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MODERN VIEWS REGARDING THE ETIOPATHOGENESIS, DIAGNOSTIC, TREATMENT AND PREVENTION OF APERT SYNDROME

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Relevance. Acrocephalosyndactyly – a group of syndromes of multiple congenital malformations (MCM), the main components of which are acrocephaly and syndactyly. The most common nosological form of this group is Apert syndrome. Given the manifestation of the syndrome at birth and severe congenital defects of the musculoskeletal system, brain, cardiovascular system and others, this disease is of practical interest to doctors of many specialties.

Objective: to generalize modern ideas about the pathogenetic mechanisms, diagnostic, treatment and prevention of Apert syndrome.

Materials and methods. Clinical case of Apert syndrome. Clinical and genealogical, biochemical, cytogenetic, instrumental methods of examination.

Results. The paper presents a clinical case of Aper syndrome in a newborn girl with multiple malformations. Modern information on pathogenetic mechanisms, diagnostic, treatment and prevention of Aper's syndrome is provided.

Conclusions. Apert syndrome belongs to a group of syndromes of multiple congenital malformations that require the attention of doctors of various specialties. The main clinical manifestations of the disease are quite specific which allows to establish the diagnosis at birth. At the core of Aper's syndrome are mutations in the FGFR2 gene. There is prenatal diagnostic of the disease. Reconstructive surgical methods of treatment have been developed. Timely comprehensive treatment and rehabilitation allow such patients to adapt to society.

Key words: acrocephalosyndactyly, Apert syndrome, FGFR2 gene mutations, syndromic craniostosis, craniofacial dysostosis.

Relevance. Acrocephalosyndactylies – a group of syndromes of multiple congenital malformations (MCM), the main components of which are acrocephaly and syndactyly. The most common nosological form of this group is Apert syndrome [1-5]. Given the manifestation of the syndrome at birth and severe congenital defects of the musculoskeletal system, brain, cardiovascular system and others, this disease is of practical interest to doctors of many specialties. Apert syndrome is inherited by autosomal dominant (AD) pattern. The frequency of Apert syndrome is 1 case per 100-200 thousand newborns. The gender ratio is 1:1. There is a link between older parents and the formation of Apert syndrome. Almost all published cases are sporadic due to the emergence of new mutations. The probability of having another baby with Apert syndrome in healthy parents was low, and the risk for children of a person with Apert syndrome is 50% [3, 4, 6]. Despite the severe external manifestations of the disease, almost half of patients have a normal level of intelligence. Early comprehensive treatment with subsequent rehabilitation allows to adapt such patients in society [7].

Objective: to generalize modern ideas about the pathogenetic mechanisms, diagnostic, treatment and prevention of Apert syndrome.

MATERIALS AND METHODS

Clinical case of Apert syndrome, used clinical and genealogical, biochemical, cytogenetic, instrumental methods of examination. Scientific publications on the definition of modern views on pathogenetic mechanisms, diagnostic, treatment and prevention of acrocephalosyndactyly have been studied.

RESULTS AND THEIR DISCUSSION

The syndrome was first described in 1894 by S. Wheaton. In 1906, the French pediatrician Eugene Apert published observations of 9 patients, and in 1920 Edwards Park and Grover Powers wrote a detailed review [3, 4]. At present, Apert syndrome is divided into 2 subtypes. Classic Apert syndrome (subtype I), which is characterized by typical for this syndrome acrocephaly and severe syndactyly, which can be compared with a «spoon» when all the fingers are fused, and a «mitten»

or «obstetrician's hand» when the thumb is free and opposite fused four fingers. Apert-Crouzon syndrome (subtype II) is an intermediate form between the classic Apert and Crouzon syndromes, i.e. in this syndrome more pronounced hypoplasia of the upper jaw. At the same time, the phenomena of syndactyly are less pronounced than in typical Apert syndrome, because both the thumbs and the little fingers are free [8].

Etiopathogenesis. Apert syndrome is based on mutations in the FGFR2 gene, which is located on the long arm of chromosome 10, locus 10q26, and encodes a type 2 fibroblast growth factor receptor. Apert syndrome is caused by one of two missence mutations in the FGFR2 gene, which involves two related amino acids: S252W and P253R, in 71% and 26% of cases, respectively. Limb deformities are more severe in patients with the P253R mutation (replacement of proline with arginine at the 253rd position of the amino acid chain). Patients with this mutation also have better results after facial and skull surgeries. The cleft palate is more characteristic of patients with the S252W mutation (replacement of serine by tryptophan at the 252nd position) [5, 7].

