

I.I. Larina*, N.M. Platonova, E.A. Troshina, A.A. Roslyakova,
D.G. Belzevich, L.S. Selivanova, M.Yu. Ukina, L.V. Nikankina,
N.M. Malysheva, A.N. Tyulpakov, L.D. Kovalevich

Endocrinology Research Centre; 11 Dmitriy Ulyanova street, Moscow, Russia

VON HIPPEL-LINDAU SYNDROME: ASPECTS OF TREATMENT AND MANAGEMENT. CASE REPORT AND LITERATURE REVIEW

Abstract

The steadily growing interest in studying of endocrine genetics is driven not only by the search for new pathologies but also by the most pressing need to develop methods for early diagnosis, treatment and management of such patients. Though 20 % of all the patients with von Hippel-Lindau syndrome do not have a family history of the disease, a genetic basis is a natural characteristic of the disease and it determinates a phenotype. Despite the non-aggressive course, in general, a relative unpredictability of the syndrome signs onset and the lack of regular monitoring can increase the risk of surgery complications and cause a disability at a young age. The presented clinical case shows the need for a multidisciplinary approach to management of the patients with von Hippel-Lindau syndrome.

Key words: *phacomatosis, Von Hippel-Lindau syndrome, pheochromocytoma, hemangioblastoma, VHL*

For citation: Larina I.I., Platonova N.M., Troshina E.A. et al. VON HIPPEL-LINDAU SYNDROME: ASPECTS OF TREATMENT AND MANAGEMENT. CASE REPORT AND LITERATURE REVIEW. The Russian Archives of Internal Medicine. 2019; 9(3): 165-171. [In Russian]. DOI: 10.20514/2226-6704-2019-9-3-165-171

DOI: 10.20514/2226-6704-2019-9-3-165-171

Anti-VEGF — anti-vascular endothelial growth factor; VHL syndrome, VHL — von Hippel-Lindau syndrome; CT — computed tomography; MIBG — ¹²³I-MIBG, metaiodobenzylguanidine; MRI — magnetic resonance imaging; RCC — renal cell carcinoma; PET — positron emission tomography; RPM — radiopharmaceutical; US — ultrasound; NMRCE — Federal State Budgetary Institution of National Medical Research Center of Endocrinology of Ministry of Health of Russia; CNS — central nervous system

Relevance

Von Hippel-Lindau syndrome is a phacomatosis with an autosomal dominant inheritance type, manifested by the formation of angiomatous, angioreticulomatous and cystic formations of the retina, central nervous system and internal organs. At the heart of the pathogenesis is a mutation in the 3p25-26 site, where the tumor suppressor gene VHL is localized. The product of the mutated gene leads to overregulation of genes

inducing systemic hypoxia, accelerating angiogenesis, initiating abnormal capillary growth and the formation of multisystem tumors with benign and, less often, malignant potential [1]. Depending on the clinical manifestations within the VHL syndrome, two phenotypes are distinguished: type 1 occurs without pheochromocytoma, includes angiomas (vascular tumors) of the retina, CNS hemangioblastoma (central nervous system), renal cell carcinoma (RCC), pancreatic, renal and splenic cysts, solid pancreatic tumors,

*Contacts. E-mail: irina.larina1993@mail.ru

rarely — adenocarcinomas, cystadenomas of the epididymus and endolymphatic sac tumor; type 2 — with pheochromocytoma, is divided into subtypes: 2A — with a low risk of kidney cancer, 2B — with a high risk of kidney cancer, 2C is represented only by pheochromocytoma [2–4]. Due to the success of genetic testing, verification of mutations has become available, resulting in timely diagnosis and medical intervention, preventing disability and death at a young age from VHL syndrome. However, the subsequent management of the patient requires a multidisciplinary approach in order to actively monitor the components of the disease and identify „sleeping“ tumors, potentially having an aggressive resource (metastasis, compression syndrome). In this article, we describe the clinical case of a patient with von Hippel-Lindau syndrome type 2, demonstrating the complexity of dynamic management of the patient with this pathology, despite the classical pattern of evolution of its components.

