SCIENTIFIC REVIEWS AND LECTURES

Neustroeva L.M., Pavlova N.I., Solovyeva N.A., Diakonova A.T., Varlamova M.A., Filippova N.P., Dodokhov V.V., Kurtanov H.A.

NEUROFIBROMATOSIS TYPE I: ETIOPATHOGENESIS, CLINIC, DIAGNOSIS, TREATMENT

ABSTRACT

The relevance of the presented review is due to the high frequency of neurofibromatosis type 1 (NF1) in the population and frequent association with the development of malignant neoplasms. It is mainly characterized by a number of macules, the color of «cafe´-au-lait «, freckles in the skin folds, Lisch nodules and neurofibromas. Because clinical manifestations depend on the patient's age, and there are a number of other overlapping syndromes and diseases, it is usually difficult to put an early clinical diagnosis. At present, there are many molecular methods for diagnosing NF1, the highest sensitivity of any of these methods is ~ 95%.

This article examines the causes, pathogenetic mechanisms of the development of the disease, its complications, molecular genetic methods of investigation.

Keywords: type 1 neurofibromatosis, Recklinghausen's disease, neurofibromin.

Recklinghausen's disease, or Type 1 neurofibromatosis (NF1) is one of the most common monogenic diseases with an autosomal dominant type of inheritance related to phacomatoses. Phakomatosis (Greek phakos - spot) is a group of hereditary diseases united by common links of pathogenesis, which are characterized by a combined lesion of the nervous system, skin, eyes and internal organs. The term «phacomatosis» was first introduced in 1920 by Jan van Der Heve, who described changes in the ocular fundus as spots (phakos-spot) [4].

Neurofibromatosis type 1 (NF1) in 1882 was first described by the German physician Frederich von Recklinghausen. The type of inheritance is autosomal dominant [3, 9]. In the presence of NF1 in one of the parents, the risk of inheriting the mutant gene by the child is 50% and 66.7% in both [6].

Prevalence

According to the literature, the incidence of Type 1 neurofibromatosis in different countries is 1: 3,000-5,000 in the general population. The prevalence in Russia is 1: 2800 - 3300 [5]. In particular, in the Republic of Sakha (Yakutia) among diseases with AD inheritance, Recklinghausen's disease ranks third. According to the Republican genetic register of hereditary and congenital pathology of the The Republic of Sakha (Yakutia) since November 1, 2008. to December 31, 2013 the number of patients from 2008 year is 78, from 2013 year is 136, there is a tendency to increase [1].

Etiology and pathogenesis

The disease is characterized by high penetrance and the emergence of new mutations, almost - 50% of de novo mutation. The cause of NF1 are heterozygous mutations in the NF1 gene. The gene encodes a protein called neurofibromin, which is an onco-suppressor regulating the RAS system. The length and complex organization of the NF1 gene causes a high incidence of spontaneous mutations [3]. The NF1 gene is localized at 17q11.2 and has 62 exons. The rate of occurrence of mutations in the NF1 gene is 2 times higher than in other loci and is 10-4 on the gene [7].

For Recklinghausen's disease, genomic imprinting is characteristic, and 90% of the mutations are of paternal origin. The disease proceeds with a more pronounced clinic when the mutant allele is inherited on the maternal line [7].

NF1 patients described more than 500 different mutations of the gene localized at 17q. The nature of the mutations is quite specific: more than 80% of them lead to the synthesis of a nonfunctional «truncated» protein, or to the complete absence of a transcript (nonsense mutations, mutations in splice sites, deletions and inserts with a «frame» shift, large deletions covering the whole gene or its significant part). The remaining mutations are internal deletions without a «frame» shift and missense mutations affecting functionally important areas of neurofibromin [3].

Protein neurofibromin produces nerve cells, as well as specialized cells of neuroglia (oligodendrocytes, Schwann cells). Neurofibromin contains in its composition the domain of protein-activators of GTPase. Through this domain, the protein - neurofibromin in healthy people interacts with the pro-oncogene product RAS. Inhibits its function and realizes suppression of cell proliferation [10].

Neurofibromin is multifunctional, except for tumor suppression it triggers other signaling pathways and cellular processes. Neurofibromin is ubiquitously expressed during embryonic development and participates in the differentiation of skeletal, cardiovascular and nervous systems [14]. According to various studies, neurofibromin has been implicated in the differentiation of neurons through interaction with a variety of proteins, influences the processes of cell proliferation and adhesion, is involved in wound healing, proliferation of fibroblasts and collagen deposition [7].

At the heart of the pathogenesis of Type 1 neurofibromatosis is a disruption in the regulation of the carrying out of the intracellular signal along the RAS pathway. This path is one of the decisive in the development of the cell and the organism as a whole, regulates such important processes as the cell cycle, growth and differentiation of the cell. Most gene mutations that encode components of the RAS pathway lead to excessive uncontrolled activity. In connection with the foregoing, RAS-party is considered a disease with an increased risk of cancer [10].