Mutations in this gene also cause Crouzon syndrome and Pfeiffer syndrome. Receptor defect in Apert syndrome is also the cause of congenital malformations of other structures, which involve fibroblasts (walls of large vessels, heart, facial bones, trachea) [9-13].

The missense mutation in exon 7 of the FGFR2 gene damages the protein in the linker region between the second and third immunoglobulin-like domains. The study of fibroblasts showed ectopic KGFR expression of the FGFR2 region, which was associated with limb pathology. This correlation was the first genetic evidence that abnormal KGFR expression is the cause of syndactyly in Apert syndrome [3, 4, 9].

Phenotypic manifestations. The main diagnostic signs of Apert syndrome are acrocephaly and bilateral "mitten" syndactyly of the hands and feet, which are observed in 100% of cases. Deformation of a skull represents the craniosynostosis connected with early closing of coronal and other sutures. These malformations are typical and specific for the clinical diagnosis «Apert syndrome» [1-3].

Babies' body length and weight are above the 50th percentile, but over time, growth retardation begins, especially in adolescence. In 50% of cases there is mental retardation of varying severity. In neuroimaging (neurosonography, computed tomography, magnetic resonance imaging) the most common findings are agenesis of the corpus callosum, ventriculomegaly. Brain defects such as internal hydrocephalus, aplasia or hypoplasia of the corpus callosum, aplasia or hypoplasia of the transparent membrane are observed in 60% of patients. The brain is enlarged vertically and reduced in anterior-posterior size. All children have an oblique position of cheekbones [11].

Typical facial changes include: hypertelorism, exophthalmos as a result of spheno-ethmoid-maxillary hypoplasia and flattening of the orbits, antimongoloid slanting palpebral fissures. These defects are associated with craniostenosis and deformation of the cuneiform bone with the displacement of its large wings to the front. The middle parts of the face are hypoplastic, the nose is short with a flattened back, with stenosis/atresia of the nasal choanae, possible deviation of the nasal septum. The cleft of a soft palate is registered in 30% of cases. Dental anomalies, prognathism were discribed. The ears are set low, there is the likelihood of hearing loss in the future [12].

Internal organs defects, noted in Apert syndrome, include congenital heart disease (CHD) and defects of blood vessels (pulmonary artery stenosis, dextraposition of aorta, ventricular septal defect, fibroelastosis) – 10-25%; anomalies of the genitourinary system (polycystic kidney disease, hydronephrosis) – 9.6%; defects of the gastrointestinal tract – 1.5%; respiratory system defects – 1.5%. In female patients, bicornuate uterus, vaginal atresia are also described, in male patients – cryptorchidism, diaphragmatic hernia [13].

Prenatal diagnostic is possible throughout pregnancy. The ultrasound marker is the thickening of the collar space in the first trimester. If Apert syndrome is suspected in the process of prenatal diagnostic, molecular genetic research (amniocentesis) at 16 weeks of gestation and examination of parents are recommended [10, 14, 15].

In order to verify the diagnosis of «Apert syndrome» cytogenetic study is recommended to exclude chromosomal syndromes and molecular genetic diagnostic, which is based on the search for mutations [11].

The differential diagnosis of Apert syndrome is made with other acrocephalosindactylies (type II-IV): Pfeiffer, Crouzon, Saethre-Chotzen, Muenke and Jackson-Weiss syndromes [10].

There is no specific treatment for Apert syndrome to date, but palliative and symptomatic measures can significantly alleviate the patient's condition and improve their quality of life. Reconstructive operations are performed to correct craniofacial changes. Surgical treatment is aimed at increasing the volume of the skull and correction of syndactyly. Neurosurgical treatment includes early cranioectomy of the coronal suture and fronto-orbital reposition [9].

