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Research Article

Von Hippel-Lindau Disease: The Importance of Early Diagnosis and Treatment

Hüseyin Erdem Ak

Department of Neurosurgery, Bilecik Seyh Edebali University, Bilecik, Türkiye

Abstract

Objectives: To provide an overview of Von Hippel-Lindau (VHL) disease, including its clinical presentation, treatment modalities, and follow-up protocols. To present a detailed analysis of patients within a family affected by VHL disease. To investigate challenges encountered in the treatment and follow-up of VHL disease, along with the optimal timing for treatment.

Methods: Diagnosis of patients was established through clinical examination, contrast-enhanced magnetic resonance imaging (MRI), and genetic testing. Surgical excision, radiotherapy, and chemotherapy were administered based on tumor localization, number, and size of lesions.

Results: VHL disease necessitates lifelong regular monitoring and treatment due to its chronic nature. Early diagnosis and planning for Gamma Knife treatment have been observed to lead to increased lifespan and improved quality of life for patients.

Conclusion: Early diagnosis and routine follow-up are crucial in managing VHL disease effectively. Multi-disciplinary approaches, including surgical intervention, radiotherapy, and chemotherapy, are essential in the treatment of VHL disease. Lifelong monitoring and treatment are necessary to optimize outcomes and improve the quality of life for individuals with VHL disease.

Keywords: Early diagnosis, Multi-system disorder, Routine follow-up, Vascular tumors, Von Hippel-Lindau disease, Ocular tumors

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Von Hippel-Lindau (VHL) disease stands as a rare condition that emerges irrespective of gender, typically surfacing during young adulthood.[1,2,9,17]

This disorder is a genetic anomaly inherited in an autosomal dominant pattern. Initially described by Von Hippel in 1911 and independently identified by Lindau in 1926.[1,5,7,13,14] VHL disease stems from mutations in the VHL gene situated at the 3p25-26 locus of the human genome. This gene governs the production of tumor suppressor proteins, notably pVHL. Dysfunctional pVHL due to gene mutations triggers the formation of various tumors and cysts.[10,11,17]

VHL disease manifests through the development of benign and malignant tumors, alongside cysts, across multiple organs including the central nervous system, kidneys, retinas, and pancreas.[3,4,7,9,10,13,15] Commonly affected sites include the brain, spinal cord, kidneys, and eyes. Symptoms vary based on age and affected organs. Most patients experience cerebellar and kidney involvement, retinal angiomas, and central nervous system hemangioblastomas, according to existing literature.[3,7,8,14,18,20]

Diagnosis relies on patient-reported symptoms, physical examination, and diagnostic tests like MRI, PET scans, and genetic testing.[1,4,11,19] Early diagnosis and prompt inter-

Address for correspondence: Hüseyin Erdem Ak, MD. Department of Neurosurgery, Bilecik Seyh Edebali University, Bilecik, Türkiye
Phone: +90 532 353 93 19 **E-mail:** erdem.ak@bilecik.edu.tr

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vention are crucial.[1,4,8,16] Treatment modalities, including surgery, radiotherapy, and chemotherapy, are tailored according to tumor localization, number, and size.[6,8,9,19] VHL disease mandates lifelong monitoring and treatment to enhance patient outcomes and quality of life.[8,18,12]

Despite advancements in diagnosis and management, the life expectancy for VHL patients remains modest at 40–52.[2,10,18] Regular clinical surveillance, symptomatic management, and timely surgical interventions are pivotal for improving patient prognosis.[2,6,10,18,20]

This brief overview underscores the significance of early detection and comprehensive management strategies in tackling VHL disease, a complex genetic disorder impacting various facets of patients' lives.[8,12,16,18,20]

Methods

This study aims to evaluate the clinical characteristics and treatment outcomes of family members with Von Hippel-Lindau (VHL) disease. Family members were extensively examined to understand the genetic characteristics of the disease and to investigate the course of the disease within the family.

The study included a male patient diagnosed with VHL disease and surgically treated for cerebellar mass, retinal lesion, and renal cortical cysts, along with his operated son with cerebellar involvement, his daughter with non-operated cerebellar involvement, and his grandchild. Other individuals diagnosed with VHL disease within the family were also included. Clinical and radiological data of the patients were analyzed to evaluate changes in the course of the disease and treatment outcomes.

