CASE STUDY

NEUROFIBROMATOSIS TYPE I AND ITS DIAGNOSTIC CRITERIA: A CLINICAL OBSERVATION

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ABSTRACT

The aim – to consider the etiopathogenesis, the main clinical manifestations, diagnostic criteria of NF1, and present a clinical case from their practice. The paper analyzes the research findings in recent publications, focused on the studied issue using the methods of continuous sampling, synthesis and generalization, bibliosemantic evaluation and content analysis. In order to attract the attention of family physicians, neurologists, dermatologists, ophthalmologists, surgeons and other specialists, we present our own clinical observation of NF1.

The patient was examined using the methods of neurological examination, as well as other laboratory and instrumental methods of research. Early diagnosis and medical examination of patients with NF1 is crucial for predicting and improving the quality of life of patients. NF1 is a complex disease where the cooperation of doctors of different specialties is important. A favorable prognosis for patients is associated with the possibility of early diagnosis of malignant transformation and timely treatment.

KEY WORDS: neurofibromatosis type I, etiopathogenesis, diagnostic criteria, clinical manifestations, clinical case

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INTRODUCTION

Recklinghausen's neurofibromatosis or neurofibromatosis type I (NF1) is the most common disease in the group of phacomatosis or neurocutaneous syndromes. This is a diverse group of systemic diseases of hereditary nature, whose major clinical manifestations are pigmented, depigmented and vascular spots in combination with tumor-like neoplasms of the skin, blood vessels, central and / or peripheral nervous system [1-5].

NF1 is one of the most common monogenic human diseases, which occurs with a frequency of at least 1:3000-1:5000 of population, comprising up to 95% of all patients with NF [5-7]. NF1 is inherited by autosomal dominant type with high penetrance and variable expression of the pathological gene. Men and women are affected equally often [5, 8].

THE AIM

The aim of this research is to consider the etiopathogenesis, the main clinical manifestations, diagnostic criteria of NF1, and present a clinical case from their practice.

MATERIALS AND METHODS

The paper analyzes the research findings in recent publications, focused on the studied issue using the methods of continuous sampling, synthesis and generalization, bibliosemantic evaluation and content analysis. In order to attract the attention of family physicians, neurologists, dermatologists, ophthalmologists, surgeons and other specialists, we present our own clinical observation of NF1. The patient was examined using the methods of neurological examination, as well as other laboratory and instrumental methods of research.

REVIEW

Etiologically, NF1 is associated with a mutation in the NF1 gene, which is located on the long arm of chromosome 17 (17q11.2) and encodes the synthesis of neurofibromin protein. The latter is a suppressor of tumors, serving as a regulator of proliferation and differentiation of many cells. With the formation of pathological neurofibromin, there is an uncontrolled proliferation in individual neurons, glia cells, Schwann cells and melanocytes. The morphological substrate of neurofibromatosis are hamartomas, which are of ectodermal origin, located mainly in the nervous tissue and skin, and have blastomatous tendencies [2, 4, 5, 7].

According to the International Statistical Classification of Diseases and Related Health Problems, X revision, NF is a class XVII disease: "Congenital anomalies (malformations), deformities and chromosomal abnormalities", heading Q85 "Phacomatosis, not classified in other headings «[6].

Table I. Nondiagnostic Cutaneous and Extracutaneous Signs to Consider in Addition to the "Classical" Diagnostic Criteria when Evaluating Patients with NF1

Genetic analysis	Molecular analysis of the NF1gene
Cutaneous signs	Anemic nevus Juvenile xanthogranuloma Mixed vascular hamartomas and cherry angiomas Hypochromic macules "Soft-touch" skin Hyperpigmentation
Extracutaneous	Choroidal hamartomas Large head circumference and hypertelorism Unidentified bright objects on neuroimaging Cerebrovascular dysplasia, moyamoya Learning, speech and behavioral disabilities, headache and seizures Neoplasms

