BOHR Journal of Cancer Research
2023, Vol. 1, No. 2, pp. 43–46
DOI: 10.54646/bjcr.2023.09
www.bohrpub.com

Von Hipple Lindau disease – management of two cases with mini review

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Received: 03 September 2023; **Accepted:** 19 September 2023; **Published:** 18 December 2023

Von Hipple Lindau syndrome (VHL) is genetically determined benign tumors of various organs with some tendency to malignant transformation. Two young male and female patients of 25 years and 18 years presented with bilateral retinal and central nervous system hemangioblastoma. One patient underwent panretinal photocoagulation and resection of cerebellar tumor and other received transpupillary thermotherapy (TTT). Proper genetic counseling and screening of the patients and close relatives were done. Though VHL is not curable, timely and proper treatment can save life and sight. The Ophthalmologist can play a role in reducing morbidity and mortality of patients and their family members by screening and proper referral.

Keywords: retinal hemangioblastoma, CNS hemangioblastoma, dilated fundus examination, TTT, patient screening

Introduction

Von Hippel-Lindau (VHL) disease, or von Hippel-Lindau syndrome, affects the multiple organ system; usually has benign tumors and cystic lesions in different viscera with a tendency to change in malignant tumors. Patients present with symptoms at their second decade though it may start at earlier age (1). This is an autosomal dominant genetic disease and mutation of a tumor suppressor gene named *vhl* gene is responsible for the disease. This vhl gene location is on short arm of the third chromosome with an incidence of 1: 36,000 live birth (2). Penetrance of this disease is very high and it has been found that more than 90% penetrance is within the age of 65 years (1). About 10% people may present without any family history and suspect as new mutation or early decease of relative which is not known to the patient. In 1904, retinal signs were identified and described by a German ophthalmologist named Eugen von Hippel and in 1926 a Swedish Pathologist Arvid Lindau established a relationship between the retinal findings with CNS and other visceral cysts (2). The disease is named after those two researchers. Here we present two cases of VHL along with treatment outcomes.

Case reports

Case 1

A young male aged 25°years presented with painless gradual loss of vision in the right eye for 2 months and complete loss of vision in the left eye for a period of 8 years. He also had occasional vertigo and mood problems but no history of diabetes and hypertension. His family history was positive as his mother and sister both had the same symptoms like him. With refraction the visual acuity of R/E was 6/18 and No Perception Light (NPL) in L/E. The intraocular pressure of R/E was normal but L/E was digitally hard and not recordable in the applanation tonometer. The anterior segment of R/E was normal and the posterior segment examination showed the course of dilated and engorged blood vessel from optic nerve to mid peripheral retina to feed the retinal hemangioblastoma, with surrounding exudative retinal detachment (**Figure 1B**). In the left eye, the conjunctiva was mildly congested with degenerative vascularized corneal scar and the eye became prephthisical (**Figure 1A**). In fluorescence angiography, the retinal lesion showed hyper fluorescence with increased intensity with

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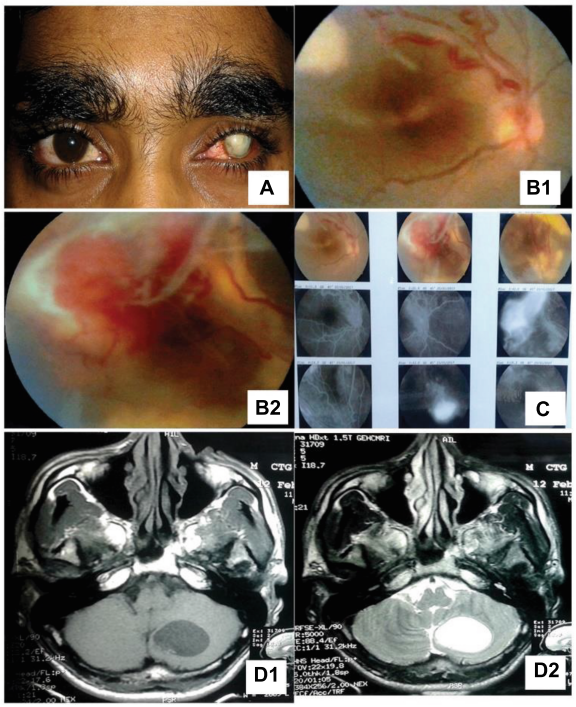