Additionally, treatment and follow-up of two male siblings and their children, along with two grandchildren from the same family, were conducted. The older siblings died at the age of 50; one underwent surgery three times, while no treatment was administered to the other. A small lesion in the cerebellum was detected in the son of one of the deceased individuals in his 30s. The son of the other sibling underwent surgery at the age of 33 due to cystic cerebellar involvement and advanced hydrocephalus. Another individual in the same family, the operated patient's 37-year-old sister, underwent Gamma Knife treatment for a cerebellar lesion when she was in her 20s. Follow-up MRIs after this treatment showed a reduction in the size of the lesion. However, it was determined that the cystic lesion in the kidney was slowly growing.

One of the deceased individual's grandchildren complains of headaches, and suspicious lesions in the cerebellum were detected on MRI. Symptoms of all these patients are being monitored, and symptom-oriented treatments are planned when the symptoms become intolerable.

This study provides important information on the genetic and clinical characteristics of VHL disease, as well as the effectiveness of treatment strategies.

Patient 1 — A.Y., a male born in 1962, presented to our outpatient clinic in 2010 with complaints of unsteady gait, headaches, weakness in the arms and legs, and occasional hematuria. The patient had previously undergone two surgeries at another center in 1992 for a cerebellar tumor diagnosis. Neurological examination revealed 3/5 muscle weakness in all extremities and decreased tone in the lower extremities. He experienced difficulty standing due to cerebellar ataxia. It was learned from the family history that the patient's brother had similar complaints, underwent surgery once, and passed away at the age of 49.

MRI revealed a cystic nodular mass lesion adjacent to the right cerebellar hemisphere, measuring approximately 3x2 cm, with intense contrast enhancement, in close proximity to the fourth ventricle, consistent with VHL. Abdominal CT with contrast revealed simple renal cortical cysts. Genetic testing could not be performed due to our facility's limitations. The patient had been diagnosed with VHL disease during previous surgeries. Following recent radiological examinations, the patient was admitted for surgery on 11.02.2010. A suboccipital craniectomy was performed to excise the cerebellar cystic mass utilizing the defect. The partially improved patient was discharged without complications. The pathological diagnosis was reported as VHL. On 30.03.2010, the patient was readmitted due to complaints of headache, nausea, and vomiting, and MRI showed communicating hydrocephalus. No recurrence of hemangioma was observed in the cerebellar region (Fig. 1). Due to worsening headaches and the development of hydrocephalus, a ventriculoperitoneal shunt was placed, resulting in resolution of the patient's symptoms. Contrast-enhanced MRI on 09.06.2010 revealed a lesion approximately 2x1 cm in size, located extracanalularly in the left half of the right eye globe. Postoperative cystic encephalomalacic areas measuring 3x2 cm adjacent to the right cerebellar hemisphere and approximately 2x1 cm posteriorly on the left were observed. A contrast-enhancing lesion, consistent with hemangioblastoma, measuring 25x22 mm adjacent to the L2-3 levels, with dimensions of 15x14 mm superiorly, was also identified on lumbar MRI. The patient began to experience difficulty walking. Photocoagulation was performed for bilateral retinal angiomas detected on MRI due to progressively decreasing vision. A contrast-enhanced cranial MRI on 24.11.2010 revealed multiple recurrences and widespread hemangioblastomas in the previously operated cerebellar region (Fig. 2). Given the recurrent nature of the disease in a short period, no further surgery was considered for the patient. Palliative treatments were administered, and routine follow-ups were conducted. In the final

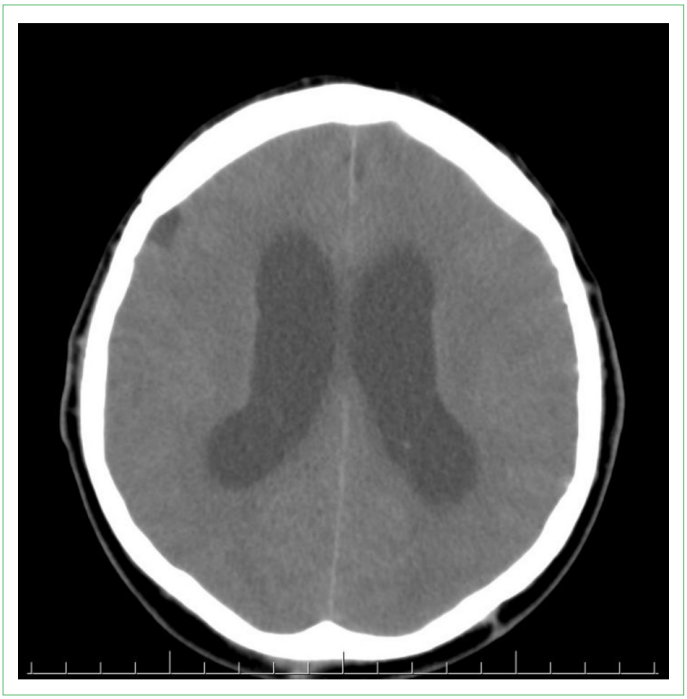

Figure 1. A.Y. Hydrocephalus after the third operation and the appearance of the operation site (2010).