Clinical manifestations of the disease

It is characterized by combined lesions of the nervous system (peripheral and central), skin, subcutaneous tissue,

often with disorders in internal organs, endocrine system and bone deformities, iris [9].

Neurofibromas are benign forms, derivatives of the nervous membrane of peripheral nerves, consisting of different types of cells: Schwann cells, fibroblasts, mast cells, endothelial cells, collagen fibers. [1]. It has been established that hormones affect the growth of the neurofibromas [11]. The first neurofibromas appear in the period of prebubertata or pubertal. At palpation, neurofibromas are usually dense to the touch, with a diameter of 1 to 2 cm or more, are painless, but if peripheral nerves are involved, soreness and sensory disturbance appear [10]. A characteristic symptom is the failure of the finger at slight pressure (the phenomenon of «bell button»). Neurofibromas are localized on the trunk and extremities; in women, they usually occur on the areola of the breast [12].

Skin manifestations are the most accessible diagnostic criteria and in most cases are the first symptoms of the disease. So, pigment spots cafe-et-lait - the first and permanent sign of type 1 neurofibromatosis and occurs in 95% of cases. Spots increase in size as the child grows [2]. At the histological analysis of pigmented spots, diffuse deposits are found in the papillate layer of the melanoblast and melanocyte derma with the inclusion of melanin in the cytoplasm [11].

Freckles (Crowe's syndrome) - pigmented spots of light brown color, ranging from 1-3mm, located in the axillary and inguinal areas, under the mammary glands, detected in most cases at 2 years of life. Skin manifestations can be accompanied by itching, which occurs in 20% of cases and reduces their quality of life [2]. Plexiform neurofibroma: are considered pathognomonic sign of the disease. Histologically, they are numerous elongated encapsulated neurofibromas, often mixed with diffuse neurofibroma, which includes the dermis and subcutaneous fat layer. At palpation there is the characteristic sensation of a «bag of worms» [12]. Plexiform neurofibromas can cause disfigurement and can disrupt functions or even endanger life [17].

Approximately 20% of patients have eye symptoms [11] that appear from birth or in the first years of a child's life. At examining the ocular fundus identify of tumor-like bumpy yellow formations in the region of the optic nerve disk or along the periphery of the fundus [4]. Almost all patients older than 20 years on the iris of the eye have «nodules Lisha», which are small whitish spots (hamartomas) on the iris of the eye [11]. The progression of eye pathology decreases visual acuity or leads to total loss of vision [4].

Quite often, in 25-50% of cases Recklinghausen's disease is accompanied by bone deformations in the form of kyphosis, characterized by early manifestation and rapid progression, which lead to irreversible cardiopulmonary and neurological disorders. To prevent them can only timely surgical intervention. In the area of scoliotic deformation, there is a violation of temperature-and-pain sensitivity, manifested by hypesthesia and thermoanesthesia. [8].

The peculiarity of the disease is characterized by a specific sequence of manifestation of clinical signs. So, from birth or from an early age, there are pigmented spots, plexiform neurofibromas, skeletal dysplasia, and other symptoms may appear later, by 5-15 years. In this case, there is a high variability in the clinical manifestations, course and rate of progression of type 1 neurofibromatosis [4]. One of the factors of such variability of manifestations of the disease, there may be individual features of the immune system [7].

Neurofibromatosis of the 1st type also has additional clinical manifestations: endocrine disorders (pheochromocytoma, dysplasia and puberty); changes in the skeleton (scoliosis - up to 15%, deformity of the chest, spondylolisthesis, non-vertebral arches, craniovertebral anomalies, skull asymmetry, pseudoarthrosis), etc. [4].

In addition to the characteristic signs of the disease, patients with Type 1 neurofibromatosis are at increased risk of developing malignant tumors. Thus, neurological tumors consist of glioma of the optic nerve, astrocytoma and schwannoma. Intracranial tumors can cause seizures. Other malignancies that are reported to be associated with this disease are Wilms' tumor, rhabdomyosarcoma, leukemia, retinoblastoma and malignant melanoma [12].

S. Fdil et al. described the case of a rare and prognostically serious complication in type 1 neurofibromatosis, spontaneous hemothorax and recommends attention to high hemorrhagic risk in patients with neurofibromatosis [16]. V.A. Filonov, T.A. Zakharicheva and co-authors in their observation described the case of a 10-year-old boy diagnosed with Type 1 neurofibromatosis complicated by intestinal bleeding. This case shows the need for additional examination of the digestive tract [6]. Patients with type 1 neurofibromatosis are particularly susceptible to internal jugular vein aneurysms due to vascular wall anomalies, which should also be considered when NF1. Thus, according to Delvecchio K et al., a case of internal jugular vein aneurysm measuring 6.9 cm × 3.8 cm × 6.5 cm in a 63-year-old patient with type 1 neurofibromatosis was described [15].

