ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 3, pp. 16249-16252, March, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

VON HIPPEL-LINDAU DISEASE: CT AND MR IMAGING FINDINGS

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DOI: http://dx.doi.org/10.24327/ijrsr.2017.0803.0111

ARTICLE INFO

Article History:

Received 15th December, 2016
Received in revised form 25th January, 2017
Accepted 23rd February, 2017
Published online 28th March, 2017

Key Words:

Von Hippel Lindau Disease; pancreatic serous cystadenoma; CNS Hemangioblastoma; multiple renal cysts; perfusion MRI; Pheochromocytoma

ABSTRACT

Von Hippel Lindau disease (VHL) is a rare, autosomal dominant inherited multisystem disorder which can be diagnosed by clinical, radiologic and genetic findings (Katabathina *et al*, 2014). We reported the spectrum of CT and MR imaging findings of sporadic VHL and familial VHL in three patients. Recurrent headache, ataxia and abdominal pain are most common symptoms. Multiple cerebellar hemangioblastomas are present in all the patients. Pancreatic serous cystadenoma, renal cysts and spinal syrinx formation was demonstrated in 33year old sporadic VHL patient.

INTRODUCTION

VHL is a rare genetic disorder characterized by de novo development of variety of benign and malignant tumors. It involves multiple organ systems and inherited as autosomal dominant pattern. Sign and symptoms of the disease depend on the organ system involvement. Two types of VHL disease has been described in literatures, namely familial and sporadic types, out of them sporadic are most common. The familial disease manifests early as compared to sporadic one. There is broad spectrum of clinical manifestations of the disease. These include retinal and central nervous system hemangioblastomas, endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas. The most common causes of morbidity and mortality in VHL are renal cell carcinoma and neurologic complications from cerebellar hemangioblastoma.

Case report

Case -1

A 33 year-old female patient with chief complaints of headache, ataxia and abdominal pain was referred for radiologic evaluation. There is no family history. Laboratory investigations revealed raised fasting blood sugar and normal pancreatic amylase and lipase. Magnetic resonance imaging (MRI) of brain revealed multiple well defined cystic lesions with mural nodules in the cerebellar hemispheres [Figure-1A, B]. The mural nodules were pial based and intensely enhancing on post contrast images [Figure-1C]. There was T2 hyperintense syrinx along the cervical spinal cord [FIGURE-1D]. Following this, contrast enhanced computed tomography (CECT) and MRI abdomen was done. CECT abdomen demonstrated bulky pancreas with multiple small pancreatic cystic lesions [Figure-2A]. There was enhancing fibrous scar with specks of calcification [Figure-2B]. MRI abdomen revealed bulky pancreas with multiple T2 hyperintense cystic lesions [Figure-2C]. The scar appeared hypointense in both T1 and T2-weighted images (WI) [Figure-2D]. Multiple small renal cysts also demonstrated [Figure-2B, C].The diagnosis of VHL with multiple cerebellar hemangioblastomas, spinal syrinx formation, pancreatic serous cystadenoma and renal cysts was made. After correction of blood sugar, she underwent excision of cerebellar hemangioblastoma. Post operatively, patient improved ataxia and headache. Patient was on insulin injection for control of blood sugar.

