Pictorial review of imaging appearances of abdominal and cerebral manifestations of Von Hippel Lindau

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Authors: J. D. Cunningham¹, E. Kelliher¹, S. Looby², M. J. Lee², M. M. Morrin²; ¹Dublin 9/IE, ²Dublin/IE
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Learning objectives

• To illustrate the spectrum of MR imaging features associated with Von Hippel Lindau Disease (VHL) in the abdomen and central nervous system.

• To describe the clinical context as well as the characteristic appearances of cerebellar haemangioblastomas, spinal haemangioblastomas, endolymphatic cystic tumors, renal cell carcinomas, phaeochromocytomas and pancreatic cystic neoplasms in VHL patients.

• To discuss the role of radiology in the surveillance of patients with Von Hippel Lindau.
Background

Von Hippel Lindau Syndrome

This autosomal dominant inherited phakomatosis is characterised by development of both benign and malignant neoplasms which become clinically apparent at a mean of 25 years of age. The pathogenesis involves mutation of the Von Hippel Lindau tumour suppressor gene on chromosome 3. Different types of mutation result in varied phenotypic manifestations of the disease eg. missense mutations are associated with phaeochromocytoma. Affected families are divided into two types with Type 2 patients at higher risk for developing phaeochromocytomas compared with Type 1. In addition to the tumours presented, VHL is associated with retinal angiomas, epididymal and broad ligament cysts.

Cerebellar Haemangioblastoma

Although classified as benign tumors due to lack of invasion of surrounding structures and distant metastases, these neoplasms cause significant morbidity due to haemorrhage or local mass effect. They are a rare cause of cryptic subarachnoid haemorrhage which should be considered in patients with SAH and negative cerebral angiography. Affecting up to 85% of VHL patients, they are the most common tumour associated with the disorder. Compared with the sporadic equivalent, multiple lesions and post operative recurrence occur with higher frequency in those with VHL. Consequently, active surveillance is generally the preferred management strategy so as to reduce the risk of treatment related morbidity from repeated surgeries. Resection is performed if patients are symptomatic or there is evidence of accelerated growth on neuroimaging.

Spinal Haemangioblastoma

Haemangioblastomas also frequently occur in the medulla and spinal cord.

Gadolinium enhanced MRI is the best imaging modality for diagnosing haemangioblastomas in VHL, however caution must be exercised with its use in patients with impaired renal function associated with VHL because of the risk of NSF. Other small enhancing lesions should be specifically sought on account of the frequency of multiple lesions in these patients. Delayed imaging post contrast can lead to false negative studies due to early lesion enhancement.
**Endolymphatic Sac Tumours**

These vascular neoplasms of the middle ear cause symptoms of tinnitus, deafness, vertigo or facial weakness. Histologically, they are papillary cystadenomas of the endolymphatic sac and tend to be slow growing. Dedicated neuroimaging sequences are required for detection, indeed they are often missed on standard cranial MRI performed for surveillance of haemangioblastoma. They are rare, only affecting approximately 14% of patients with Von Hippel Lindau. Imaging is usually reserved for individuals with abnormal audiology tests. (see section on imaging findings)

**Phaeochromocytoma**

Individuals with Type 2 Von Hippel Lindau are at the highest risk of phaeochromocytoma which are often multiple and extra-adrenal. VHL patients are often asymptomatic and may not demonstrate increased catecholamine production. Therefore, imaging for clinically occult phaeochromocytoma should be performed prior to any operative intervention for another VHL associated mass due to the risk of intraoperative sympathetic overactivity with resultant severe hypertension.