FIGURE 1 | Pictures of ocular and CNS presentation of first case. **(A)** Left eye is prephthisical (conjunctival congestion, opaque cornea). **(B)** B1 and B2 are color fundus photos showing the retinal hemangioblastoma with a dilated feeder vessel from optic disc to peripheral retina. **(C)** Fundus fluorescence angiography of right eye showing leakage of dye at tumor site. **(D)** D1 and D2 are MRI of brain showing a hypo intense globular lesion on the left side of the cerebellum in T1 image, which became hyper intense in T2 image.

late leakage (**Figure 1C**). MRI of brain and spinal cord revealed a hypointense globular lesion on the left side of cerebellum in T1 image, which became hyperintense in T2 image (**Figure 1D**). No abnormality was detected in ultrasonogram of the whole abdomen, routine blood test, and in 24 h urinary catecholamine. His hearing was also normal. He was diagnosed as a case of VHL with retinal and CNS hemangioblastoma and underwent laser photocoagulation (green laser) around the lesion and directly to the lesion twice in the right eye at 4-week intervals. For CNS hemangioblastoma, he was referred to the neurosurgeon and hemangioblastoma was removed. But by this time, his ocular treatment was hampered and he came to us with a vision of HM in his R/E due total retinal detachment. He had a 6-year-old daughter and she was found to be normal in screening protocol. The family was counseled about the importance of regular screening.

Case 2

An 18-year-old girl presented with severely decreased vision in her left eye for 1°month, which gradually decreased for a period of 3−4 months. She also complained about occasional numbness in her right hand. She was non-diabetic and non-hypertensive. She gave a history of her grandmother's blindness at an early age. Ocular examination revealed a visual acuity of 6/9 and 3/60 with no improvement in refraction. Anterior segment of both eyes were normal. Dilated fundus examination showed three small-sized (less than half disc diameter) retinal capillary hemangioma in the right eye at mid periphery and seven different sized tumors with tractional and exudative retinal detachment in the left eye (**Figures 2A, B**). Her intraocular pressure and blood pressure were normal with normal systemic evaluation. MRI of brain and spinal cord showed elongated fusiform lesion causing expansion of spinal cord, which enhanced with gadolinium at the level of cervical 5 and 6 vertebra with normal brain image. USG of the whole abdomen showed cystic lesion in pancreas (**Figure 2F**). Her 24 h urine catecholamine and audiometry were normal. She was diagnosed as VHL with retinal and CNS hemangioblastoma with probable pancreatic lesion. For retinal tumors she received multiple sessions of transpupillary thermotherapy (TTT) directly over the lesions in her both eyes at 8-week intervals at high power. After three sessions, the right eye hemangioma completely resolved (**Figure 2C**) and left eye received two more sessions and showed some reduction of size of the tumor and exudative retinal detachment but tractional detachment became worse (**Figures 2D, E**). One year after treatment her vision in the right eye became 6/6 and finger count one meter in the left eye. The patient was advised for left eye retinal surgery due to tractional retinal detachment but she refused. No new lesion occurred within this period. The patient also consulted a neuro surgeon and gastroenterologist for her other lesions of spinal cord and pancreas. Genetic counseling regarding the disease was done. She had two sisters and one brother, who were screened and found normal.

Discussion

The tumors related to VHL disease include hemangioblastomas in brain, spinal cord, and retina; clear cell carcinoma and cysts in kidney; neuroendocrine tumors of pancreas (pNET); benign tumors of the adrenal glands (pheochromocytomas); and inner ear tumor (endolymphatic sac tumors) (1). Among these tumors, hemangioblastomas of the central nervous system are commonest affecting about 60−80% cases with an average presenting age of 33 years. Hemangioblastoma of cerebellum accounts up to 69%, spinal cord 53%, brainstem 22%, cauda equina 11%, and supratentorial area 7% cases (1). Our first case had cerebellar and second case had spinal cord hemangioblastoma. As these tumors create pressure effect on vital structures like CNS, kidney, pancreas, etc., the patient may suffer from moderate illness to severe illness and even death may occur.