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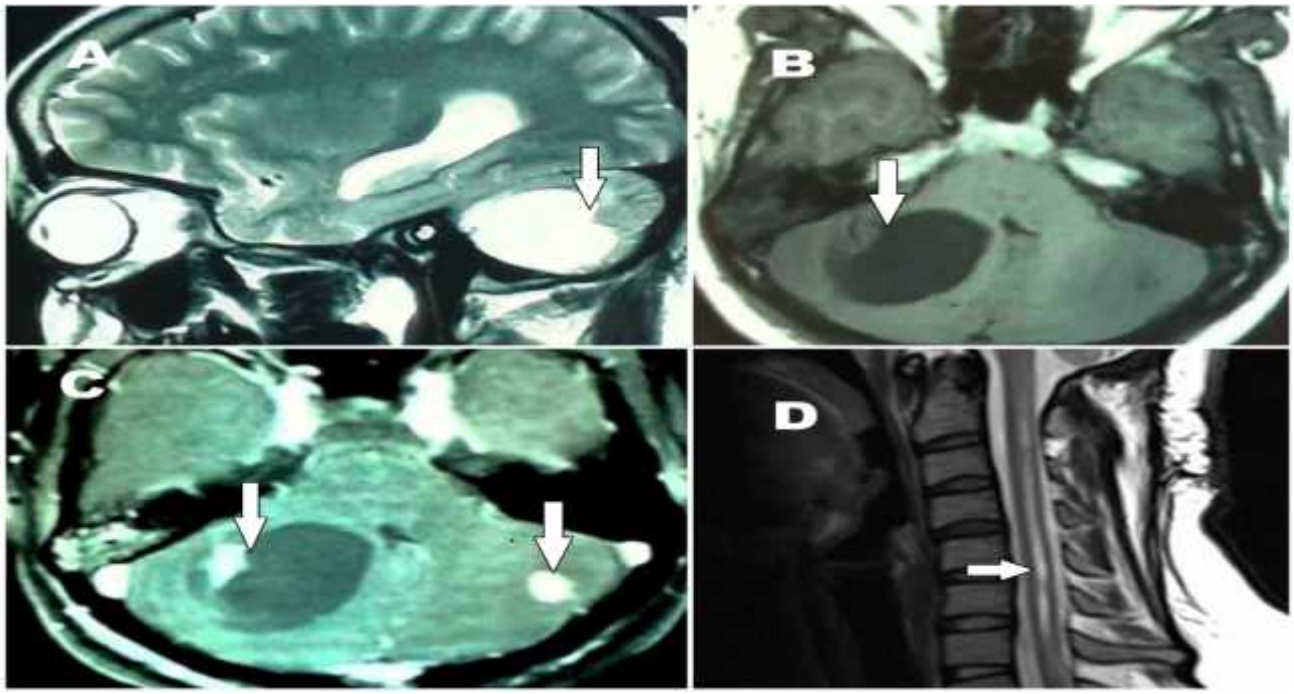

Figure 1 A 33 year-old female VHL patient with chief complaints of headache, ataxia and abdominal pain without family history. **A**. Sagittal T2WI show hyperintense cystic lesion with isointense mural nodule in right cerebellar hemisphere (long arrow). **B**. Axial T1WI shows multiple hypointense cerebellar lesions with isointense mural nodule (long arrow). **C.** Axial post contrast T1WI demonstrated enhancing mural nodules (long arrow). **D.** Sagittal T2WI shows T2 hyperintense syrinx along the cervical spinal cord (short arrow).