Description of the clinical case

Patient B., 25 years old, first admitted to Department of Therapeutic Endocrinology of NMRCE of Ministry of Health of Russia in May, 2017, with complaints of heart pain, palpitations, weakness, nausea, vomiting, decreased appetite up to aversion to food, sleep deterioration. It is known from medical history that since 2005 (from the age of 14 years) the patient noted an episodic increase in blood pressure to 160/100 mm Hg., palpitations, and this was the reason for his hospitalization in the Department of Pediatric Endocrinology of Endocrinology Center of RAMS in 2006, which was meant to exclude the endocrine cause of hypertension. Upon questioning the patient and relatives it found that his grandmother (father's mother) in 1968 (at the age of 24 years) was diagnosed with bilateral adrenal pheochromocytoma with metastasis (for which radiotherapy was carried out without a positive effect, surgical treatment), in 1984 — paraplegia of the lower extremities (MRI — multiple formations of the spinal cord). In 1996, the patient's father underwent surgery for bilateral adrenal pheochromocytoma, and in

2005 with the appearance of neurological symptoms (pain, paresthesia) in the lower extremities, further examination revealed hemangioblastomas of the spinal cord (subsequently manifesting with development of persistent tetraparesis), according to a genetic study — a mutation of *Trp157Ile* in exon 3 of the *VHL* gene. Taking into account positive hereditary epy history with successive manifestations of multiple tumor growth and cardiovascular events, the nucleotide sequence of exon 3 of the *VHL* gene was analyzed for genetic verification of the disease by polymerase chain reaction and subsequent sequencing by Sanger: a heterozygous mutation of *Trp157Ile* in exon 3 gene was revealed, confirming the presence of the above-mentioned syndrome in the patient. Along with this, according to the results of a comprehensive examination, the formation of the right adrenal gland measuring 1.5×1.4×1.1 cm was diagnosed, with a noradrenaline type of secretion, which is a predominantly characteristic of the von Hippel-Lindau syndrome: increased normetanephrine — 673 µg/day (normal range of 35–445 µg/day), with normal levels of metanephrine 167 µg/day (normal range of 25–312 µg/day). To exclude the extra-renal location of the paraganglioma, a scintigraphy with ¹²³I-MIBG was performed. As a result, the focus of abnormal accumulation of RPM was observed only in the right suprarenal region. With ultrasound, MRI of the abdominal cavity and kidneys, as well as scintigraphy, the left adrenal gland was intact. Ophthalmological examination revealed: angiomatic node in the lower-outer quadrant of the retina of the left eye — angiomatic node in the lower-outer quadrant and the area of the equator of the retina in the right eye, in connection with which the patient had a session of laser photocoagulation. Brain MRI data are not represented. Thus, based on the clinical picture, the results of genetic and laboratory and instrumental studies, the final clinical diagnosis was articulated as follows: von Hippel-Lindau syndrome. Pheochromocytoma of the right adrenal gland. Hemangiomas of the retina in both eyes. After preoperative preparation with doxazosin at a dose of 8 mg/day to achieve stable hemodynamic parameters (BP within 120/70–80 mm Hg.) 08.04.2007 right-hand laparoscopic

adrenalectomy with a tumor was performed in the Surgical Department of NMRCE without development of adrenal insufficiency afterwards. After discharge, the patient continued to be followed-up in the Clinic of Eye Microsurgery n.a. S.N. Fedorov, where he repeatedly underwent laser photocoagulation of the retina for newly formed hemangioblastoma (no subjective deterioration of vision). In 2008 during the MRI of the brain and spinal cord focal masses of the cerebellum, cervical, thoracic spinal cord were revealed, and this was his reason for 2 sessions of CyberKnife in Germany in 2008 and 2013. Since 2014, for the first time the patient noticed episodes of palpitations, increased sweating. During abdominal MRI it was revealed the mass of the left adrenal gland measuring 2.7×2.3×2.5 cm with characteristic for pheochromocytoma hyperintensive signal on T2-weighted images (in relation to adrenal tissue); hormonal study confirmed hypersecretion of methylated catecholamines in daily urine, and therefore in April 2015 in the Surgical Department the patient underwent left-sided adrenalectomy. A histological study of adrenal preparations from 2007 and 2015 revealed a similar pattern: tissue of the adrenal glands with nodular hyperplasia and rearrangement of the cortical layer. A tumor of large polymorphic cells with hyperchromic nuclei and nuclear inclusions with mixed growth pattern was found in the adrenal medulla: alveolar, forming mainly large nests, turning into diffuse, without signs of penetration of the capsule. In the central parts of the tumor hemorrhages were determined (Fig. 1–3).