Table II. Clinical characteristics of the defined subtypes of neurofibromas

Neurofibroma Types	Location	Clinical Signs	Presentation
Cutaneous	Epidermis and dermis	Moves with skin, bluish tinge, local pruritus. Size: ~2 mm to 3 cm	Asymptomatic; most common type; presents in late teens
Subcutaneous	Deep to dermis	Skin moves over, firm and rounded feel, located along peripheral nerves. Size: ~ 3 to 4 cm	Tenderness on palpation; tingling in distribution of affected nerve
Nodular plexiform	Localized interdigitation with normal tissues	"Bag of worms" feel	May be present from birth, enlarges during the first decade of life
Diffuse plexiform	Infiltrate widely and deeply	Smooth slightly irregular skin thickening	-

When diagnosing NF1, it is necessary to use diagnostic criteria approved by the International Committee of Experts at the National Institute of Health (NIH) of the US (NIH – diagnostic criteria) in 1987 [7-15].

The diagnosis of NF1 (Recklinghausen's disease) is confirmed if a patient has at least 2 of the following signs:

1) six or more pigment spots (cafe-au-lait lesions) with a diameter of more than 5 mm in children of prepubertal age and more than 15 mm in postpubertal age;
2) two or more neurofibromas of any type or 1 plexiform neurofibroma;
3) freckles in the axillary or inguinal folds;
4) optic nerve glioma;
5) two or more Lisch nodules on the iris (hamartoma of the iris), which are detected during the study with a slit lamp;
6) dysplasia of the sphenoid bone or congenital thinning of the cortical layer of long bones with or without pseudoarthrosis;
7) the presence of NF1 in immediate relatives (parents, children, siblings) according to the above criteria.

These diagnostic criteria are highly specific for adults with NF1 [9].

Although these "classic" criteria for the diagnosis of NF1 are widely used and agreed upon, in recent years, additional new cutaneous and extradermal features have been described (Table I) [3].

It should be emphasized that these signs can occur in any combination, but none of them in itself is sufficient for the diagnosis of NF1 [8].

Skin manifestations are the most accessible diagnostic criteria and in most cases are the first symptoms of this multisystem disease. Signs of skin pigmentation – spots of color («café-et-lait» lesions), small pigment spots such as freckles in the inguinal and axillary folds (Crowe's symptom), generalized hyperpigmentation, tumors on the skin – neurofibromas are among the main manifestations of the skin syndrome in NF1 [4, 7, 9].

Pigment spots such as «café-et-lait» lesions of medium size (diameter 1-5 cm) are observed in 95% of patients with NF1; they appear either at birth (34%) or in childhood (66%) and are a classic symptom for NF1. They are monochrome spots from light white to dark brown, which are uniform in structure, round or oval in shape, with smooth edges and clear borders. Sizes can vary from a few millimeters to several centimeters, but diagnostically significant are spots with a diameter of more than 5 mm in children before puberty and more than 15 mm after puberty [5, 8, 9, 10]. In patients with NF1, melanocytes supersaturated with melanin and giant melanosomes are found in the areas of the spots [4, 5, 9].

Freckles are small hyperpigmented spots of a clearly rounded shape, 1-3 mm in diameter, with a more intense color than «café-et-lait» spots, brown in color. The

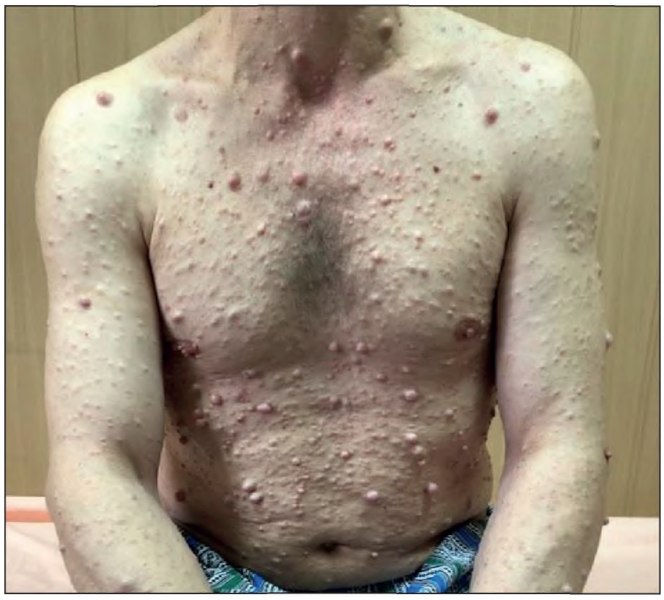

Fig. 1. Multiple cutaneous and subcutaneous neurofibromas on the anterior surface of the chest abdomen and upper extremities in patient V.