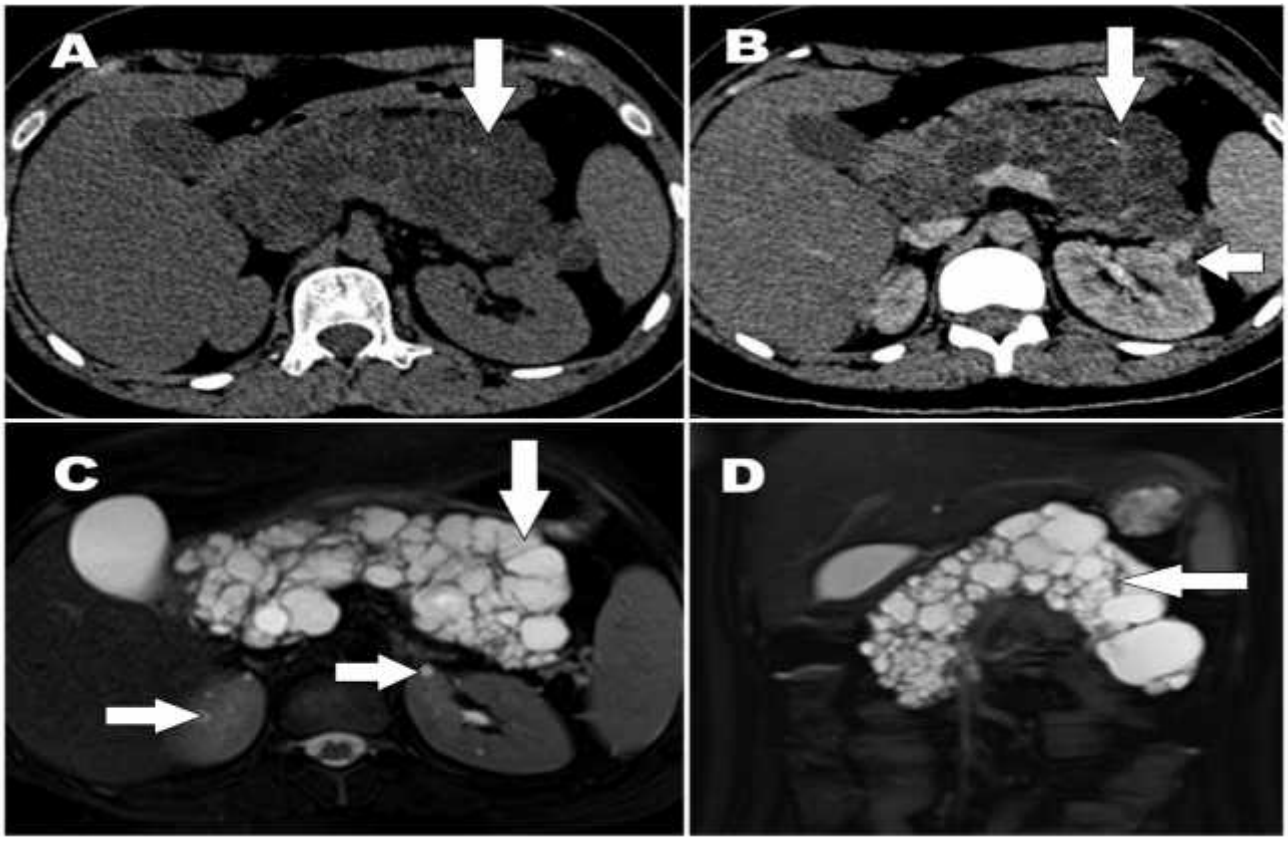

Figure 2 A 33 year-old female VHL patient with chief complaints of headache, ataxia and abdominal pain without family history. **A**. Axial NCCT abdomen show bulky pancreas with multiple intraparenchymal hypodense lesions and specks of calcification (long arrow). **B.** Axial CECT abdomen shows multiple nonenhancing cysts with enhancing septa (long arrow) and left renal cystic lesion (short arrow). **C**. Axial T2WI demonstrated multiple pancreatic hyperintense cystic lesions of variable sizes (long arrow) and renal lesions (short arrow). **D**. Coronal T2WI show hyperintense cystic lesions with hypointense septa (long arrow).

Case-2

A 19 year-old male patient referred to radiology department for evaluation of recurrent headache and ataxia. There was family history of central nervous system hemangioblastomas in mother treated by surgery. His father and two female siblings were found to be free of the disease. Laboratory investigations revealed normal blood sugar and pancreatic enzymes. Magnetic resonance imaging (MRI) of brain revealed multiple well defined cerebellar cystic lesions with pial based mural nodules [Figure-3A]. The mural nodules were intensely enhancing on post contrast images [Figure-3B]. There was increased perfusion on perfusion imaging [Figure-3C]. There was retinal lesion with features of retinal detachment in right eye [Figure-3D]. The diagnosis of VHL with multiple cerebellar and retinal hemangioblastomas was made. Following this, CECT and MRI abdomen was done and found to be normal. Cerebellar hemangioblastoma were excised and the symptoms completely resolved.

The gene has delayed or variable expression nbut high degree of penetrance. The clinical manifestation of the disease is about 40 types distributed in 14 different organs. The organs involved are pancreas (35-77%), central nervous system (44-72%), kidneys (25-60%), eyes (25-60%), adrenal gland (10-20%), epididymis (25-60%) and inner ear (10-25%) (Katabathina *et al*, 2014). The lesions include retinal and CNS hemangioblastomas, renalcell carcinomas and cysts, endolymphatic sac tumours, pancreatic cysts and tumours, pheochromocytomas, and epidydimal cystadenomas.

CNS hemangioblastoma is the most common presentation of VHL disease and can be fatal. Cerebellum (44%–72%) and spinal cord (13%-50%) are mostly involved (Katabathina *et al*, 2014). Signs and symptoms often begin in the second to third decades of life and typically include headache, ataxia and cord symptoms. The exact neurologic deficit depends on the site of the primary lesion.