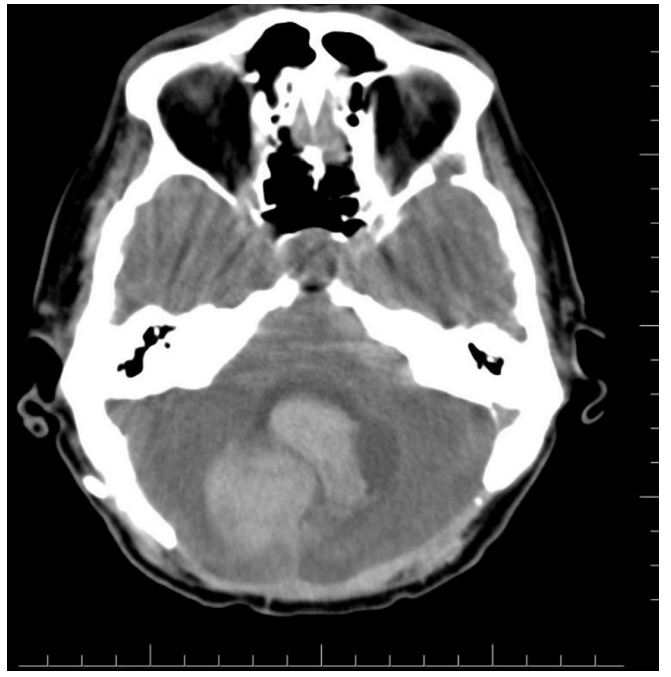

Figure 2. A.Y. Recurrent VHL appearance after third surgery (2010).

stages, the patient became unable to see and walk. Our patient passed away at the age of 50, two years after his initial presentation to us.

Patient 2 — The deceased patient's elder brother, who was 12 years older than him, also underwent surgery once for a cerebellar cystic mass despite the delayed diagnosis, but unfortunately passed away at the age of 49.

Patient 3 — The son (MY), born on 22.05.1994, of the first patient (AY) presented to our clinic on 03.03.2022 with complaints of severe headaches and unsteadiness while walking. MRI revealed a cerebellar cystic mass (Fig. 3). No pathology was detected in other organ scans. Due to familial characteristics, the patient was diagnosed with VHL. Surgical intervention was planned, and on 29.03.2022, the cystic mass was excised via suboccipital craniectomy. The diagnosis was confirmed by pathological examination. The patient's symptoms resolved, and he was discharged without complications. Gamma knife treatment was administered in the postoperative period. Regular follow-ups are being conducted. A contrast-enhanced cranial MRI on 29.09.2022 revealed a 5 mm contrast-enhancing focus at the surgical site, reported as a postoperative change (Fig. 4). A follow-up cranial MRI on 12.04.2023 showed no apparent changes or recurrence compared to the previous MRI. However, a contrast-enhanced abdominal MRI on 29.05.2023 revealed multiple cystic lesions, with the largest measuring 10 mm in diameter, scattered throughout the pancreatic body and tail. Hypointense cystic lesions, measuring 20x18 mm on the right kidney and 22x18 mm on the left kidney, were also observed. The patient continues to lead a normal life with no significant complaints, and follow-up and treatment are ongoing. The most recent contrast-enhanced cranial MRI image of M.Y. (Fig. 5).