Retinal hemangioblastoma is not the commonest one but may be the earliest symptom of presentation and

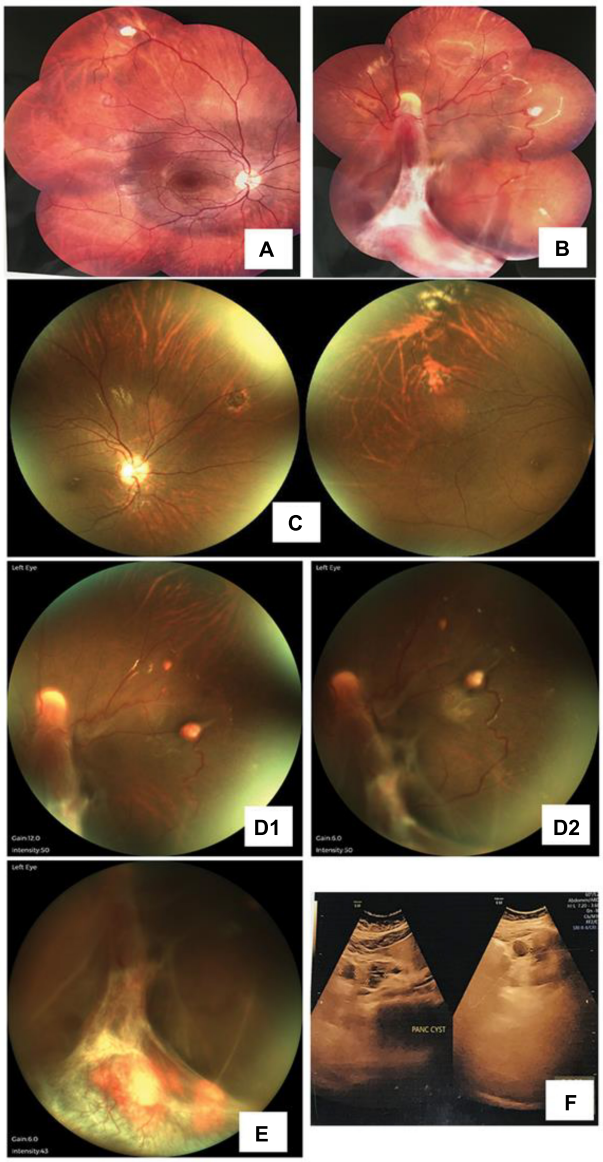

FIGURE 2 | Pre- and post-treatment pictures of retinal hemangioblastoma and pancreatic cyst of second patient. **(A)** Pretreatment Montage picture of right eye. **(B)** Pretreatment Montage picture of left eye. **(C)** Right eye – Resolution of tumor with TTT laser. **(D)** D1 and D2. Left eye- Slow response with TTT after 3rd and 4th sessions. **(E)** Increased tractional retinal detachment with successive TTT. **(F)** Ultrasonography of abdomen showing pancreatic cyst.

accounts for about 60% cases (1). Histologically, retinal hemangioblastomas and CNS hemangioblastomas are similar (3). Predominantly, these tumors are of two types of tumor cells: neoplastic cells, which represent reactive angiogenesis and VHL-inactivated clear cells called stromal cells (2). CNS hemangioblastoma develops with in the age range of less than 10−30 years and median age is 21 years (1). Our second case presented at 18 years and first case was 35 years old but they presented to ophthalmologist in delay. Retinal hemangioblastoma is detected by dilated fundus examination with indirect ophthalmoscope and fundus fluorescence angiography. The tumor is identified by tortuous and dilated retinal vessels from optic disc to the angiomatous lesion around which hemorrhage and exudative retinal detachment may be found if the tumor is moderate to big sized. Other ocular findings are macular oedema, exudative and tractional retinal detachment, vitreous hemorrhage, secondary glaucoma, poor vision, vision loss, and painful blind eye. The worse condition happens if it is left untreated or it does not respond to treatment. A major study on VHL showed a visual outcome of 20/200 and worse in 8% patients and eight percent of these eyes needed enucleation (4).

Literature search showed the frequency of presentation of other tumors are pancreatic neuroendocrine tumors or cysts (35−70%), Renal cell carcinoma or cysts (30−70%), Endolymphatic sac tumors (6−15%), Pheochromocytoma (10−20%), and Epididymal cystadenoma (25−60%) (1). Our second case had pancreatic cysts but was non-diabetic.

Depending on low and high risk of occurrence of pheochromocytoma, the VHL diseased persons are clinically classified into two groups – VHL type 1, who are at a very low risk of pheochromocytoma and VHL type 2, who are at high risk of pheochromocytoma (5). Type 2 is again classified on the basis of the presence of renal cell carcinoma (RCC) as type 2a (with low risk of RCC), 2b (with high risk 0f RCC), and 2c (without RCC, only pheochromocytoma) (6).

