OLGU SUNUMU/CASE REPORT
J Turgut Ozal Med Cent 2015;22(3):187-90

Journal of Turgut Ozal Medical Center
www.jtomc.org

An Unusual Cause of Extremity Weakness: Von Hippel-Lindau Disease and Advantages of Radiologic Imaging on Diagnosis

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Abstract
Von Hippel-Lindau disease is a rare autosomal dominant disease with the disorder matched with the short arm of chromosome 3. The prevalence of Von Hippel-Lindau disease has been estimated to be between 1:35000-1:40000. Retinal hemangioma and central nervous system (CNS) hemangioma are the main manifestations with later accompanying adrenal pheochromacytoma, paraganglioma, renal cell carcinoma, islet cell tumors, pancreatic cysts and neuroendocrine tumors, epididymal cysts, or cystadenoma and endolmphatic sac tumor of the inner ear. The disease is a multisystem disorder with phenotypic variability.
A 50-year-old man presented with a 2-month history of weakness of the right upper and lower limbs. Magnetic resonance imaging revealed cerebellar and spinal hemangioblastomas. In this case report, we present the radiologic images and clinical features of apatient with von Hippel-Lindau disease along with symptomatic central nervous system hemangioblastomas and multiple renal and pancreatic cysts.
Key Words: Hemangioblastoma; Pancreatic Cyst; Renal Cyst; Von Hippel-Lindau Disease.

Ekstremite Güçsüzlüğünün Nadir Görülen Bir Sebebi: Von Hippel Lindau Hastalığı ve Radyolojik Görüntülemenin Tanıdaki Katkıları

Özet
Von Hippel Lindau Hastalığı, 3. kromozomun kısa kolundaki hasar nedeniyle oluşan nadir görülen otozomal dominant bir hastalıktır. Von Hippel Lindau Hastalığı'nın prevelansı 1:35000-1:40000 olarak bildirilmiştir. Retinal hemanjiom ve merkezi sinir sistemi hemanjiomları hastalığın ana belirtileri olmakla beraber adrenal feokromasitoma, paraganglioma, böbrek hücre tümörleri, pankreatik kistler, nöroendokrin tümörler ve epididim kistleri daha sonra eşlik edebilir. Bu hastalık fenotipik değişkenlik gösteren multi sistemik bir hastalıktır.
Elli yaşında erkek hasta, 2 aydır devam eden sağ üst ve alt ekstremitede güçsüzlük öyküsü ile başvurdu. Manyetik rezonans incelemelerinde serebellar ve spinal hemanjioblastomlar; pankreatik ve renal kistler saptandı. Bu olguda merkezi sinir sisteminde semptomatik hemanjiomları, çoklu renal ve pankreatik kistleri olan Von Hippel Lindau tanısı alan olgunun radyolojik görüntülerini ve klinik seyrini sunmayı amaçladık.
Anahtar Kelimeler: Hemanjioblastom; Pankreatik Kist; Renal Kist; Von Hippel Lindau Hastalığı.

INTRODUCTION

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant neoplasia syndrome that results from germline mutations in the VHL genes which lead to the development of several benign or malignant tumors and cysts in many organs (1-3). The main manifestations, described initially, are retinal hemangioma and central nervous system (CNS) hemangioma, the latter of which is frequently cerebellar or spinal cord hemangioblastoma. In time, the syndrome has been identified to complicate with other neoplasms, adrenal pheochromacytoma, paraganglioma, renal cell carcinoma, islet cell tumors, pancreatic cysts and neuroendocrine tumors, epididymal cysts, or cystadenoma and endolmphatic sac tumor of the inner ear (4,5).

We report a case of VHL disease with weakness of extremity caused by CNS hemangioblastomas that has also renal and pancreatic cysts.

CASE REPORT

A 50-year-old man was admitted to the department of orthopedics due to complaints of weakness of the right upper and lower limbs for a 2-month duration. There was no trauma in his recent history. Right hemiparesis and bilateral Hoffman's signs were detected by the neurological evaluation.

The patient was referred to radiology clinic for magnetic resonance imaging (MRI). Cervico-dorsal spine and posterior fossa MRI showed intramedullary mass lesions at cervicomedullary junction level and C5, D2 and D11-

12 vertebral levels varied in size by about 5-14 mm. Also, three mass lesions were revealed in the cerebellum with a large peripheral edema. These lesions were hypo- to isointense on T1 and hyperintense on T2 weighted images, which showed nodular contrast enhancement on intravenous gadolinium administration (Figure 1).