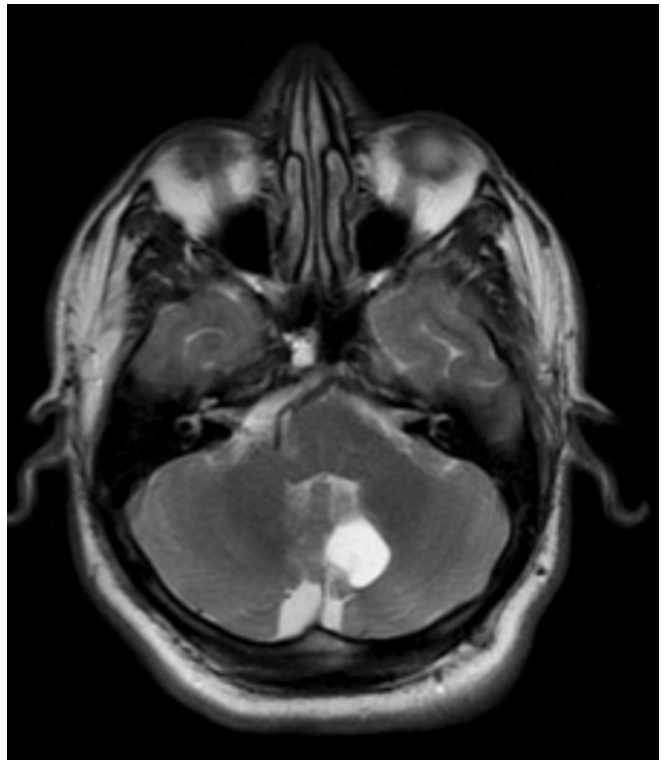

Figure 3. First MRI Figure of M.Y. (03.03.2022).

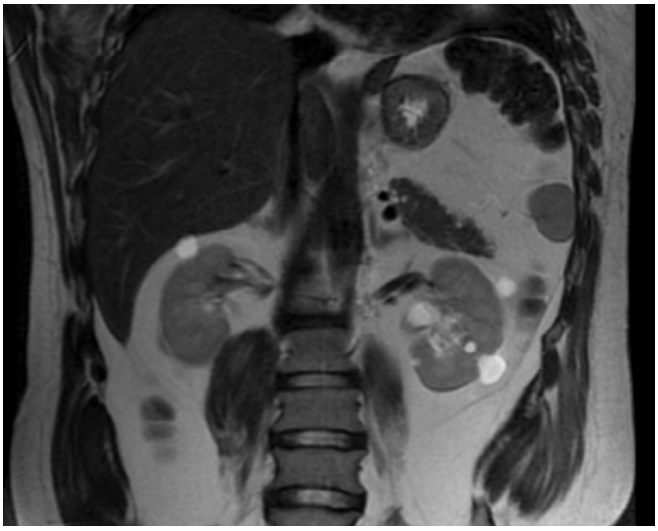

Figure 4. M.Y. contrast-enhanced abdominal MRI (29.05.2023).

Patient 4 — The daughter (AB), born on 6.12.1987, of the first patient (AY), underwent a routine MRI on 03.12.2010, revealing a cystic collection area approximately 2x1.5 cm in size surrounding the middle ear bones on the left side . Abdominal MRI showed a pelvic localization in the left kidney and several cortical cysts measuring 8 mm in diameter in the right kidney. Gamma knife treatment was administered on 14.01.2011. Leksell Gamma Knife model C Gamma Plan 4 C was used to apply radiotherapy to a single matrix area at a dose of 14 Gy (maximum dose 28 Gy) through the isocenter, covering 50% of the isodose area. Additionally, on 20.02.2012, Gamma Knife radiotherapy was administered for the second time. A contrast-enhanced MRI on 23.05.2016 reported a significant reduction in the size of the existing mass, almost to a millimetric size. Lastly, a contrast-enhanced MRI on 25.10.2022 revealed that the mass in the right ponto-cerebellar angle had almost disappeared. Multiple cortical cysts, the largest measuring 2-2.5 cm in size, were observed at the level of the right kidney on abdominal CT. The patient, who currently has no complaints, undergoes routine check-ups. No symptoms or findings were detected in other family members.

Patient 5 — The grandchild (SB), born in 2007, of the first operated patient (AY), underwent cranial MRI due to occasional severe headaches, revealing nonspecific focal findings in the cerebellar region. The patient is still under follow-up.

Patient 6 — The son (BY) of the deceased patient, born in 1985, underwent Gamma Knife treatment upon the detection of cerebellar involvement on cranial MRI. Subsequent examinations revealed that the mass in the cerebellum of the patient, who had no other organ involvement, had gradually decreased over time.