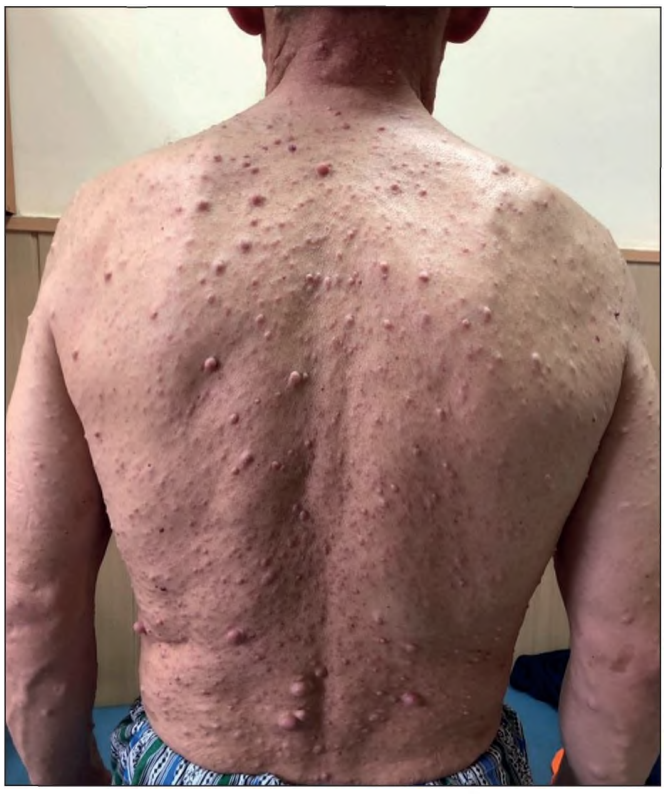

Fig. 2. Multiple cutaneous and subcutaneous neurofibromas on the back of patient V.

frequency of detection of freckles in NF1 varies from 21% to 93.7% [4, 5, 9].

Neurofibromas are the most characteristic manifestation of Recklinghausen's disease. They are benign formations that are derived from the nerve sheath of peripheral nerves, consisting of different types of cells: Schwann cells, fibroblasts, mast cells, endothelial cells, collagen fibers. Neurofibromas occur in the form of skin, subcutaneous