Immunohistochemistry on sections from paraffin blocks was performed automatically in Bond max Leica immunostainer with antibodies to chromogranin A, synaptophysin, S100, Ki-67. The results confirmed a diffuse positive reaction with antibodies to chromogranin A and synaptophysin (Fig. 4), which proves the neuroendocrine nature of masses; negative reaction with markers of the adrenal cortical layer: proteins melan A and alpha-inhibin; positive reaction with antibodies to S-100 was noted (Fig. 5), however, the proliferation index Ki-67 was less than 1 %, which in total directly indicates the low malignant potential of both tumors.

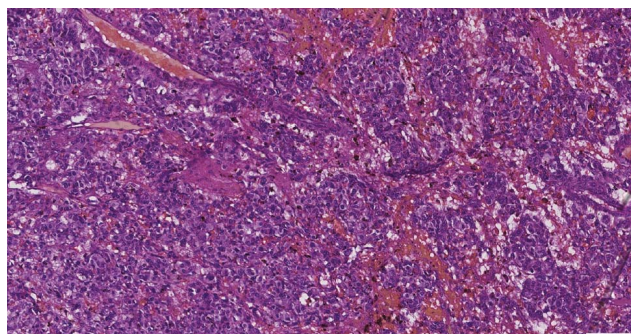


Figure 1. Pheochromocytoma of the right adrenal gland. Stained with hematoxylin and eosin. Magnification 100×

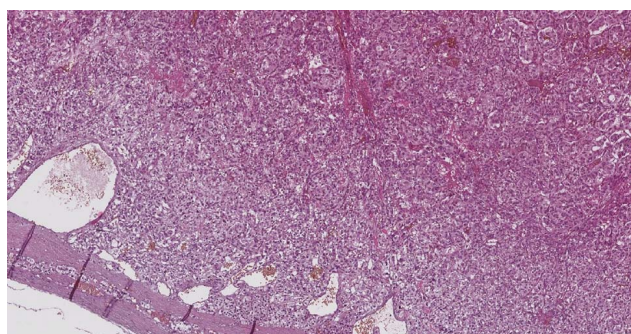


Figure 2. Pheochromocytoma of the left adrenal gland. Stained with hematoxylin and eosin. Magnification 100×

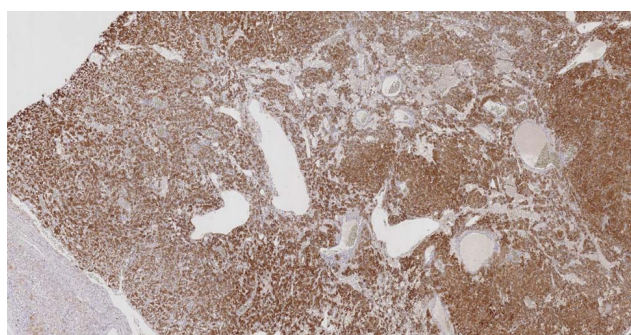


Figure 3. Positive reaction of tumor cells with synaptophysin. Magnification 100×

In the postoperative period, replacement therapy of adrenal insufficiency with hydrocortisone 60 mg/day was prescribed. After discharge, at the place of residence, the patient independently adjusted the dose of the drug, without consulting a doctor. Since November 2016, the relapse of heart attacks and sweating, persisting despite an increase in the dose of hydrocortisone, occurred. Since April 2017, heart pain of compressive nature began,

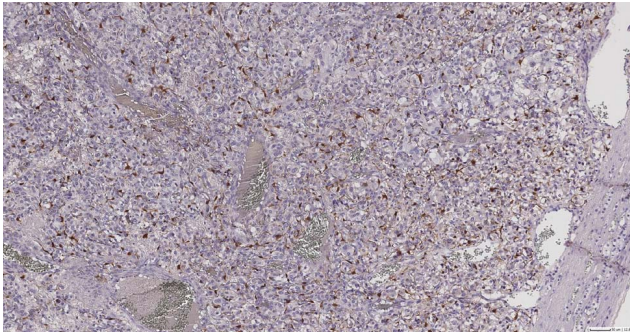


Figure 4. Positive reaction of sustentacular cells with anti-S100 antibodies. Magnification 100×