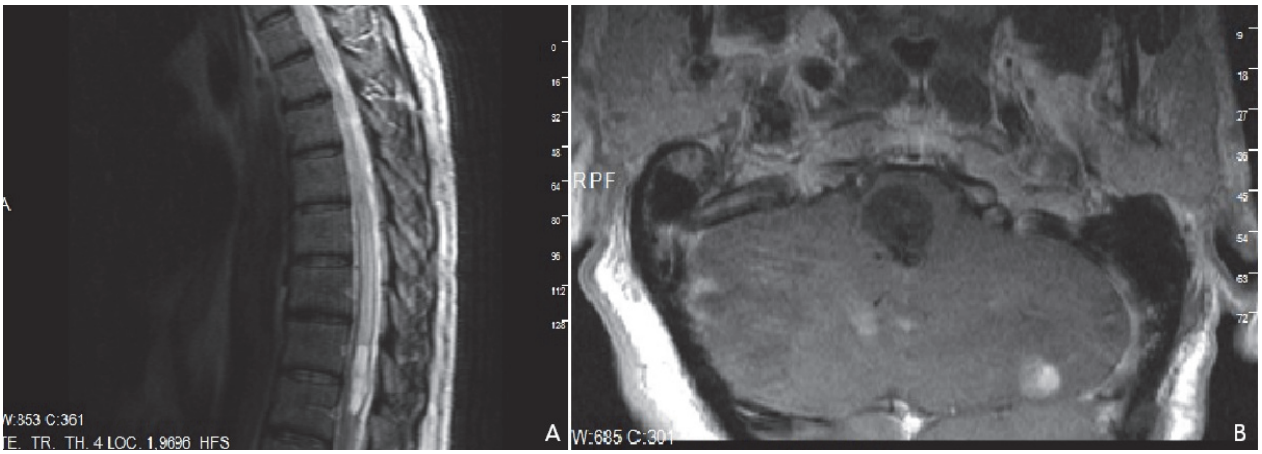

Figure 1. Spinal hemangioblastoma (A) T2 weighted sagital MRI images show hyperintense cystic lesion at D11-12 vertebra levels. (B) Cerebellar hemangioblastomas on T1 weighted post contrast images show hypointense cystic lesion with eccentric enhancing nodular component.

In the cervical and dorsal regions of the spinal cord, we detected syringomyelic changes accompanied by cystic lesions. These cerebellar and spinal lesions were evaluated as hemangioblastomas based on MRI findings. Multiple hemangioblastomas of the CNS occur frequently in VHL disease. Accordingly, the patient underwent additional investigation. On abdominal sonography, cysts were detected in the pancreas and kidneys. Then, we performed an abdomen MRI with half-fourier acquisition single-shot turbo spin-echo (HASTE) sequence and observed multiple cortical cysts in both kidneys and multicystic lesions in pancreatic head, corpus, and tail (Figure 2).

Although retinal angiomas are common with VHL, there were no signs of this after the fundoscopic examination of the patient.

At the department of neurochirurgia, the patient underwent a craniotomy for the removal of the cerebellar lesions. Histological examination supported the idea that the cerebellar lesions were hemangioblastomas. At length, all the findings were diagnostic for VHL disease.

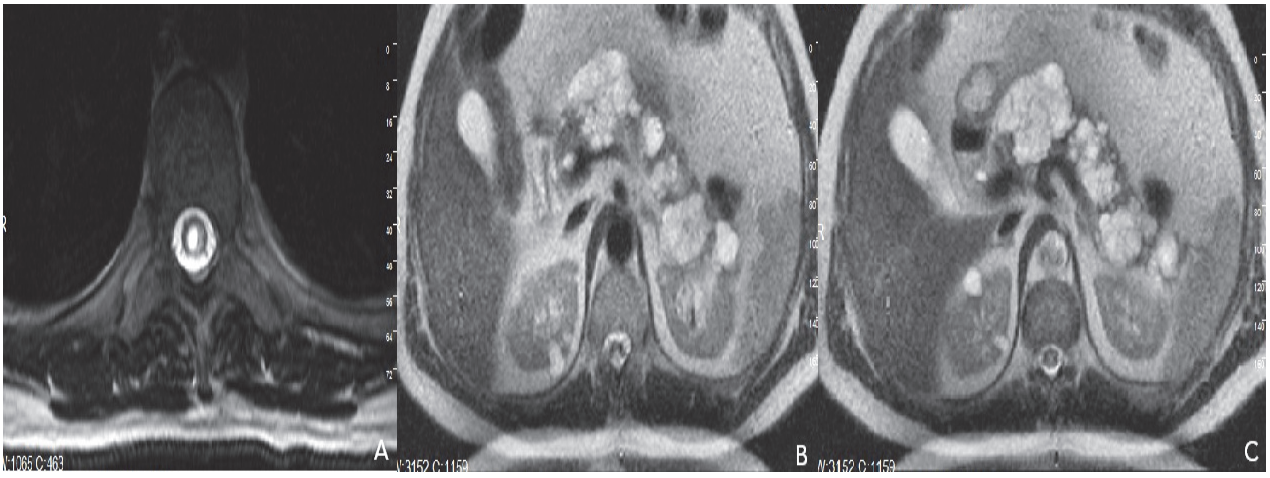

Figure 2. (A) Syringohydromyelic changes of spinal cord in dorsal region T2 weighted axial images. (B) MRI images with HASTE sequence showing bilateral multipl renal cysts. (C) MRI images with HASTE sequence showing pancreatic cysts.