**Renal Cell Carcinoma**

Two thirds of patients with VHL are affected by multiple renal cysts which should be scrutinised for any enhancing solid components. The major concern is development of renal cell carcinoma which is exclusively clear cell carcinoma histologically and may be multifocal or bilateral. Tumour may develop in pre-existing renal cysts or in non cystic renal parenchyma. Papillary or oncocytic renal cell carcinomas are not associated with VHL. The early identification of RCC with improved imaging, particularly MRI, allows increased use of nephron sparing therapeutic strategies rather than radical nephrectomy. (see section on imaging findings)

**Pancreatic Tumours**

While pancreatic cysts are common in people with VHL (seen in up to 70%), serous cystadenomas and neuroendocrine tumours are much rarer, affecting approximately 10% and 15% of patients respectively. Cysts and serous cystadenomas are usually asymptomatic. Complications of pancreatitis, exocrine or endocrine dysfunction are exceptionally rare and von Hippel Lindau patients are not at increased risk of pancreatic adenocarcinoma. Neuroendocrine tumours may be non-functioning or result
in hypersecretion of pancreatic hormones like VIP or insulin, respectively manifesting with diarrhea or hypoglycemic episodes clinically. There is risk of liver metastases with these tumours.
Fig. 2: T1 axial MR post contrast shows avidly enhancing nodule posterior to the spinomedullary junction and two further enhancing cerebellar nodules in keeping with haemangioblastomas. (circles)

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Fig. 4: Well circumscribed intramedullary haemangioblastoma in the lower cervical cord in a patient with VHL. It demonstrates high signal on T2 weighted MRI. (left, arrow) Avid enhancement is seen post contrast administration (mid and left, arrows).

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**Fig. 7:** (From left to right): Lesion in right adrenal gland is isointense to liver on T1, demonstrates high signal on T2, and enhancement on post contrast T1. Findings in VHL patients can be subtle with less marked T2 hyperintensity than is typically seen in sporadic phaeochromocytomas. (incidental note of VHL associated right upper pole renal cyst)

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**Fig. 10:** PNET (pancreatic neuroendocrine tumour) in a patient with VHL. There is a 2.5 cm ill defined mass in the tail of pancreas that is of heterogenous signal intensity on T1 and T2 weighted imaging and enhances post contrast. This lesion had increased in size since previous imaging.

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Cerebellar Haemangioblastoma

Haemangioblastomas vary in MR radiological appearance. 65% are macrocystic with a variably sized cyst and a small mural nodule which is hypervascular. 25% are solid with marked vascularisation. 6% are simple cysts with no mural nodule. 4% are solid but contain small mm cysts. Perinodular cystic fluid may demonstrate high signal on T1 and T2 weighted MRI due to variable protein content. The mural nodule is isointense on T1 and hyperintense on T2. The nodule but not the cyst enhance post contrast. Occasionally foci of increased signal on T1 can be seen in the solid component which represent stromal lipid or meth-haemoglobin from haemorrhage.
Fig. 1: (top row): Axial T2 and FLAIR MRI show right cerebellar nodular mass (star) with peripheral cyst (sun) and mass effect. The peripheral curvilinear signal void (arrows) is evidence of the vascular component and represents a dilated feeding vessel. (bottom row): Axial contrast enhanced T1 weighted MRI shows enhancing cerebellar mass (star). Enhancement is typically intense as in this case due to lesion vascularity. A smaller enhancing nodule is seen in left cerebellar hemisphere (circle).

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Fig. 2: T1 axial MR post contrast shows avidly enhancing nodule posterior to the spinomedullary junction and two further enhancing cerebellar nodules in keeping with haemangioblastomas. (circles)

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Spinal Haemangioblastoma

Appearances are similar to intracranial haemangioblastoma, ie. a well circumscribed cystic neoplasm with highly vascular mural nodule of variable size, typically abutting the pia mater. Spinal involvement is intramedullary in 75% of cases. Radicular and intradural extramedullary involvement occurs in 20% and 5% respectively. The majority of tumours are found in the cervicothoracic spine. These well circumscribed enhancing tumours that typically expand the cord and contain an internal cystic component.
**Fig. 4:** Well circumscribed intramedullary haemangioblastoma in the lower cervical cord in a patient with VHL. It demonstrates high signal on T2 weighted MRI. (left, arrow) Avid enhancement is seen post contrast administration (mid and left, arrows).

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Angiography remains vital for defining afferent and efferent vessels and assisting in endovascular embolisation. On angiography, nodules stain intensely in a homogenous or mottled fashion. Irregular vessels and AV shunting can also be identified. Cysts are characterised by an avascular area causing vascular displacement.
**Fig. 5:** (top left to right): Sagittal T2 and post contrast T1 MRI show serpiginous signal voids (open square brackets), intramedullary cysts (arrows) and enhancing nodules in keeping with extensive haemangioblastoma. (circles) (bottom row): Spinal angiogram in same patient shows contrast staining of the nodular component and irregular feeding vessels of haemangioblastoma.