According to retrospective registry studies on congenital anomalies among patients with NF1 in the Finnish population conducted by Leppävirta J, Kallionpää RA.and co-authors, it was found that people with NF1 have an increased risk of serious congenital anomalies. Their study demonstrated results showing that abnormalities in the circulatory system, urinary system and abnormalities in the eyes, ear, face and neck are more common among children with NF1 [14].

Based on Leppävirta J, Kallionpää RA and co-authors of a retrospective analysis of the course of pregnancy of women with NF1, they revealed: increased caesarean section risk, premature birth, complications of pregnancy, including placental abruption, preeclampsia [15].

Diagnostics

Criteria for diagnosis were developed by the International Committee of Experts on Neurofibromatosis in 1988. Diagnosis Type 1 neurofibromatosis can be diagnosed if the patient has at least 2 symptoms [2].

1. Presence of 5 or more pigment macules in the color of « cafe´-au-lait «, more than 5 mm in size, and at least 6 spots with a diameter of more than 15 mm in post-pubertal age.
2. Freckle in the axillary and / or inguinal regions.
3. At least 2 neurofibromes of any type or one plexiform neurofibroma.
4. Dysplasia of the wing of the sphenoid bone or congenital thinning of the cortical layer of long bones with or without pseudoarthrosis.
5. Optic glioma.
6. Two or more Lisch nodules (iris hamartomas);
7. The presence of NF1 in relatives of the first line of kinship.

These clinical criteria are highly specific in adults with NF1 and children 8-9 years of age. In young children, the diagnosis can be more problematic. Only about half of the children with NF1 and

the family history of NF1 meet the criteria for diagnosis by the age of 1 year.

Molecular genetic testing to identify mutations in the NF1 gene assists clinicians in refining the diagnosis to patients who are suspected of type 1 neurofibromatosis, but who do not meet the diagnostic criteria, with an atypical course of the disease. Molecular genetic testing can be useful for a child with a tumor (eg, an optical glioma), in which a diagnosis of NF1 may influence the further management and selection of treatment tactics. Molecular genetic testing of an adult with NF1 is necessary if prenatal or preimplantation genetic diagnosis is expected in pregnancy or in pregnancy planning [17].

Taking into account that the majority of mutations in the NF1 gene lead to the synthesis of a «truncated» neurofibromin, the mutation analysis is carried out primarily on the RNA / protein level of the RTT-method. This method can be supplemented by a number of other traditional technologies of mutational screening, such as: SSCP (conformational polymorphism analysis of single-stranded DNA), heteroduplex analysis, gradient denaturing gel-electrophoresis, blot-hybridization, direct sequencing of individual gene exons, and (taking into account the probability of chromosomal rearrangements), fluorescence in situ hybridization and cytogenetic analysis. The use of various combinations of these methods makes it possible to detect mutations in the NF1 gene in 47% - 95% of cases [7].

Observation and treatment

Treatment is mostly symptomatic and depends on manifestations of type 1 neurofibromatosis.

Surgical treatment is indicated with sharp morbidity and an increase in the size of the tumor, ulceration, compression or displacement of vitally important organs.

Epileptic seizures should be carefully examined, as neurosurgical intervention is sometimes very useful for the patient [12].

In case of complications manifested by malignancy of the tumor, therapy with cytostatic drugs and radiation therapy are indicated.

It is necessary to conduct an annual medical examination, an annual ophthalmological examination, especially in children, regular evaluation of children's development, regular monitoring of blood pressure, MRI to monitor clinically suspicious intracranial tumors and tumors of other localization, medico - genetic consultation. [16].

Diagnostics of the spine is a selection criterion for evaluating a scoliotic curve with Cobb angles in the first place. CT allows a full three-dimensional evaluation of the spine and ribs. MRI is an additional study, especially for the evaluation of root, prevertebral and paraspinal soft tissues [13].

Conclusion

In conclusion, due to the high prevalence of Recklinghausen's disease and the high risk of developing malignant tumors, early detection at the level of the child's service determines the tactics of conducting, monitoring the patient, examining family members and identifying the carriers of the mutant gene. Important vocational training and alertness of primary care physicians. Continuity between specialists of different profiles is of decisive importance in the prognosis and quality of life of the patient. The main aspect of medical care is the medical and genetic counseling of family members to reduce the risk of the birth of patients with severe forms of type 1 neurofibromatosis.

Because an increased incidence of congenital anomalies may also reflect an increased risk of serious anomalies, careful monitoring is required during pregnancy and the neonatal period if the mother or father has NF1. Particular attention should be paid to identifying any signs of anomalies in the cardiovascular or urinary systems, to conduct research and determine the tactics of treatment and follow-up.

