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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Photocoagulation for retinal hemangioblastoma in Von Hippel–Lindau disease

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SUMMARY

Introduction Von Hippel–Lindau disease is a hereditary, autosomal dominant, tumor syndrome with a predisposition to developing various benign and malignant tumors. Retinal hemangioblastoma is often the presenting manifestation. We report a case of Von-Hippel–Lindau disease in a 13-year-old girl with bilateral eye involvement.

Case outline The patient was referred to the Eye Clinic, University Clinical Center of Serbia, with a diagnosis of Coats disease. Clinical examination revealed that best corrected visual acuity was 20/20 on her right eye, while her left eye showed counting fingers at 20 cm distance. Dilated fundoscopy of the right eye revealed multiple tortuous feeding vessels leading to orange-reddish, sharply demarcated multiple lesions on the far periphery of the upper retina, corresponding to retinal hemangioblastoma. the left eye showed edematous optic nerve head, tortuous retinal vessels, exudates, and retinal detachment including macula. Considering that the patient had multiple bilateral retinal hemangioblastomas and that her father had pathohistologically proven brain hemangioblastoma and numerous visceral tumors, Von Hippel–Lindau disease was assumed. Focal argon laser photocoagulation was performed in the region of all visible vascular tumors and feeding vessels in the right eye. The patient's visual acuity remained unchanged five months after the disease detection.

Conclusion The importance of education about dominant inheritance pattern of Von Hippel–Lindau disease cannot be overemphasized. Role of an ophthalmologist is critical in early diagnosis of both retinal hemangioblastoma and Von Hippel–Lindau disease.

Keywords: Von Hippel–Lindau disease; retinal hemangioblastoma; photocoagulation

INTRODUCTION

Von Hippel–Lindau disease (VHL) is a hereditary, autosomal dominant tumor syndrome. Patients are predisposed to develop various benign and malignant tumors, especially retinal hemangioblastomas (RH), central nervous system (CNS) hemangioblastomas, and renal tumors; however, other neoplasms can also occur, including adrenal gland, pancreatic, inner ear, epididymal, and endolymphatic sac tumors. The disease arises from a VHL tumor suppressor gene mutation located on the third chromosome. It usually presents in early adulthood. The penetrance is over 90% until the seventh decade [1, 2]. Incidence varies internationally from around one in 36,000 to one in 91,000 [1].

RH is often the presenting manifestation of the disease [2]. Clinically, the tumor appears as red, orange, or pink, well-demarcated oval lesions, with tortuous and dilated feeding vessels. The peripheral retina and the optic nerve head (ONH) can be affected. Exudation is often seen around the lesion and in the macular region [1, 3]. Bilateral involvement and multiple RH are usual [3, 4].

Diagnosis and screening of VHL demand a multidisciplinary approach in which an ophthalmologist plays an important role. Timely diagnosis is essential since the disease is both vision- and life-threatening. Genetic testing and clinical assessment are recommended in patients with known family history even when asymptomatic, as well as in all patients with hemangioblastoma. Screening consists of regular physical evaluation, ophthalmic and audiological examination, brain and abdominal magnetic resonance imaging (MRI), all of these beginning from early childhood [1, 2].

We report a case of VHL in a 13-year-old girl with bilateral eye involvement.

CASE REPORT

A 13-year-old girl was urgently referred from a regional eye center to the Eye Clinic, University Clinical Center of Serbia, with retinal detachment in the left eye and diagnosis of Coats disease. Medical, ocular, and family history were taken from the girl's mother. She reported that girl was healthy, had no known medical conditions, had a full-term delivery, and complete immunization was performed. The history of ocular diseases and trauma was also negative. While taking a detailed family history, we found

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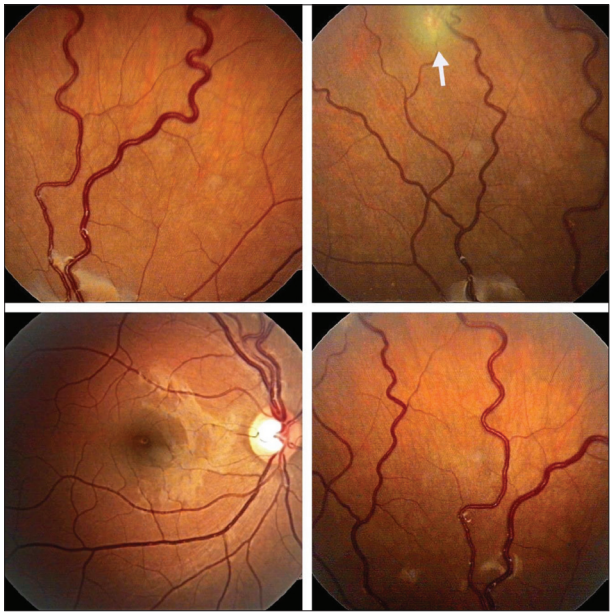