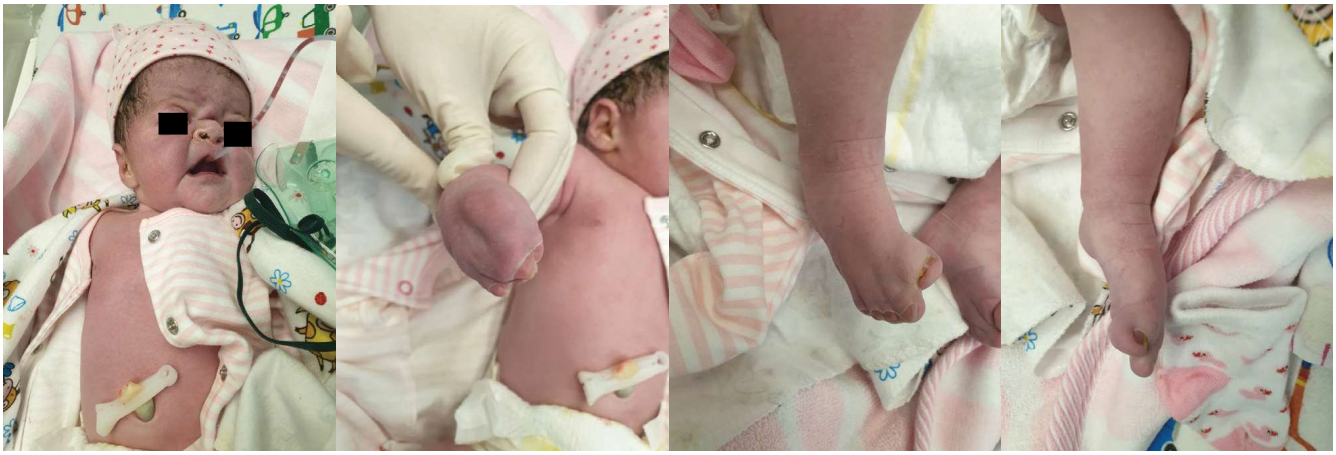
Prevention consists in planned management of pregnancy, at the burdened family anamnesis, obligatory medical and genetic consultation, which consists in specification of the genetic diagnosis, explanation of risk of transfer of a disease to descendants, possibilities of molecular genetic research, detection of a mutation with the subsequent prenatal diagnostic. Prenatal ultrasound diagnostic of Apert syndrome is difficult due to the late formation of synostosis, which can be detected in the early third trimester of pregnancy [15].

The minimum set of observations includes regular examinations by surgeons, neurologists, ophthalmologists, pediatricians. At high intracranial

pressure immediate decompression of a skull is required. Respiratory abnormalities can lead to early death and require active treatment. Hearing can be severely reduced due to chronic otitis or abnormalities of the inner ear. Exophthalmos increases the risk of corneal ulcers. Children do not adapt well in society. Life prognosis is favorable, life expectancy up to 60 years [10, 15].

As an illustration, we present a clinical observation of Apert syndrome in a newborn girl with multiple congenital malformations. The child's parents are phenotypically healthy, the mother is 27 years old, the father is 28. The marriage is registered, not blood related. The mother of the child has a history of menstrual irregularities and operated on an ovarian cyst, taking Duphaston. During pregnancy there was edema of the lower extremities, at 37 weeks there was polyhydramnios. Heredity of both parents is burdened by oncopathology. Parental work is related to chemical and physical factors. According to the mother, the child's father drinks alcohol every week.

The child was examined by a neonatologist, geneticist and narrow specialists in the first days of life. The girl is from the first desired, unplanned pregnancy, which took place against the background of anemia, the threat of miscarriage and polyhydramnios. She was born at 38 weeks of gestation naturally. Apgar score at birth – 7/7 points. Anthropometric data at the birth of the child: body weight – 3050 g, body length – 50 cm, head circumference – 33 cm, chest circumference – 33 cm. The child's condition is serious. There are signs of craniofacial dysostosis (acrocephaly), beveled occiput, narrowing of the nasal passages, depressed nasal bridge, exophthalmos, cleft hard and soft palate, skin and bone syndactyly of both hands, skin syndactyly of the toes of both feet, moderately pronounced deformity. Neurological status: physiological reflexes of the neonatal period are suppressed, muscle tone and tissue turgor are reduced. A feed is per a feeding tube.



Due to the development of respiratory disorders (respiratory failure of the II degree) the girl was transferred to the intensive care unit. Later, the child was treated in the neonatal pathology department. General condition at admission of moderate severity due to neurological symptoms and multiple congenital malformations. The child underwent a comprehensive examination. Ultrasound scan of the heart: a patent foramen ovale up to 3.0 mm, additional chord of the left ventricle. Ultrasound scan of the abdominal cavity: no pathology detected. Neurosonography: interhemispheric gap – 2 mm, vascular plexuses are inhomogeneous; partial agenesis of the corpus callosum; moderate dilatation of the lateral ventricles. Cytogenetic study: normal female karyotype 46, XX. The parents refused the molecular genetic research.

Conclusions of specialists of narrow specialties. Pediatric neurologist: hypoxic-ischemic lesion of the CNS, acute course, CNS depression syndrome. Congenital defects of the CNS: partial agenesis of the corpus callosum, ventriculodylation of the first degree. Otolaryngologist: cleft soft and hard palate. Ophthalmologist: no pathology detected. Orthopedist: skin and bone syndactyly of both hands, skin syndactyly of the toes of both feet, moderate varus deformity of the feet. Geneticist: Apert syndrome. In order to correct craniofacial changes and defects of the hands and feet, reconstructive surgical treatment is recommended by an orthopedic surgeon and a maxillofacial surgeon. The family underwent medical and genetic counseling, planning for the next pregnancy and mandatory prenatal screening were recommended.