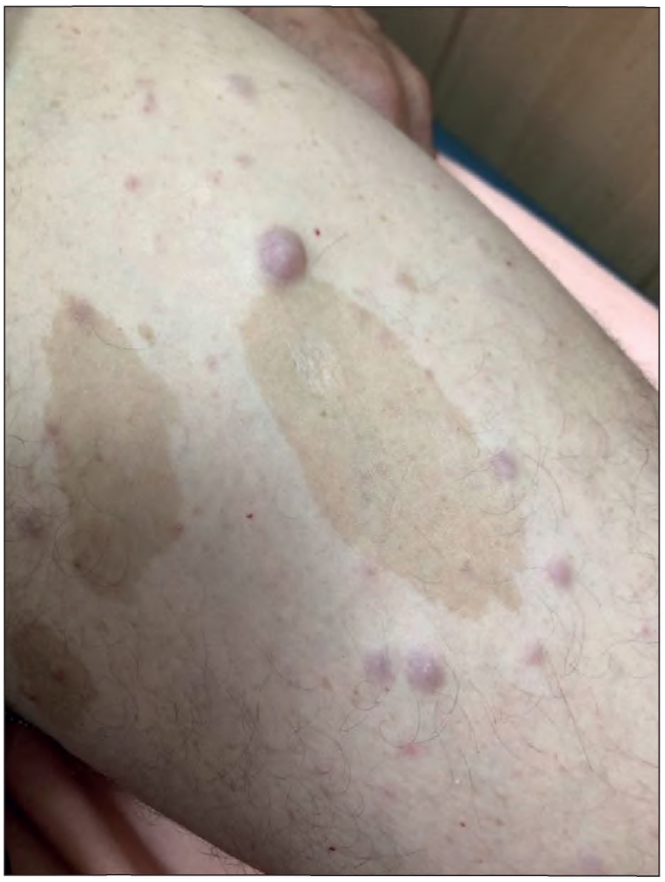

Fig. 3. Pigment spots cafe-au-lait lesions skin neurofibromas on the front and inner surface of the left thigh

and plexiform (nodular and diffuse) tumors [8, 12, 13]. Characteristics of each of them are presented in Table II.

Approximately 20% of patients have ophthalmic manifestations – Lisch nodules and optic nerve glioma [4, 8, 11]. Lisch nodules (iris hamartomas or melanocyte nevi) are one of the diagnostic criteria for the disease and are convex superficial clusters of pigment cells (from barely noticeable in size to 5 mm in diameter) on the iris, which can be seen in the study with a slit lamp. In children under 6 years of age, Lisch nodules are found in 15-20% of patients, and in adults – up to 95%. These nodules consist mainly of melanocytes, Schwann cells and fibroblasts. Optic nerve glioma is a benign tumor, rare in young children, more often manifested at the age of ten years in the form of a gradual decrease in vision. Optic nerve glioma occurs in 15-20% of patients with NF1 [7, 9, 10, 14-16].

Nervous system lesions in NF1 are of various nature – cognitive disorders of varying degrees (from mild to severe), attention deficit hyperactivity disorder, paralysis and paresis, syncopal paroxysms, epileptic seizures (focal, generalized), changes in the autonomic nervous system, headache, hearing and visual impairment [5, 7, 17-19]. It is very important to recognize and correctly interpret nonspecific neurological complaints, such as headache, in time [20]. The prognosis for patients with syncopal paroxysms depends almost entirely on the nature of the underlying disease [17].

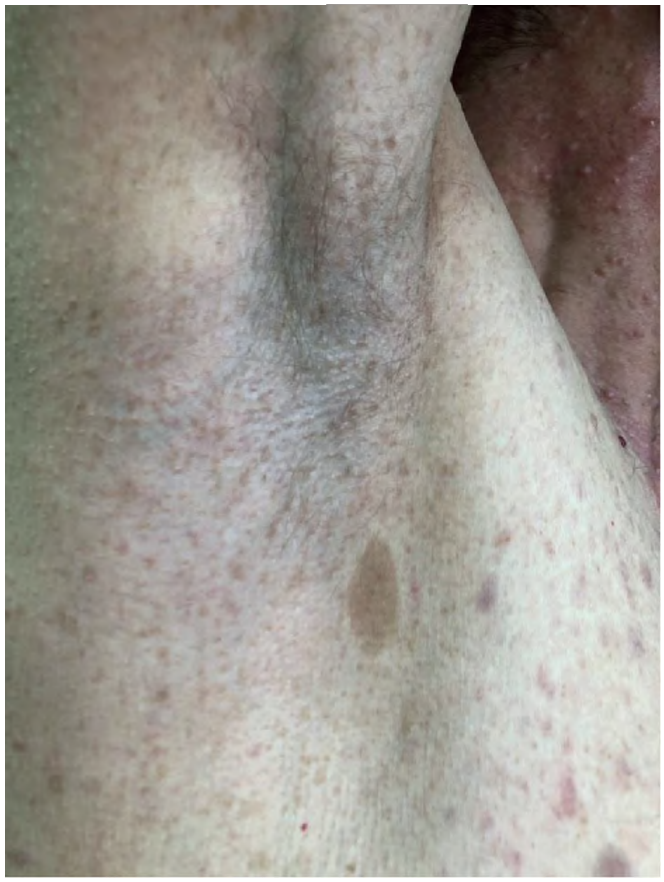

Fig. 4. Freckles in the axillary area

NF1 is characterized by additional clinical manifestations: endocrine disorders (pheochromocytoma, growth and puberty disorders); skeletal changes (scoliosis - up to 15%, chest deformity, spondylolisthesis, non-junction of vertebral arches, craniovertebral abnormalities, cranial asymmetry, pseudoarthrosis); cardiovascular manifestations (congenital heart defects, stenosis and aneurysm of the renal arteries, arterial hypertension), cerebral arteriopathy, etc. [5, 6, 9].