Figure 1. Color photos of the right eye on admission where a single retinal hemangioblastoma is clearly identifiable in extreme superior periphery (arrow)

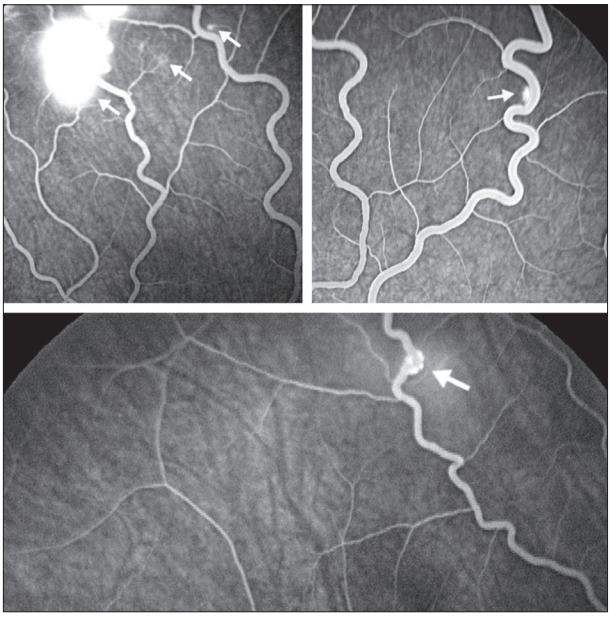

Figure 3. Fluorescein angiography of the right eye on admission, showing areas of leakage in the superior periphery, which corresponds to retinal hemangioblastomas (arrows)

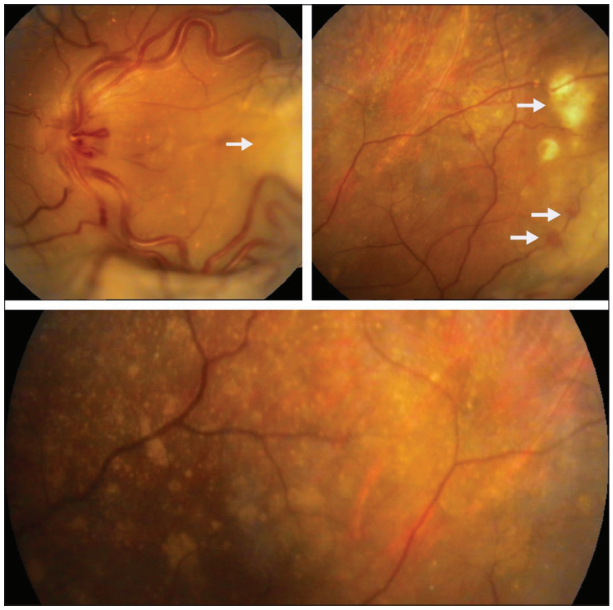

Figure 2. Color photos of the left eye on admission showing retinal detachment with underlying retinal hemangiomas (arrows)

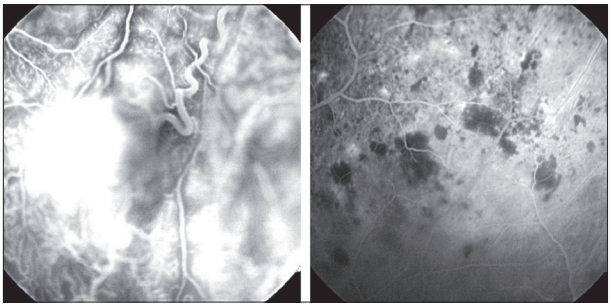

Figure 4. Fluorescein angiography of the left eye of typical peripheral retinal hemangioblastomas showing early hyperfluorescence and marked late-phase leakage while subretinal exudation was seen as blocked hyperfluorescence

out that the girl's father had died two months prior from kidney disease. Additionally, 17 years prior, he had a brain tumor surgery.

