pupils are round D = S, the reaction of the pupils to light is direct and friendly, the movement of the eyeballs is in full volume, the sensitivity on the face is preserved, the points of exit of the trigeminal nerve are painless. The face is symmetrical, nasolabial folds D = S, no nystagmus, increased pharyngeal reflex, phonation is not disturbed, head rotation and shoulder elevation are not disturbed, the soft palate does not sag, the tongue is in the midline. Tendon reflexes of the upper extremities of medium vivacity D = S, knee reflexes are reduced D = S, reflexes of the lower extremities are *flaccid* D = S, Achilles of medium vivacity D = S. There are no pathological reflexes. Dystonic muscle tone. Movement stereotypes: *crossed out* hand movement, waving his hands, waving his right hand behind the body, shaking objects in the mouth area, fingering fingers, *pinching*. Holds the head in the midline. Sits unstable, stands up with support, stands briefly with legs wide apart. Intelligence is reduced, understanding of active speech is incomplete, does not distinguish between significant adults, there is no active speech. Passive speech is selective. Emotionally labile.

The results of the examinations: ECG: no pathology. Standard EEG: there is a slowdown in the formation of the main cortical rhythms. Typical forms of epic activity have not been registered. TNSG: PRBZH on the right 4 mm, on the left 4 mm. III ventricle 3 mm. MRI of the brain: data for the presence of additional formations, foci of a pathological signal in the cerebral parenchyma were not obtained. Local expansion of the retrocerebellar subarachnoid space of the PCF. Ultrasound of the genitourinary system: horseshoe kidney.

Genealogical history: not burdened. The parents' marriage is unrelated.

Clinical blood test: no features

Biochemical blood test: alkaline phosphatase 431 U/L, AST 52 U/L, ALT 21 U/L, urea 4.4 mmol/L, lactate 2.56 mmol/L, otherwise no peculiarities

General urine analysis: no pathology.

Ophthalmologist's consultation: the optic discs are pale pink, the boundaries are clear. Arteries of normal caliber, veins are somewhat dilated.

Orthopedic consultation: equino-varus deformity of the right foot. Hallux valgus of the left foot. Deformation of the hands of both hands (flat, spatulate hands with clinodactyly of the little fingers, thumbs located proximally).

Speech therapist consultation: speech development dysphasia. Sensorimotor alalia.

Psychiatric consultation: delayed neuropsychic development.

Endocrinologist consultation: lag in physical development threatened by iodine deficiency. Short stature.

Consultation with an audiologist: bilateral sensorineural hearing loss, I–II degree.

Consultation with a geneticist: undifferentiated genetic pathology, karyotype 46, XX. Direction for whole genome sequencing.

Whole genome sequencing: a previously undescribed heterozygous mutation in exon 28 of the NIPBL gene was identified, leading to an amino acid substitution at position 1805 of the protein. Heterozygous mutations in the NIPBL gene have been described in patients with Cornellia de Lange syndrome, type 1.

Based on the examinations, the following diagnosis was established: Cornellia de Lange syndrome, type 1. Delayed physical, static-motor and mental development. Short stature. Congenital kidney anomaly: horseshoe kidney. Sensorineural hearing loss I–II degree

The priority areas in this case are improving the patient's quality of life, stimulating the development of the mental and motor spheres, socialization of the child in the children's society.

CONCLUSION

This clinical case demonstrates the need for early diagnosis of genetic disorders in order to build the correct social and medical rehabilitation of children with these clinical manifestations. Confirmation of genetic analysis leads to predicting the developmental lines of these children in order to develop rehabilitation measures, including the need for coordinated work of such specialists as defectologists, speech therapist,

neuropsychologist, and ergotherapist. It is also required to consult pregnant women about the presence of various orphan diseases, their manifestations and consequences for the formation of the correct social strategy in society.

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