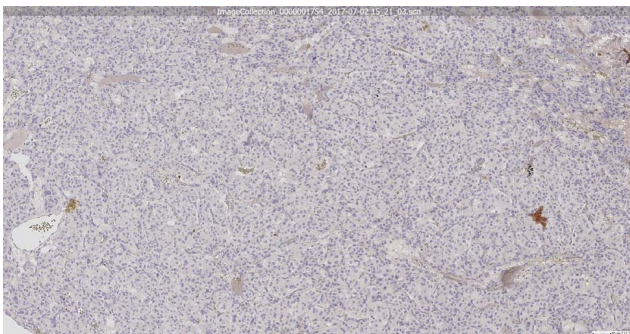


Figure 5. No reaction with antibodies against the Ki-67 protein (cellular marker for proliferation). Magnification 100×

which was the reason for cardiologist to prescribe at the place of residence potassium + magnesium asparaginate 4 tablets per day, and the patient subjectively noted a positive change in the form of pain relief. In May 2017, the patient had an outpatient appointment at NMRCE with complaints of heart pain, severe weakness, nausea, vomiting, aversion to food, heartbeat up to 130/minute while taking 60 mg of hydrocortisone per day. Summarizing the clinical manifestations and the data of the presented analyses (hyperkalemia up to 5.2 mmol/l (3.5-5.1), hyponatremia 134 mmol/l (136-145)), the patient's condition was regarded as a pronounced decompensation of adrenal insufficiency, in connection with which he was hospitalized in the Department of Therapeutic Endocrinology. Upon examination, the patient's height and weight were 184 cm and 82 kg respectively; there were obvious clinical signs of adrenal insufficiency: severe weakness, nausea, blood pressure reduced to 90/60 mm Hg, tachycardia 100 bpm, positive changes in well-being with the injection

of hydrocortisone 100 mg in the injectable form. Given a history of bilateral adrenalectomy, a typical water-electrolyte imbalance (hyperkalemia in combination with hyponatremia), an increase in renin of more than 500 $\mu\text{m}/\text{ml}$ (2.8–39.9) and a decrease in aldosterone to 26.9 $\rho\text{mol}/\text{l}$ (54.5–57.0), the patient's condition was regarded as severe, caused by mineralocorticoid insufficiency. During treatment with fludrocortisone 0.1 mg with adjustment of hydrocortisone dose to 30 mg/day, a state of compensation for primary adrenal insufficiency was achieved. Taking into account the genetically confirmed von Hippel-Lindau syndrome, a further examination plan was drawn up with an emphasis on the dynamic control of the „target organs“. Levels of catecholamine metabolites remained within normal limits in daily urine: normetanephrine 435.42 $\mu\text{g}/\text{day}$ with normal range of up to 445 and metanephrine 82.08 $\mu\text{g}/\text{day}$ with normal range of up to 312. However, taking into account the history of metastatic pheochromocytoma in the grandmother, the state after bilateral adrenalectomy, the level of normetanephrine at the upper normal level is regarded as suspicious with respect to the probable non-adrenal localization of paragangliomas and metastases. Despite the rare occurrence of non-adrenal localization of pheochromocytoma in *VHL* syndrome and the results of histological studies, scintigraphy with ^{123}I -MIBG was performed: there is no evidence of relapse. In abdominal and renal US no focal pathology was found, urological examination revealed right testicular cysts and cysts of left epididymis. In the ocular fundus no new hemangiomas were revealed, the old ones were completely desolated during treatment. In MRI of the brain and spinal cord — mass in the left hemisphere of the cerebellum, intramedullary masses of the cervical spine without growth changes; moderate negative changes were found: at the level of Th 6-7, mass measuring 6×5mm, with perifocal edema for 3 cm — which, according to the neurosurgeon's consultation, required MRI monitoring after 6 months. As a result of hospitalization in 2017, the patient was discharged in a satisfactory condition with recommendations for treatment and an outpatient follow-up plan. The patient was subsequently admitted in the Department again a year later with complaints of episodic