**References:** Radiology department, Beaumont Hospital - Dublin 9/IE

**Endolymphatic Sac Tumours**

These are found in a retrolabyrinthine location and typically demonstrate heterogenous signal on T2 weighted imaging. Foci of hyperintensity and hypointensity on non contrast T1 MRI are due to subacute haemorrhage and calcification respectively. Post contrast there is avid enhancement. CT is also an important modality for evaluation as tumours can have a thin peripheral calcified rim which is the expanded petrous cortex. The margins are described as moth eaten or geographic and it contains spiculated bone. They grow gradually toward the external ear laterally or medially into the cerebellopontine angle.
Fig. 6: Axial T2 and axial and coronal T1 post contrast MRI show extensive enhancing soft tissue in the left middle ear cavity and involving the left mastoid temporal bone. (circles) There is mild encroachment on left cerebellopontine angle.

References: Radiology department, Beaumont Hospital - Dublin 9/IE

Phaeochromocytoma

Fig. 7: (From left to right): Lesion in right adrenal gland is isointense to liver on T1, demonstrates high signal on T2, and enhancement on post contrast T1. Findings in VHL patients can be subtle with less marked T2 hyperintensity than is typically seen in sporadic phaeochromocytomas. (incidental note of VHL associated right upper pole renal cyst)

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Renal Cell Carcinoma
**Fig. 8**: (top right): Multiple bilateral renal cysts on T1 and T2 axial MRI. A complex cyst in left upper pole demonstrates heterogeneous signal intensity. (left, top and bottom): pre and post contrast T1 axial MR is suspicious for peripheral nodular enhancement in left upper pole renal cyst. (bottom right): Subtraction of pre-contrast T1 from post-contrast T1 is useful in this setting to confirm true enhancement of the cyst peripherally (arrow). Cysts that are hyperintense on T1 and T2 weighted images either have either haemorrhagic or proteinaceous content.

**References:** Radiology department, Beaumont Hospital - Dublin 9/IE

**Pancreatic Tumours**

**Fig. 9**: (From left to right): Pre and post contrast T1 and T2 weighted axial MRI demonstrates two pancreatic cysts in tail of gland, which are high signal on T2, low signal on T1 and do not enhance post contrast.

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**Fig. 10:** PNET (pancreatic neuroendocrine tumour) in a patient with VHL. There is a 2.5 cm ill defined mass in the tail of pancreas that is of heterogenous signal intensity on T1 and T2 weighted imaging and enhances post contrast. This lesion had increased in size since previous imaging.

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**Surveillance**

Radiology is playing a key role in surveillance for tumour development which has significantly improved survival and quality of life of patients with Von Hippel Lindau syndrome in recent years. Screening strategies focus on RCC, phaeochromocytoma and haemangioblastoma, the three manifestations that most frequently contribute to morbidity and mortality. The importance of imaging is not only to identify neoplasms early in their development but also to monitor small asymptomatic tumours for progression over time which may alleviate the need for surgical intervention. Annual abdominal ultrasound is recommended for adolescents, followed by renal or adrenal MRI if abnormal. Annual contrast enhanced cranial and whole spine MRI should also be performed in this age-group. The adult population should undergo the same surveillance with the addition of renal MRI every other year.
Fig. 3: T2 and post contrast T1 axial MR show cysts with small peripheral enhancing nodules in another patient with Von Hippel Lindau associated haemangioblastoma

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Conclusion

This pictorial overview of the findings associated with Von Hippel Lindau Disease demonstrates the role of MR imaging in the evaluation of lesions involving both the nervous system and abdomen.
Personal Information

Dr. Jane Cunningham,

2\textsuperscript{nd} year Radiology Resident,

Beaumont Hospital,
Beaumont Road,
Dublin 9,
Ireland.

jane\textsubscript{cunningham}0708@gmail.com
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