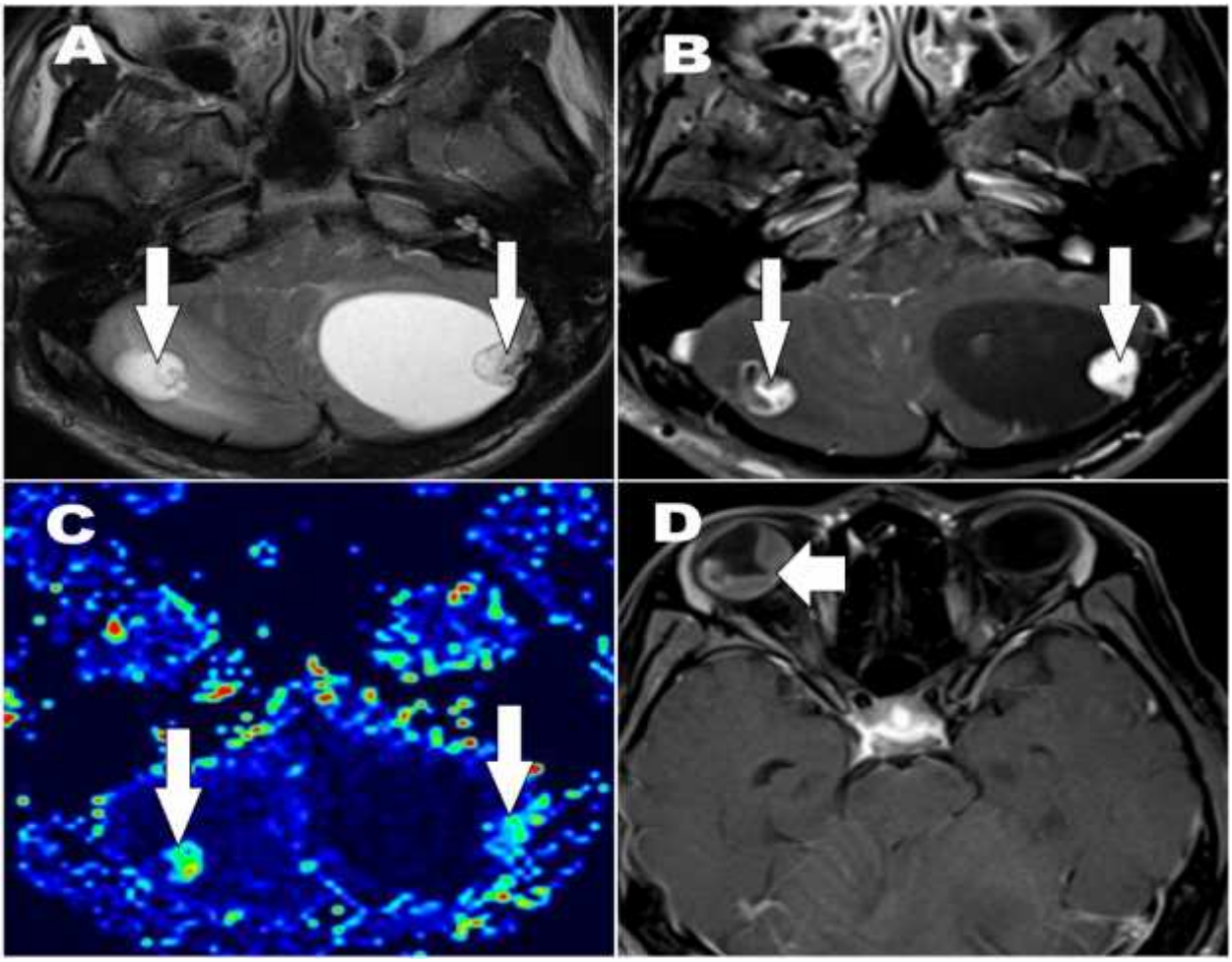

Figure 3 A 19 year-old male VHL patient with chief complaints of recurrent headache and ataxia and family history of hemangioblastoma. A. Axial T2WI shows multiple hyperintense cystic lesions with isointense mural nodule in bilateral cerebellar hemispheres (long arrow). B. Axial post contrast T1WI show enhancing mural nodules in cerebellar lesions (long arrow). C.MR Perfusion image show increased tumour perfusion value in mural nodule (long arrow). D.Axial post contrast T1WI demonstrated enhancing lesion in right eye with features of retinal detachment (short arrow).

DISCUSSION

VHL disease is a rare autosomal dominant genetic disorder characterized by various benign and malignant tumours in the CNS and other visceral organs.VHL gene inactivation at the short arm of chromosome 3 is the established cause (Katabathina *et al*, 2014).

Familial type of VHL disease occurs at a younger age and have worse prognosis (Katabathina *et al*, 2014). The morbidity and mortality of CNS disease is due to frequent surgeries associated with tumour recurrence.

Retinal hemangioblastomas are histologically identical to the CNS hemangioblastomas. It is the first and most frequent manifestations of VHL disease and can develop in up to 60 % patients. These are bilateral and multifocal eye lesions with mean age of presentation around 25 years. About 5% lesions present as early as 10 years (Katabathina *et al*, 2014).