attacks of palpitations. Taking into account the increased risk of tumors from chromaffin tissue, in the first place, the recurrence of paraganglioma was excluded during the examination: in daily urine: normetanephrine — 531.13 µg/day (up to 445), methanephrine 64.532 µg/day — (up to 312). The status of ocular fundus according to ophthalmoscopy remained stable: the field of view on the white color was unchanged, no new hemangiomas were diagnosed. The examination of the pancreas showed no evidence of the presence of masses. With ultrasound of the scrotum, cysts of both epididymis persist — on the right side up to 17 mm, on the left side — up to 5 mm — without significant change compared to May 2017. Negative change was verified by MRI of the spinal cord and brain in comparison with 2017: at the level of Th 6-7, the mass has size of 9×6 mm with perifocal edema with length of 6 cm (in May 2017 — dimensions 6×5mm, with perifocal edema over 3 cm); at the level of Th12-L1, three masses located at a short distance from each other with dimensions of 6 mm, 5 mm and 3 mm, with moderately pronounced perifocal edema (in May 2017 — at the level of Th12, masses with dimensions of 5 mm, 3 mm and 2 mm, respectively, with moderate perifocal edema); in the left hemisphere of the cerebellum there is a focus with a diameter of 5 mm, with an ambient area hyperintensive to flair and T2-weighted images measuring 8×19 mm (in May 2017 — a focus with a diameter of 4 mm, with an ambient area hyperintensive to flair and T2-weighted images of size 10×19 mm), a new focus up to 2 mm in the left parietal lobe, intensively accumulating contrast drug, with peripheral edema. Given the progression of MRI, according to the recommendations of the neurosurgeon at the center, the patient was referred to NMRC of Neurosurgery n.a. N.N. Burdenko to consider an option of radiosurgical treatment. The concomitant clinical problem in this episode was the newly revealed right kidney mass measuring 3.8×3.9 cm according to renal US, and during further examination by MRI of retroperitoneal space there was the pattern of cystic solid tumor measuring 44×42×46 mm in the lower pole of the right kidney with signs of hemorrhage (Bosniak II) in the presence of intact layers of paranephric fat tissue. Due to the fact that PCC in 30 % of cases is part of

the phenotypic manifestations of *VHL* syndrome and is the main cause of death in mutant gene carriers, the patient consulted an oncurologist. According to the expert opinion, this type of Bosniak cyst has a malignant potential with a probability of no more than 20 %, and therefore it was recommended to continue monitoring with a repeat of CT after 6 months.

Discussion

Genetically programmed formation of benign and malignant tumors in carriers of *VHL* gene mutation throughout life allows us to note that the difficulties in monitoring this cohort of patients are mainly due to the polysystemic lesions involving the central nervous system, visceral organs such as kidneys, pancreas, adrenal glands, and reproductive system organs, as well as the need for strict dynamic monitoring of the predicted manifestation of „silent“ tumors with wide range of localization. Pheochromocytoma may be the debut of *VHL* syndrome, especially in childhood. In 70 % of cases it is a benign mass of adrenal localization, in 50 % of cases it has bilateral localization with exclusively noradrenaline type of secretion [5]. Non-adrenal paragangliomas in *VHL* syndrome occur in 30 % of cases [2]. A feature of the biochemical phenotype of such tumors is a more pronounced expression of tyrosine kinase, inducing higher concentrations of continuously secreted catecholamines. Diagnosis is carried out using MRI, CT with contrast enhancement, PET with 6-18F- fluorodopamine, ¹²³I MIBG — scintigraphy. Although ¹²³I MIBG scintigraphy is the „gold standard“ among all functional methods for pheochromocytoma imaging, in *VHL* the relative lack of storage granules or reduced expression of membrane norepinephrine and vesicular monoamine transporters can lead to a false negative result. The primary method of treatment is surgical, subject to mandatory preoperative preparation with alpha-blockers [6]. In 60–80 % of patients, clinical manifestations of von Hippel-Lindau syndrome are largely due to the occurrence of hemangioblastomas in the central nervous system — benign tumors of blood vessels. The primary diagnostic method is the MRI of the brain and spine with contrast enhancement.