CONCLUSIONS

Thus, Apert syndrome belongs to a group of syndromes of multiple congenital malformations that require the attention of pediatricians, geneticists, cardiologists, neurologists, orthopedists and doctors of other specialties. The main clinical manifestations of the disease are quite specific, which allows to

establish the diagnosis at birth. Apert syndrome is based on mutations in the FGFR2 gene, which can be detected by molecular genetic research. At present, there are opportunities for prenatal diagnostic of the disease. Reconstructive surgical treatments have also been developed. Timely comprehensive treatment and rehabilitation allow such patients to adapt to society.

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СУЧАСНІ ПОГЛЯДИ НА ЕТІОПАТОГЕНЕЗ, ДІАГНОСТИКУ, ЛІКУВАННЯ ТА ПРОФІЛАКТИКУ СИНДРОМУ АПЕРА

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Актуальність: Акроцефалосиндактилії – група синдромів множинних уроджених вад розвитку (МУВР), основними компонентами яких є синдромальний краніостоз та синдактилія. Найбільш поширеною нозологічною формою з цієї групи є синдром Апера. Враховуючи маніфестацію синдрому вже при народженні та тяжкі вроджені вади опорно-рухового апарату,

головного мозку, серцево-судинної системи та інші, це захворювання представляє практичний інтерес для лікарів багатьох спеціальностей.

Ціль: узагальнити сучасні уявлення щодо патогенетичних механізмів, діагностики, лікування та профілактики синдрому Апера.

Матеріали та методи. Клінічний випадок синдрому Апера. Клініко-генеалогічний, біохімічний, цитогенетичний, інструментальний методи обстеження.

Результати. В роботі наведено клінічний випадок синдрому Апера у новонародженої дівчинки з вродженими множинними вадами розвитку. Надано сучасну інформацію щодо патогенетичних механізмів, діагностики, лікування та профілактики синдрому Апера.

Висновки. Синдром Апера відноситься до групи синдромів множинних уроджених вад розвитку, які потребують уваги лікарів різних спеціальностей. Основні клінічні прояви захворювання доволі специфічні, що дозволяє встановити діагноз вже при народженні. В основі синдром Апера є мутації гену FGFR2. Існує пренатальна діагностика захворювання. Розроблені реконструктивні хірургічні методи лікування. Своєчасне комплексне лікування та реабілітація таких пацієнт надають їм змогу адаптуватися у соціумі.

Ключові слова: акроцефалосиндактилія, синдром Апера, мутації гену FGFR2, синдромальний краніостоз, черепно-лицевий дизостоз.

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЕ ОБ ЭТИОПАТОГЕНЕЗЕ, ДИАГНОСТИКЕ, ЛЕЧЕНИИ И ПРОФИЛАКТИКЕ СИНДРОМА АПЕРА

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Актуальность. Акроцефалосиндактилии – группа синдромов множественных врожденных пороков развития (МВПР), основными компонентами которых служат синдромальный краниостоз и синдактилия. Наиболее распространенной нозологической формой из этой группы является синдром Апера. Учитывая манифестацию синдрома уже при рождении и тяжелые врожденные пороки опорно-двигательного аппарата, головного мозга, сердечно-сосудистой системы и другие, это заболевание представляет практический интерес для врачей многих специальностей.

Цель: обобщить современные представления о патогенетических механизмах, диагностике, лечении и профилактике синдрома Апера.

Материалы и методы. Клинический случай синдрома Апера. Клинико-генеалогический, биохимический, цитогенетический, инструментальный методы обследования.

Результаты. В работе приведен клинический случай синдрома Апера у новорожденной девочки с врожденными множественными пороками развития. Предоставлена современная информация о патогенетических механизмах, диагностике, лечении и профилактике синдрома Апера.

Выводы. Синдром Апера относится к группе синдромов множественных врожденных пороков развития, которые требуют внимания врачей различных специальностей. Основные клинические проявления заболевания довольно специфические, что позволяет установить диагноз уже при рождении. В основе синдрома Апера являются мутации гена FGFR2. Существует пренатальная диагностика заболевания. Разработанные реконструктивные хирургические методы лечения. Своевременное комплексное лечение и реабилитация дают возможность таким пациентам к адаптации в социуме.

Ключевые слова: акроцефалосиндактилия, синдром Апера, мутации гена FGFR2, синдромальный краниостоз, черепно-лицевой дизостоз.