Most endolymphatic sac tumors (ELSTs) occur sporadically, but very rare association with VHL disease. ELSTs are slow growing papillary adenomatoid tumors. These are found in 10-15 % VHL patients and 30 % are bilateral (Katabathina *et al*, 2014; Kobayashi N *et al*, 2012). The renal manifestations include simple or complex cysts (59%-63%), renal cell carcinoma (30%-45%) including clear cell renal cell carcinoma. Sixty six percent patients show renal cortical cysts and are the most common renal lesions. Multiple cysts are common and bilateral in 75% cases (Katabathina *et al*, 2014). Rarely malignant renal tumours including solid and cystic tumours also noted.

The prevalence of adrenal and extra-adrenal pheochromocytomas in VHL disease is about 10% - 20% and can be the only manifestation in type 2C patients. VHL disease–associated pheochromocytomas are usually multiple, bilateral and younger age at presentation with mean age being 30 years (Katabathina *et al*, 2014; Kobayashi N *et al*, 2012). However it has very low malignant potential as opposed to the sporadic lesions. The extra-adrenal lesionsoccur mostly in the organ of Zuckerkandl, other sites are glomus jugulare, carotid body, periaortic, perisplenic and intrarenal lesions.

Pancreatic lesionsare simple cysts, serous cystic neoplasm (SCN), neuroendocrine tumors and rarely adenocarcinomas. The most common type of pancreatic lesions is multiple cysts where as SCNs present in only 10% patients (Kobayashi N *et al*, 2012). Ten to sixty percent men develop epididymal papillary cystadenomas which originate from the Müllerian connective tissue. Bilateral and multiple lesions are pathognomonic of VHL disease (Katabathina *et al*, 2014).

The identification of deletion or mutation in VHL gene by genetic mapping confirms the diagnosis. As genetic testing is not always possible, so sets of clinical criteria are used to diagnose the disease. The diagnostic criteria are more than one CNS hemangioblastoma, one CNS hemangioblastoma and any visceral manifestations or any CNS or visceral manifestations in a known VHL family history. VHL disease is clinically classified into two types on the basis of presence of pheochromocytomas with companion tumour in Type 2.Imaging plays important role in the identification of CNS and visceral lesion and also helps in treatment planning and follow-up. Asymptomatic patient and high-risk gene carriers must be screened regularly by clinical examinations and radiological imaging (Katabathina *et al*, 2014). MRI can be preferred over CT for screening of the disease to avoid unnecessary high dose ionizing radiation.

CNS or retinal hemangioblastomas can be solid, cystic or solid-cystic and highly vascular lesions with intense contrast enhancement. Most of the tumours are cystic with a solid enhancing mural nodule. The MR imaging characteristics are low to medium signal intensity on T1WI and high signal intensity on T2 weighted images (T2WI) in cystic area. The solid nodules are isointense and best demonstrated in contrast-enhanced T1weighted images (T1WI) (Katabathina *et al*, 2014; Lupescu I G *et al*, 2011). The nodules are pial based. Serous cystadenomas are benign microcystic lesion and show central specks of calcificationson CT scan. The tumours have larger peripheral cysts and show peripheral contrast enhancement. T2WI MR sequence show high signal intensity and can be difficult to differentiate from simple cysts. The visualization of central enhancing septa within the tumour favors the diagnosis of microcystic adenoma. However, both lesions are treated conservatively (Lupescu IG *et al*, 2011; Katabathina *et. al*, 2014).

Most of the VHL patients need multiple major operations and the major causes of the morbidity and mortality in postoperative VHL patient. So it is important to decide the perfect time for the operation which can be possible in advancement of imaging. In the last two decade, the morbidity and mortality of patients has been reduced drastically due to improvements in the management strategy. Tumour resection, stereotactic radiosurgical ablation, photocoagulation and cryotherapy ofthe retinal lesions are the treatment choices available.

CONCLUSION

VHL is an autosomal dominant slowly progressive genetic disease presenting with various CNS and visceral tumours. Non-invasive radiological imaging, especially MRI brain and CT abdomen are important for early detection of disease spectrum and their timely management. Patients and their relatives need to be regularly screened throughout lifetime.

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How to cite this article:

Ranjit Meher *et al*.2017, Von Hippel-Lindeau Disease: Ct And Mr Imaging Findings. *Int J Recent Sci Res.* 8(3), pp. 16249-16252. DOI: http://dx.doi.org/10.24327/ijrsr.2017.0803.0111

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