A clinical examination revealed that best corrected visual acuity measured on the Snellen chart was 20/20 on her right eye, while her left eye showed counting fingers at 20 cm distance. Intraocular pressures were within normal limits. The left pupil was slightly wider and the light reflex was slower. Both anterior segments and eye motility were normal. Dilated indirect fundoscopy of the right eye revealed multiple tortuous feeding vessels leading to orange-reddish, sharply demarcated multiple lesions on the far periphery of the upper retina, corresponding to RH. The macular region and ONH of the right eye were unaffected (Figure 1). The left eye showed edematous ONH, tortuous retinal vessels, exudates, and retinal detachment including macula (Figure 2). Optical coherence tomography and optical coherence tomography angiography could not be performed on the left eye due to massive exudation and retinal detachment, while both were normal on the right eye. The patient was admitted to the hospital for further evaluation and treatment. On admission, b-scan ultrasonography and fluorescein angiography were conducted. Ultrasonography of the right eye was normal, while, on the left eye, it showed a hemorrhagic retinal detachment of the lower retinal parts, including the macular region, with a large intraretinal cyst. Fluorescein angiography of the right eye showed tortuous feeding vessels with early and marked late phase leakage from the clinically visible tumors (Figure 3). Left fluorescein angiography corresponded with clinically described retinal detachment with diffuse leakage from retinal vessels of the upper, attached retina and underlying RH (Figure 4). Prompt focal argon laser photocoagulation (LPC) was performed in the region

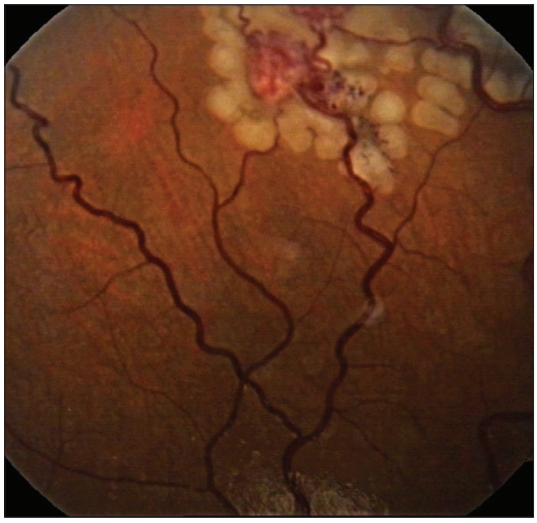

Figure 5. Color photo of the right fundus after the first focal laser photocoagulation treatment

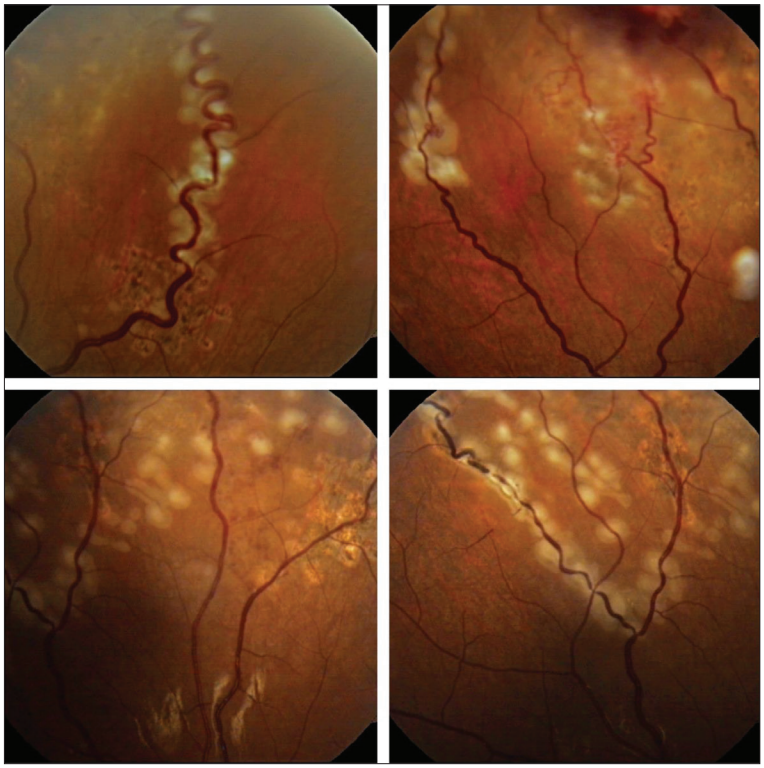

Figure 6. Color photos of the right eye after additional focal laser photocoagulation treatments a month (top row) and two months (bottom row) after discharge