The patient was not aware of any family history of VHL disease. He was informed about the heredity of the disease and suggested medical examination for his family.

The postoperative period was uneventful. The postoperative imaging revealed that the cerebellar hemangioma resection was complete. Six weeks after the surgery, there was a marked regression of the weakness of extremities at the neurologic examination. We did not detect any issues in the patient's follow up.

DISCUSSION

VHL disease is a rare autosomal dominant disorder (6,7). The VHL gene is localized at the short arm of (3p25-26) chromosome (1). Germline mutations in the VHL gene lead to the development of multiple tumors and cysts in many organ systems (3). Affected individuals might develop CNS lesions including cerebellar, spinal cord, brainstem, nerve root, and supratentorial hemangioblastomas as well as retinal hemangioblastomas and endolymphatic sac tumors. Visceral features of the disorder include renal cysts and neuroendocrine tumors as well as epididymal and broad ligament cystadenomas (8,9). For isolated cases without a clear family history as in our case, two or more hemangioblastomas or one hemangioblastoma and a visceral manifestation are required to diagnose VHL (10).

Hemangioblastomas originate from the blood vessels composed of both endothelial and stromal cells (11). CNS hemangioblastomas commonly involve cerebellum, spine, and medulla. Contrast enhanced MRI is the best imaging technique for the detection of hemangioblastoma in CNS (12). Imaging of VHL should include pre- and post-contrast T1 weighted images with thin sections through the posterior fossa and spinal cord in CNS. Small (10 mm or less) hemangioblastomas are isointense on T1 weighted images and hyperintense on T2 weighted images and post-contrast series show homogenous enhancement. Larger (>10 mm) hemangioblastomas are hypointens or show mixed signal intensity on T1 weighted images and are heterogeneous on T2 weighted images showing heterogeneous post-contrast enhancement. A hemangioblastoma larger than 24 mm is invariably accompanied by vascular flow voids (13). In the present case, CNS lesions were hypo- to isointense on T1 and hyperintense on T2 weighted images, which showed nodular contrast enhancement on intravenous gadolinium administration. In the cervical and dorsal regions of spinal cord syringomyelic changes were seen accompanied by cystic lesions. These cerebellar and spinal lesions were evaluated as hemangioblastomas based on MRI findings.

Some untreated spinal hemangioblastomas may remain asymptomatic. As they grow, they may compress surrounding neural elements and cause symptoms. Most common symptoms are progressive low back and lower extremity pain and weakness (14). Also cyst formation is an important clinical problem in patients with hemangioblastomas. The mass effect of the cyst is a major cause of morbidity and mortality. Sudden death may occur when the fourth ventricle is obstructed by the expanding cystic lesion that causes obstructive hydrocephalus which, in turn, may result in brain stem compression and/or sudden death (15).

Although cerebellar hemangioblastoma and retinal hemangioma are the most common initial manifestations in VHL disease, the fundoscopic examination of our case showed no signs of this (16).

Renal cysts are present in 59-63% of individuals with VHL. Renal cell carcinoma (RCC) develops in 25-45% of VHL patients (6, 9). Solid tumours have been observed to grow somewhat faster than sporadic RCC (17).

Various types of pancreatic lesions have been described in VHL patients including pancreatic cysts, serous microcystic adenomas, and adenocarcinomas (18). The correct differentiation of benign asymptomatic serous cystic tumors from other cystic neoplasms of the pancreas with malignancy potential is crucial. Laparotomy is frequently necessary for a definitive and complete histological diagnosis (3). The renal and pancreatic lesions of the present case were evaluated by abdominal ultrasonography and MRI using HASTE sequence. This sequence shows delineation of cystic lesions and its internal contents better (10).

VHL disease generally entails CNS hemangioblastomas, renal and pancreatic cysts. Our case was characterized by multiple hemangioblastomas in the central nervous system and abdominal solid organ cysts, which was in accordance with VHL criteria. Our case was also a rare presentation of VHL since only a minority of hemangioblastomas was defined in the spinal cord that caused weakness of extremities.

Presented at the 7th European Emergency Medicine Congress, EuSem on 03-06 October 2012 in Antalya.

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Received/Başvuru: : 16.12.2014, Accepted/Kabul: 20.01.2015

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For citing/Atıf için

Gormeli CA, Aydin ZB, Gormeli G, Aydin H, Dursun R, Kahraman A, Ozdemir Z, Durak MA. An unusual cause of extremity weakness: von hippel-lindau disease and advantages of radiologic imaging on diagnosis. J Turgut Ozal Med Cent 2015;22:187-90 DOI: 10.7247/jtomc.2014.2441