Diagnosis of this disease is mainly on clinical examination and a positive family history, though 20% may have a negative family history. The recent developed biomarkers for oncology like liquid biopsy, different tumor markers, activity markers of disease, etc., do not play an active role in detecting or in monitoring the progression of this disease. Only pheochromocytoma can be diagnosed by urinary and plasma catecholamine metabolites and fractionated metanephrines (2).

Von Hipple Lindau syndrome (VHL) can only be confirmable by genetic testing. Patients with a negative family history may be due to new mutation and genetic test should be done for these patients to confirm the diagnosis. Due to unavailability of the genetic test in our country, we were not able to do. In the absence of a genetic test, there are some other supportive criteria by which VHL can be suspected, such as- (1) More than one hemangioblastomas in CNS and/or eye, or (2) One hemangioblastoma in CNS/eye and associated RCC, cysts in pancreas or epididymis, tumor of endolymphatic sac or pheochromocytoma, (3) multiple bilateral clear cell renal cell carcinomas in young patients.

Tests that are used for clinical diagnosis are (7):

- MRI with contrast of brain and spinal cord
- Dilated fundus examination by indirect ophthalmoscope
- USG/MRI of the whole abdomen with special attention to pancreas, kidney, and adrenal gland
- Catecholamine metabolites of urine and blood

As it has a potential for malignancy and can cause serious life-threatening complications, the affected person with their first-degree relatives should undergo lifelong screening.

Screening protocol for patients (1):

- Diseased person

- Yearly eye and physical checkup.
- Brain and spinal cord imaging 3 yearly up to 50 years of age and after that, 5 yearly.
- Yearly USG and 3 yearly with CT scan of kidney (with contrast is gold standard)
- Yearly 24 h urinary VMA.

- The relatives at risk:

- Yearly physical checkup.
- Yearly eye checkup (dilated fundus) starting from the age of 5 years.
- Brain and spinal cord imaging 3 yearly from 15 to 50 years of age and after that, 5 yearly up to 60 years of age.
- Yearly USG and 3 yearly with CT scan of kidney from the age of 20 years up to 65 years.
- Yearly 24 h urinary VMA

Management of Von Hippel-Lindau (VHL) disease depends on the site of involvement and size of the tumors. Most of the peripheral retinal hemangioblastomas are treated with laser photocoagulation therapy or cryotherapy (1). Photocoagulation is very effective in the case of tumors of 1.5 mm or smaller size and it is effective in more than 90% cases (8). Cryotherapy is indicated in anteriorly situated tumors which are less than 3 mm in size (1). Vitreoretinal surgery and VEGF inhibition are other treatment options. Radiation therapy is indicated in refractory cases (1). Our first case received laser photo coagulation for two sessions, which were insufficient and the patient developed total retinal detachment. The second case showed a good response to TTT in the right eye as the tumors were very small. In the left eye, the size of tumors became stable but not so much decreased and exudative retinal detachment was resolved. The tumors of left eye were more than two discs in diameter, which is why it was slowly responding. In cases of craniospinal hemangioblastoma, asymptomatic tumors are kept in observation. Surgery can be done safely and it is often curative. The small tumors can be treated with stereotactic radiosurgery (1). Minimal invasive surgeries are reserved for all other symptomatic tumors of this syndrome. This syndrome needs multidisciplinary team management to save life and vision.

Recently, Belzutifan, an oral medication, received FDA approval to treat VHL patients who have non-metastatic RCC, CNS hemangioblastoma, and neuroendocrine tumors of pancreas with vhl gene mutation. This medicine is a HIF2α inhibitor that targets hypoxia-inducible factor-2 alpha (HIF2a) which causes regression of tumor.(9)

In Von Hipple Lindau syndrome (VHL), patient's life expectancy is 40−52 years with an average of 59.4 years in case of males and 48.4 years in case of females. Mortality and morbidity are mainly due to tumors of central nervous system and renal cell carcinoma and their complications (1).

Conclusion

Von Hipple Lindau syndrome (VHL) is a non-curable disease and lifelong screening is needed for patients and their relatives. Timely and proper treatment can save life and sight both. The Ophthalmologist can play a role in reducing morbidity and mortality of patients and their family members by screening and proper referral. The other physician also has role to save vision by timely referral to ophthalmologist.

Author contribution

SR: concept, design, manuscript preparation, photography. FH: literature review, manuscript writing. SB: manuscript review, grammatical correction. All authors contributed to the article and approved the submitted version.

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