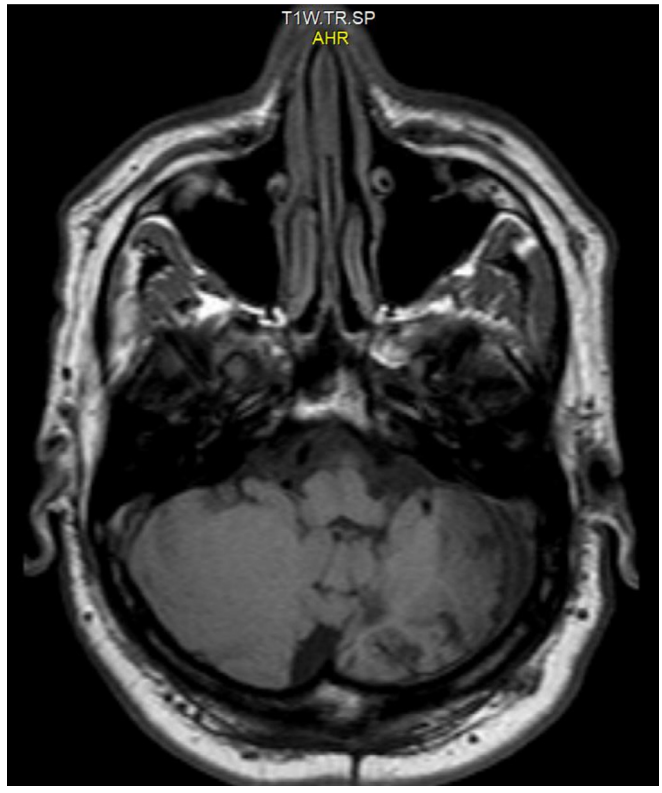

Figure 5. Control MRI one year after M.Y.in surgery.

Discussion

The complexity of Von Hippel-Lindau (VHL) disease, a rare genetic disorder affecting multiple organs, becomes apparent when considering the diverse clinical courses observed in affected individuals.[1,2,3,6,15,18] Our observations highlight the variability in symptoms and outcomes among patients, emphasizing the need for tailored approaches to diagnosis and treatment.

Central nervous system (CNS) hemangioblastomas represent a prominent manifestation of VHL disease, often leading to significant morbidity and mortality.[17,20] Despite being benign, these tumors can exert mass effects on CNS structures, as evidenced by the involvement of the cerebellum, spinal cord, and brainstem in our patients.[5,11,14,16] Tragically, the aggressive nature of these tumors contributed to the premature demise of one patient, underscoring the challenges in managing this condition despite advancements in clinical care.[2,3,6]

Diagnosis primarily relies on contrast-enhanced magnetic resonance imaging (MRI), supplemented by positron emission tomography (PET) scans for comprehensive screening.[1,4,5,20] While these diagnostic modalities aid in identifying CNS hemangioblastomas, the absence of genetic testing in our setting limits our ability to detect VHL mutations early on.[9,11,14] This underscores the importance of expanding ac-

cess to genetic testing to facilitate timely interventions and improve patient outcomes.[1,3,4,9]

Treatment of VHL disease necessitates a multidisciplinary approach, with microsurgical resection being the preferred method for CNS hemangioblastomas.[6,11,17] However, the recurrence observed in our patients despite surgical intervention highlights the challenges in achieving long-term remission. Moreover, the emergence of cystic lesions in extracranial organs like the pancreas and kidneys underscores the need for comprehensive surveillance to detect disease progression early.[5,6,9,15,18]

Retinal hemangioblastomas, a common manifestation of VHL disease, were observed in one patient during the terminal stages of the disease. While laser photocoagulation and cryotherapy offer treatment options for retinal lesions, preventing vision loss remains a challenge.[1,2,3,10,17] Additionally, renal involvement, often presenting as painless hematuria, emphasizes the importance of vigilant monitoring for asymptomatic organ involvement.[2,6,11,13,16]

The case of a patient undergoing Gamma Knife radiosurgery demonstrates the potential efficacy of early intervention in mitigating disease progression.[4,9,20] However, the variability in disease presentation and outcomes among family members underscores the need for personalized treatment strategies tailored to individual patients.

In conclusion, VHL disease poses significant challenges due to its heterogeneous nature and unpredictable clinical course. Early diagnosis and comprehensive surveillance are paramount for optimizing treatment outcomes and enhancing quality of life. Despite the grim prognosis associated with this condition, proactive family screening and personalized interventions offer hope for improving patient prognosis and long-term survival. Each patient's journey with VHL disease is unique, highlighting the necessity of individualized care approaches in managing this complex disorder.

Disclosures

Ethics Committee Approval: This study was approved by Bilecik Seyh Edebali University Ethics Committee (Date: 02.05.2024, Number: E-10333602-050.04-253967).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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