of all visible vascular tumors in the right eye in order to prevent visual loss on the only functional eye (Figure 5). Considering that the patient had multiple bilateral RH and that her father had a brain lesion and kidney disease, VHL was assumed. During hospitalization, brain MRI, pediatric, and nephrological physical exams were obtained, which were all normal.

On the first follow-up, 10 days after discharge, partial vitreous hemorrhage and bleeding over the tumor were observed. LPC spots were partially pigmented. The visual acuity on the right eye was 20/20. The left eye findings were unchanged. A thorough inspection of the father's medical documentation revealed that he had pathohistologically proven brain hemangioblastoma. Furthermore, he was diagnosed with multiple kidney and pancreatic tumors and suspected to have VHL, while additional diagnostics could not be performed due to his poor general health, at that time. On the second and third follow-ups (a month and two months after discharge, respectively), partial tumor regression was observed; still, additional LPC treatment was applied to the multiple tumor lesions and feeding vessels of the right eye to ensure the prevention of further complications (Figure 6). Regular monthly follow-ups have been conducted and the patient's visual acuity on the right eye remained stable five months after the disease detection.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

RH can be either sporadic or, more often, a part of the VHL. A Danish retrospective national study from 2018 reported genetically confirmed VHL in 84% of their patients with RH [5]. These findings highlight the importance of thinking about VHL in all patients with RH and distinguishing cases with sporadic disease of those associated with VHL, since malignant visceral neoplasms could be present in the latter form.

VHL disease is typically confirmed through genetic testing. Individuals with first-degree relatives suffering from VHL should also undergo genetic testing in order to detect those with the risk of tumor evolution and provide them with an appropriate surveillance. If genetic testing is unavailable, the diagnosis can be established based on clinical criteria of at least one VHL manifestation and a first-degree relative with confirmed disease or at least two VHL tumors affecting different organs, of which at least one has to be hemangioblastoma [1, 2]. According to these standards, we can conclude that our patient's father could have been clinically diagnosed with VHL, as well as our patient based on RH findings and positive family history. The patient's mother was unaware of the disease's hereditary nature and the need for surveillance of all descendants. When family history is present, screening should ideally consist of genetic testing and/or evaluation of organ systems diseases connected to VHL. The screening protocol for RH starts from the first year and includes a dilated indirect fundoscopy once a year [1, 2, 6, 7].

RH represents one of the most common tumors found in VHL, occasionally diagnosed in childhood, as presented in our case [1, 2]. The average age of presentation is 25 years, being the lowest compared to other VHL-related tumors. The earliest reported onset was in the first year of life [6]. Additionally, patients diagnosed with VHL have

an earlier occurrence of RH compared to sporadic cases. Consequently, RH is the first sign of VHL in up to 77% of patients, which emphasizes the important role of an ophthalmologist in disease detection [2–6]. A cohort study that consisted of 335 subjects, examined the epidemiology of RH in VHL and found no correlation to age, sex, and laterality. The same study noticed a higher prevalence of bilateral RH (57.9%), a predilection for peripheral retina compared to juxta-papillary RH (84.7%), and an average tumor number of 2.5 ± 1.8 per eye [8]. Our patient had bilateral disease and multiple tumors with typical appearance, affecting the peripheral retina, which encompasses characteristic clinical presentation of VHL. Still, she was referred to our institution with suspicion of Coats disease. When retinal exudation is present, Coats disease and retinal macroaneurysm can be a differential diagnosis; however, our patient did not have visible retinal exudation on her right eye. Other conditions that may resemble RH include retinal vasoproliferative tumors, microvascular abnormalities, congenital retinal arteriovenous malformations and papillitis, juxta-papillar choroiditis or choroidal neovascularization in case of juxta-papillary RH [7]. For that reason, examination of the dilated fundus is important to identify any existing changes, especially in the far periphery, where changes can easily be overlooked.