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The authors:

Neustroeva Lena Mikhaylovna– Junior researcher of the laboratory of the Laboratory of Population Genetics Tel.: 8 (914) 825 26 01. E-mail: Nlm31@mail.ru.

Pavlova Nadezhda Ivanovna – PhD, temporary acting chief scientific officer - head of the laboratory of heritable pathology. Tel.: +7 (914) 289 39 36. E-mail: solnishko_84@inbox.ru;

Solov'eva Natal'ya Alekseevna – PhD, temporary acting chief scientific officer - head of the Laboratory of Population Genetics. Tel.: 8 (924) 171 34 89. E-mail: sonata608@yandex.ru;

D'yakonova Aleksandra Timofeevna – Junior researcher of the laboratory of heritable pathology Tel.: 8 (914) 238 68 93. E-mail: dyakonovaa@bk.ru;

Varlamova Marina Alekseevna – Junior researcher of the laboratory of heritable pathology Tel.: 8 (914) 298 87 60. E-mail: varlamova.m@yandex.ru.

Filippova Natal'ya Pavlovna – PhD, associate professor, senior researcher of the Laboratory of Population Genetics. Tel.: 8 (914) 303 43 95. E-mail: inniah1970@list.ru;

Dodokhov Vladimir Vladimirovich – PhD, researcher of the Laboratory of Population Genetics. Tel.: 8 (964) 422 02 78. E-mail: dodoxv@mail.ru;

Kurtanov Khariton Alekseevich – PhD, Chief Scientific Officer - Head of the Department of Molecular Genetics. Tel.: +7 (914) 106 00 30. E-mail: hariton_kurtanov@mail.ru.

T.E. Burtseva, T.I. Nelunova, V.G. Chasnyk, S.A. Evseeva, Ya.A. Munkhalova

GENETIC AND EXTERNAL ENVIRONMENTAL RISK FACTORS FOR CONGENITAL HEART DISEASE IN CHILDREN (LITERATURE REVIEW)

ABSTRACT

The article presents a literature review of main risk factors of the development of congenital heart defects in children - genetic and environmental ones.

Keywords: congenital heart disease, children, risk factors, genetics, environment, pollutants.

Genetic risk factors for congenital heart disease in children. Genetically determined mechanisms of formation of congenital anomalies in the fetus include violations of maturation of male and female gametes, as well as pathology of intrauterine development. A variety of mutations (chromosome rearrangements such as translocations, inversions) damage the conjugation of chromosomes in meiosis and the death of maturing germ cells in the meiosis stage. Persons with chromosomal diseases (Down's disease, Klinefelter's syndrome) have severe spermatogenesis disorders associated with the defeat of the AZF locus gene complex located in the long arm of the male Y chromosome, mutations in the CFTR gene or the androgen receptor (AR) gene [6, 3].

The ovum of the female organism is even more sensitive to various exogenous and endogenous factors for several decades, which is associated with the complexity and long duration of hormonal regulation of the processes of oogenesis [1, 21]. Therefore, the prevention of hereditary conditioned congenital pathology should, first of all, be aimed at preserving women's health.

The formation of congenital developmental anomalies can be caused by the influence of damaging factors of different nature during preembryonic development (20 days from the moment of conception), embryonic (up to the 12th week of pregnancy) and fetal development [23]. Critical periods at this stage are implantation and placentation, when the selection of damaged embryos takes place [1].

Anomalies of fetal development, according to some studies, are associated with polymorphism of folate metabolism genes, since mutant genes can cause hyperhomocysteinemia, which has an embryotoxic effect. In addition, the deficiency of methyl groups is thus capable of altering the processes of cell proliferation and differentiation, making it more difficult to divide chromosomes during oogenesis [25]. The study of the polymorphism of folate cycle genes (*MTHFR, MTRR* genes) in families in which births of children with congenital heart diseases were observed showed a significant increase in the frequency of carriage of the MTHFR 677T allele in women and the MTRR 66G allele in men. The authors explain the negative effect of these alleles on embryogenesis by pathological changes in fetal cell division and differentiation during methylation failure [12].

Similar results were obtained in another study of the relationship of MTHFR 677T polymorphism and the risk of developing congenital malformation. The relative risk in fetal analysis was 1.26 without clear evidence of heterogeneity and 1.52 in the analysis of mothers with significant heterogeneity of the results [18].

In the genesis of congenital heart disease, the state of connective tissue in the process of ontogenesis is of great importance, since it is precisely involved in the construction of the heart's framework. The effects of various damaging factors, as well as genetic conditioning, can lead to connective tissue dysplasia and cardiac dysplasia. Atypically located chords of the left ventricle, prolapse of the mitral and tricuspid valves, aneurysm of the