Primary diagnosis of NF1 should be performed by pediatricians, general practitioners of family medicine, as well as narrow specialists: neurologists, ophthalmologists, dermatologists, surgeons in the process of dynamic dispensary observation of the population. The leading role belongs to the fact that the process of development of clinical symptoms of NF is progressive, therefore, the dispensary supervision by doctors of different profiles of this group of patients and timely implementation of a set of additional diagnostic methods including CT and MRI of the brain and spinal cord are is essential [5, 7, 18].

The method of choosing tactics for patients on NF1 consists in observation and symptomatic treatment depending on the manifestations of the disease [6]. Surgical treatment is indicated for pain and increase in tumor size, compression or displacement of vital organs, suspected malignant tumor degeneration [4, 7]. Radiation therapy and chemotherapy are performed in the case of malignancy of tumors (from 3% to 20% of all cases of NF1) [7, 9, 21].

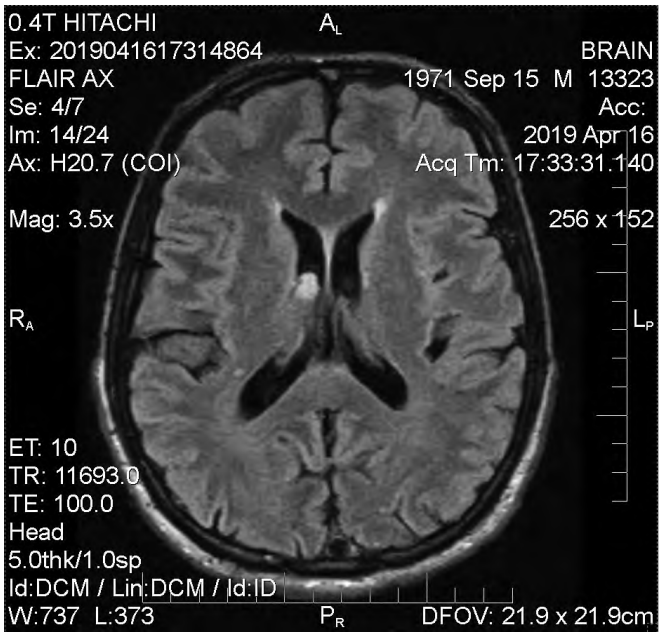

Fig. 5. MRI of the brain of patient V. (Apr 16, 2019)

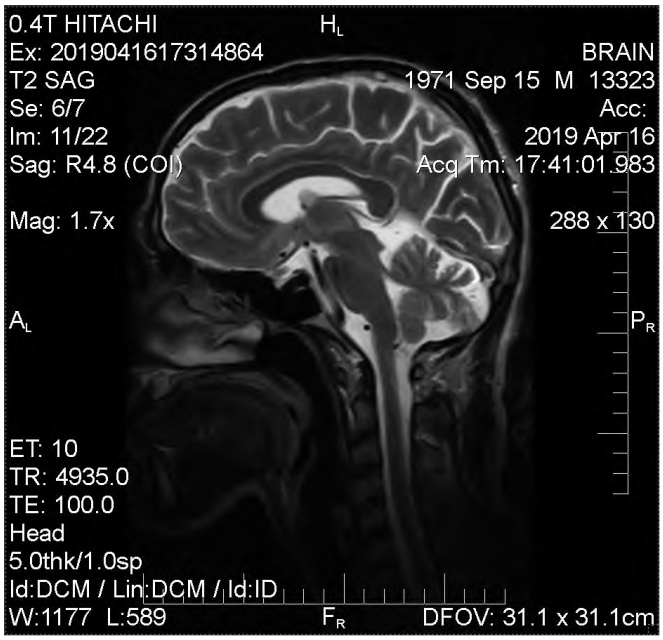

Fig. 6. MRI of the brain of patient V. (Apr 16, 2019)

The prognosis depends on the degree of manifestation of clinical signs. Malignant degeneration of neurofibromas is one of the important causes of death among patients with NF1 [4, 7, 9].