In the nervous tissue, the growth of the tumor, surrounded by a thin shell, provokes the development of compression syndrome with exudation into the surrounding structures. Craniospinal localization of the lesion is subject to surgical treatment, but since CNS hemangioblastomas are characterized by chaotic growth, it is not used until the appearance of clinical symptoms. Stereotactic radiosurgery is used to treat small CNS tumors (less than 3 cm in diameter), as well as in inoperable cases [7, 8]. For verification of retinal hemangioblastoma regular examination of the ocular fundus is required, as in 5–8 % of patients their development leads to blindness and severe visual impairment. The primary method of treatment is immediate laser coagulation or cryotherapy (the most effective for tumors with a diameter of less than 3 mm); vitreoretinal surgery is used in cases of retinal detachment. Tumors located near the optic nerve are subject to anti-VEFG therapy, which helps to reduce edema and exudate formation [9, 10]. In *VHL*-syndrome type 1 or 2B formation of benign liver cysts, kidney cysts or RCC, which is manifested in 45 % of patients, characterized by asymptomatic course and diagnosed using CT, is observed. And in 60 % of patients with *VHL* by the age of 60 years, PCC manifests and it is the main cause of death in this group of patients. Metastasis correlates with size of the mass, therefore surgical treatment is indicated in tumors larger than 3 cm (US standard) /5 cm (European standard) [5, 11]. Gold standard of PCC treatment — organ-preserving surgery: open and laparoscopic partial nephrectomy. Currently, the most promising alternative methods are cryotherapy and radiofrequency ablation [3, 11]. 12–77% of patients with *VHL* syndrome have both benign and malignant neoplasms, including cysts and, in 7–12 % of cases, there are neuroendocrine tumors [12]. Most of these tumors are slow-growing. Diagnosis is carried out using MRI and endoscopic ultrasound. If the tumor is more than 2.8 cm and there are no metastases, surgical treatment is indicated. If the tumor is no more than 2.8 cm, dynamic control is required [13]. The tumor of the endolymphatic sac of the inner ear is found in 41 % of patients, which is benign, often bilateral and clinically manifested by deafness, tinnitus, dizziness and imbalance. Treatment is surgical [14, 15]. In 25–60 % of men

during US, papillary cystadenoma of the epididymis is visualized, and in women a tumor of the broad ligament of the uterus (isolated cases are described). Masses, as a rule, are benign and do not require treatment [16]. About 20 % of patients with de novo mutation in the *VHL* gene do not have a family history, while in the prevailing percentage of cases (up to 80%) there is a hereditary history, which opens up the possibility of regular screening for the majority of patients [12]. According to the recommendations, the management of patients with confirmed *VHL* syndrome from an early age (2–5 years) should include an annual ophthalmological examination, analysis of methylated catecholamines, from the age of 11 years — MRI of the brain and spinal cord at least 2 times a year and an annual abdominal ultrasound, replaced by CT from 20 years. In the absence of manifestations of the syndrome, the frequency of examinations is reduced: Brain MRI every 3–5 years and abdominal CT every 2 years [2, 6, 17]. As patients grow older, genetic counseling at the stage of preconception care with an explanation of possible risks, as well as with consideration of possible pre-implantation genetic diagnosis is of great importance when planning their families [3, 18]. Surgical treatment of individual components of the syndrome, such as tumors of the pancreas and kidneys, require joint postoperative follow-up by an endocrinologist and a surgeon, for the purpose of timely optimal management of possible complications: disorders of carbohydrate metabolism and secondary hyperparathyroidism secondary to renal failure after resection of the kidney. The most dangerous consequence of bilateral adrenalectomy for pheochromocytoma is undoubtedly adrenal insufficiency, when complex therapy with the inclusion of not only glucocorticoids but also mineralocorticoids is required [19].

Conclusion

The presented clinical case confirms the fact that von Hippel-Lindau syndrome is a severe comorbidity requiring a multidisciplinary approach to examination, treatment and observation. Due to the high penetrance of the pathological gene, early genetic examination and detection of mutation carriers allows regular screening for the spectrum

of its constituent pathologies to ensure timely diagnosis and treatment.

Conflict of interests

The authors declare no conflict of interests.

References:

1. Wang Y., Liang G., Tian J., et al. Pedigree Analysis, Diagnosis and Treatment in Von Hippel-Lindau Syndrome: A report of Three Cases. *Oncology Letters*. 2018; 15(4): 4882–4890. doi:10.3892/ol.2018.7957.
2. Ershova E.V., Yukina M.Yu., Troshina E.A., et al. Von Hippel-Lindau Syndrome. *Obesity and Metabolism*. 2011; 2(8): 65–68. doi:10.14341/2071-8713-4955. [In Russian].
3. Varshney N., Kebede A.A., Owusu-Dapaah H., et al. A Review of Von Hippel-Lindau Syndrome. *J Kidney Cancer VHL*. 2017; 4(3): 20–29. doi:10.15586/jkcvhl.2017.88.
4. Safronova Yu.V., Glukhov D.V., Strukova S.S., et al. Hippel-Lindau Disease. *Oncology Bulletin of the Volga Region*. 2016; 4(26): 72–75 [In Russian].
5. Yukina M.Yu., Troshina E.A., Beltsevich. D.G., et al. Pheochromocytoma/Paraganglioma: Clinical and Genetic Aspects. *Problems of Endocrinology*. 2013; 3(59): 19–26. doi:10.14341/probl201359319-26. [in Russian].
6. Chittiboina P., Lonser R.R. Von Hippel-Lindau Disease. *Handbook of Clinical Neurology*. 2015; 132: 139–56. doi:10.1016/B978-0-444-62702-5.00010-X.
7. Vortmeyer A.O., Alomari A.K. Pathology of the Nervous System in Von Hippel-Lindau Disease. *Journal of Kidney Cancer and VHL*. 2015; 2(3): 114–129. doi:10.15586/jkcvhl.2015.35.
8. Lonser R.R., Butman J.A., Huntoon K., et al. Prospective Natural History Study of Central Nervous System Hemangioblastomas in von Hippel-Lindau Disease. *Journal of Neurosurgery*. 2014; 5(120): 1055–62. doi:10.3171/2014.1.JNS131431.
9. Crespigio J., Berbel L.C.L., Dias M.A., et al. Von Hippel-Lindau Disease: A Single Gene, Several Hereditary Tumors. *Journal of Endocrinological Investigation*. 2018; 41(1): 21–31. doi: 10.1007/s40618-017-0683-1.
10. Girmens J.F., Erginay A., Massin P., et al. Treatment of von Hippel-Lindau Retinal Hemangioblastoma by the Vascular Endothelial Growth Factor Receptor Inhibitor SU5416 is More Effective for Associated Macular Edema than for Hemangioblastomas. *American Journal of Ophthalmology*. 2003; 136(1): 194–196. doi:10.1016/S0002-9394(03)00101-6
11. Chretien Y., Chauveau D., Richard S., et al. Treatment of von Hippel-Lindau Disease with Renal Involvement. *Progrès en Urologie: Journal de l'Association Française d'Urologie et de la Société Française d'Urologie*. 1997; 7: 939–947. doi:10.1053/gast.2000.18143.
12. Maher E.R., Neumann H.P., Richard S. Von Hippel-Lindau Disease: a Clinical and Scientific Review. *European Journal of Human Genetics*. 2011; 19(6): 617–23. doi:10.1038/ejhg.2010.175.
13. Krauss T, Ferrara A.M, Links T.P et al. Preventive Medicine for von Hippel-Lindau Disease-Associated Pancreatic Neuroendocrine Tumors. *Endocr Relat Cancer*. 25(9): ERC-18-0100 2018. doi:10.1530/ERC-18-0100.
14. Blansfield J.A., Choyke L., Morita S.Y., et al. Clinical, Genetic and Radiographic Analysis of 108 Patients with von Hippel-Lindau Disease (VHL) Manifested by Pancreatic Neuroendocrine Neoplasms (PNETs). *Surgery*. 2007; 142: 814–818. doi:10.1016/j.surg.2007.09.012.
15. Yaghobi J.A., Azadeh P. Von Hippel-Lindau Disease With Multi-Organ Involvement: A Case Report and 8-Year Clinical Course With Follow-Up. *The American journal of case reports*. 2017; 18: 1220–1224. doi:10.12659/AJCR.907356.
16. Ward T.L, Zarrin-Khameh N. Papillary Cystadenoma: An Incidental Finding in Tubal Ligation. *Case Rep Obstet Gynecol*. 2018; 2018: 7964238. 2018 Apr 23. doi:10.1155/2018/7964238
17. Choyke P.L., Glenn G.M., Walther M.M., et al. Von Hippel—Lindau Disease: Genetic, Clinical, and Imaging Features. *Radiology* 1995; 194: 629–642. doi:10.1148/radiology.194.3.7862955
18. Simpson J.L., Carson S.A., Cisneros P. Preimplantation Genetic Diagnosis (PGD) for Heritable Neoplasia. *Journal of the National Cancer Institute. Monographs*. 2005; 34: 87–90. doi:10.1093/jncimonographs/lgi027.
19. Grossman A., Johannsson G., Quinkler M., et al. Therapy of Endocrine Disease: Perspectives on the Management of Adrenal Insufficiency: Clinical Insights from Across Europe. *European Journal of Endocrinology*. 2013;169(6): R165–75. doi:10.1530/EJE-13-0450

Ⓐ

Article received on 03.04.2019

Accepted for publication on 09.04.2019