RH is benign in terms of its biological features. It can, however, lead to visual impairing complications which correlate with the tumor size. Exudation from the lesion, vitreous hemorrhage and traction of the nearby retina are the commonest [8, 9]. It is a slow-growing tumor that sometimes allows observation with close follow-up instead of prompt treatment. Even so, treatment is required in most cases. Specific guidelines for the treatment of RH have not been published yet, therefore decision on the most appropriate treatment method is based on clinical experience and literature data. LPC, with the aim to destruct the tumor or the feeding vessels, is the mainstay of treatment, except for RH near the macula or ONH [10, 11]. Krivosic et al. [9] treated 100 eyes with LPC alone and reported success with inactivating RH in 97% of subjects while maintaining baseline visual acuity during the next four and a half years. The success rate was absolute in cases of small RH (less than 1 disc diameter) [9]. LPC carries a risk of bleeding or subretinal exudation and cannot be used when complications, such as exudative or tractional retinal detachment occur [12]. Therefore, early intervention, when the tumor is still small, can significantly affect the outcome. Other treatment modalities include cryotherapy, photodynamic therapy, transpupillary thermotherapy, radiotherapy, intravitreal anti-vascular endothelial growth factor therapy, and pars plana vitrectomy [10, 11, 12]. A recent review report suggests that the tumor size followed by tumor location and concomitant complications are the main factors in choosing a therapeutic option. They propose that small peripheral tumors (less than 1.5 mm) without tumor-related complications should be treated with LPC. Medium-sized lesions (1.5–4.5 mm) could be managed with either cryotherapy, transpupillary thermotherapy, or radiotherapy. For tumors larger than 4.5 mm and those with vitreoretinal complications, vitreorectomy is preferable [11]. Juxta-papillary RH are a specific therapeutic challenge. Photodynamic therapy in these cases can be beneficial [9, 12]. Combined therapies are also reported [9, 13]. Our patient's right eye was successfully treated with LPC and the visual acuity was unchanged during a five-month-long follow-up. However, she still has profound visual impairment in her left eye, which could have been prevented if ophthalmological examinations had been performed as recommended, from the first year of life.

The importance of education about the disease-dominant inheritance pattern and adequate screening of patients with VHL and their close relatives cannot be overemphasized. The role of an ophthalmologist is critical in early diagnosis of both RH and VHL since the disease can be blinding or even lethal.

Conflict of interest: None declared.

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Ласерска фотокоагулација за ретинални хемангиобластом у Фон Хипел–Линдауовој болести

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САЖЕТАК

Увод Фон Хипел–Линдауова болест је аутозомно доминантно наследни туморски синдром са предиспозицијом за развој различитих бенигних и малигних тумора. Ретинални хемангиобластом је често прва манифестација болести. Приказујемо случај Фон Хипел–Линдауове болести код 13-годишње девојчице са захватањем оба ока.

Приказ болесника Болесница је упућена на Клинику за очне болести Универзитетског клиничког центра Србије са дијагнозом Коатсове болести. Клинички преглед показао је најбоље кориговану видну оштрину 20/20 на десном оку, а на левом оку бројање прстију на удаљености од 20 центиметара. Преглед десног ока у мидријази показао је бројне извијугане исхрањујуће крвне судове који су водили до бројних наранџасто-црвенкастих, оштро ограничених лезија на крајњој периферији горње ретине, који су одговарали ретиналним хемангиобластомима. Лево око је показало оток главе очног нерва, извијугане крвне судове, ексудате и аблацију ретине која је захватала макулу. Узимајући у обзир да је болесница имала бројне обостране ретиналне хемангиобластоме и да је њен отац имао патохистолошки доказан хемангиобластом мозга као и разне висцералне туморе, постављена је сумња на Фон Хипел–Линдауову болест. Фокална фотокоагулација са аргонским ласером је учињена у регији свих видљивих васкуларних тумора и исхрањујућих крвних судова на десном оку. Видна оштрина је остала непромењена пет месеци после откривања болести.

Закључак Значај едукације о доминантном типу наслеђивања Фон Хипел–Линдауове болести не може бити пренаглашен. Улога офталмолога је кључна у раној дијагнози како ретиналног хемагниобластома, тако и Фон Хипел–Линдауове болести.

Кључне речи: Фон Хипел–Линдауова болест; ретинални хемангиобластом; фотокоагулација