Due to the significant spread of this disease and the presence of severe and complicated forms in some patients, the study and description of cases of NF in different populations are extremely relevant [2].

CLINICAL CASE

In order to attract the attention of family physicians, neurologists, dermatologists, ophthalmologists, surgeons

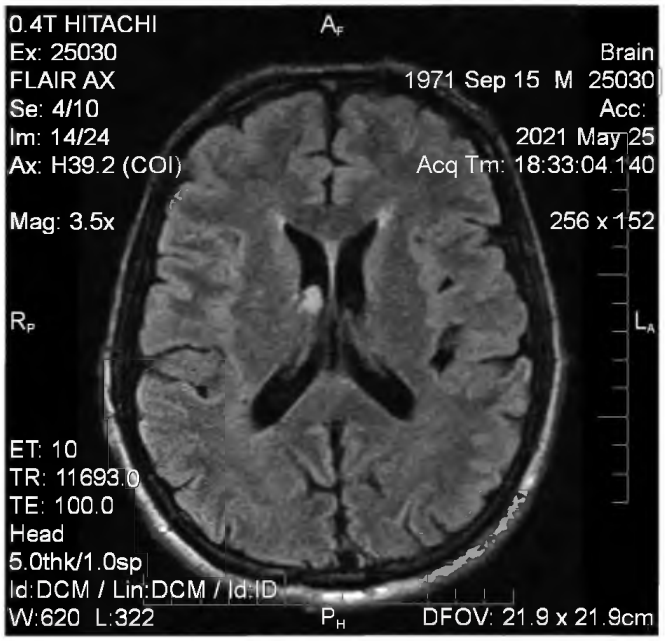

Fig. 7. MRI of the brain of patient V. (May 25, 2021)

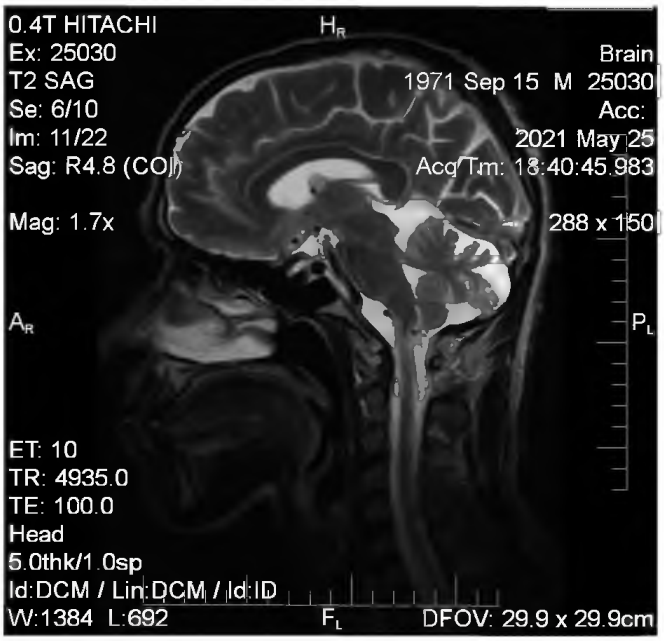

Fig. 8. MRI of the brain of patient V. (May 25, 2021)

and other specialists, we present our own clinical observation of NF1.

Patient V., 49 years old, first consulted a neurologist with complaints of periodic diffuse pressing headache, shakiness when walking, dizziness, increased blood pressure to 200/110 mm Hg, general weakness, memory loss, distraction, the presence of multiple tumor-like neoplasms on the torso, neck, upper and lower extremities, single neoplasms – on the face, which did not trouble the patient.

From the anamnesis of the disease: the patient considers himself to be ill from the age of 18, when tumor-like formations appeared on the trunk for the first time without a reason, which gradually increased in diameter and spread to other parts of the patient's body. In addition to the cosmetic defect, tumor-like neoplasms are painless, they do not trouble the patient. Pigment spots of the cafe-au-lait color appeared in the patient's childhood, he did not pay attention to them.

Life anamnesis: the patient has been suffering from hypertension for about 5 years. Hereditary history is not burdened.

Objective examination revealed the following abnormalities: multiple dome-shaped, soft, fleshy bluish-red and of normal skin color tumor-like formations of different sizes on the skin and / or in the skin thickness of the torso, neck, limbs (neurofibromas), which are painless on palpation. On easy pressing of rounded knots, there is a feeling of falling in of a finger (the phenomenon of the «bell push button») (Fig. 1, 2).

On the skin of the trunk and extremities, there are pigment spots (more than 6 spots) of the type of the cafe-au-lait color, which have different shapes and sizes (Fig. 3), in the axillary areas – small round pigmented spots with a color up to brown of the freckle type (Fig. 4).

In the neurological status: focal neurological symptoms are not detected. There are diffuse brisk deep reflexes, decreased abdominal reflexes, cognitive disorders (according to the MMSE scale – 27 points, indicating mild cognitive dysfunction in the patient).

Additional laboratory and instrumental methods of examination: general analysis of blood and urine, blood glucose within normal limits. In the biochemical analysis of blood: dyslipidemia with an increase in the fraction of atherogenic lipoproteins, coagulation parameters, the level of thyroid hormones – within normal limits.

Chest radiography – no pathology was detected.

ECG: sinus bradycardia. Normal position of the electrical axis of the heart.

Ultrasound of the abdominal cavity, adrenal glands: Liver cyst. Pancreatic cyst. Cysts of the right kidney.

Ultrasound of the thyroid gland: in the right and left lobes of the thyroid gland, there are multiple isoechoic nodes with cystic areas and the hydrophilic rim.

EEG: moderate diffuse changes in the bioelectrical activity of the brain by the type of disorganization of the main cortical rhythms. Paroxysmal activity and focal pathology at the time of examination were not registered.

On MRI of the brain without intravenous contrast (April 16, 2019): on a series of MR tomograms of the brain in sagittal, axial and frontal projections, in the projection of the anterior horn of the right lateral ventricle at the level of Monroe's orifice, there is an area of hyperintense MR-signal on FLAIR, weakly hyperintensive on T2BI, isointensive on T1BI with clear, uneven contours, irregular shape, conditional dimensions up to 10x10x9mm with a small diffusion restriction.

In the temporal areas, periventricular to the temporal horns of the lateral ventricles, near the hippocampus on both sides, there are areas of weakly hyperintensive MR-

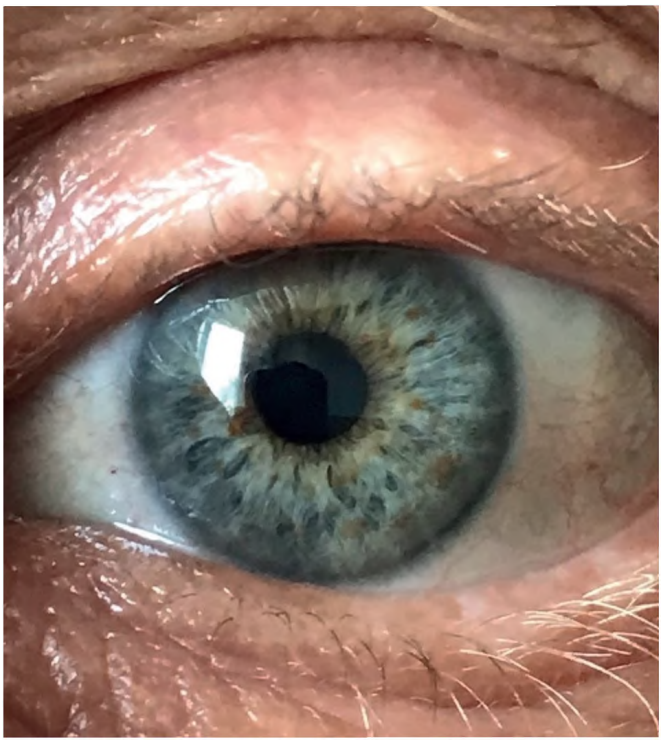

Fig. 9. Lisch nodules on the iris

signal on FLAIR and T2BI with fuzzy, uneven contours, conditional sizes from 16x7mm to 33x16mm (Fig. 5, 6).

Conclusion: MR signs of the local area of the altered MR signal in the projection of the anterior horn of the right lateral ventricle (possibly the subependymal node), which requires dynamic monitoring; MR signs of areas of the changed MR signal symmetrically on both sides in the temporal lobes

On MRI of the brain with intravenous contrast (Dotavist 15 ml) (25.05.2021): there is a new area of the altered MR signal hyperintensive on FLAIR, weakly hyperintensive on T233, isointensive on T133 with clear, uneven contours, irregular in shape, irregular shape, 11x9x11mm in the right hemisphere of the brain periventricularly to the posterior parts of the body of the right lateral ventricle at the border of the temporal and parietal lobes. In comparison with the MRI data from 16.04.2019 apart from this – MR-pattern without dynamics. After intravenous contrast enhancement, the absence of pathological accumulation of contrast agent is determined (Fig. 7, 8).

Ophthalmologist's consultation: In the fundus – the optic discs are pale pink, clear borders, retinal arteries are constricted, veins are moderately dilated. Visual acuity of both eyes = 1.0. During the examination with a slit lamp, small Lisch nodules on the iris of both eyes were found (Fig. 9).

Consultation of the ENT specialist: no pathology not detected.

Cardiologist's consultation: Hypertensive disease of the II degree, grade 2, risk III. Coronary heart disease: Diffuse cardiosclerosis, sinus bradycardia. Heart failure of the I grade, functional class II.

DISCUSSION

Thus, as a result of the examination of the patient, there are at least four criteria for the diagnosis of NF1:

- the presence of more than 6 pigment spots of the café-et-lait color with a diameter of more than 15 mm;
- in the axillary areas, there are small pigmented spots of round shape with a color up to brown of the "freckles" type;
- Lisch nodules on the iris of both eyes, which were detected during the study with a slit lamp;
- multiple neurofibromas on the skin and in the skin thickness of the torso, neck, limbs.

In addition to the «classic» criteria for the diagnosis of NF1, the patient had additional extradermal signs: the areas of weakly hyperintense MR-signal on T2-weighted mode are determined on the brain MRI; mild cognitive disorders, headache.

The presence of hyperintensive foci is one of the natural manifestations of NF1 in patients, which is visualized on the brain MRI in T2-weighted mode. These are hyperintensive foci, whose clinical significance is unknown, which is why they were called unidentified (unestablished) bright objects. They are found in the amount of 60% to 93% in children with NF1. The association between unidentified bright objects and the retardation of children with NF1 in development has been established [3, 5, 6].

According to MRI of the brain, the presented patient has disease progression, which is manifested by the appearance of a new area of the altered MR signal in the right hemisphere of the brain. The patient is recommended to consult a neurosurgeon and oncologist to determine further management of the patient (taking into account the changes in the brain MRI) and constant monitoring by a neurologist, ophthalmologist, dermatologist, surgeon, gastroenterologist, nephrologist, and endocrinologist.

It is essential to remember that the process of development of clinical symptoms in NF1 is dynamic – it is slow, but continuously progressive [5, 7, 18].

CONCLUSIONS

NF1 is a complex problem of modern medicine, due to the significant phenotypic and clinical variability of the disease, age-dependent onset, hereditary nature, the complexity of its diagnosis and treatment, reduced quality of life of patients. The most prognostically unfavorable complication of NF1 is malignant degeneration of neurofibromas.

Therefore, early diagnosis and medical examination of patients with NF1 is crucial for predicting and improving the quality of life of patients. NF1 is a complex disease where the cooperation of doctors of different specialties is important. A favorable prognosis for patients is associated with the possibility of early diagnosis of malignant transformation and timely treatment.

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A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article