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Von Hippel-Lindau (VHL) Disease

- Autosomal dominant mutation of tumor suppressor gene on chromosome 3
- Usually presents in early adulthood, but may find earlier if known family history
- Different VHL subtypes exist (type 1, type 2A-C) but I don't think they are likely to ask you about these on the ABR core exam
- Sites of disease are CNS/head and abdominal
- Diagnosis requires
    - Retinal and CNS hemangioblastoma (multiple hemangioblastomas=VHL), or
    - Hemangioblastoma and one of the following:
        - Cysts in kidney, liver, pancreas, or epididymis
        - Renal malignancy
        - Pheochromocytoma
    - Or, family history and one of the following
        - Hemangioblastoma of any site
        - Renal malignancy
        - Pheochromocytoma
- Classic findings in VHL
    - Hemangioblastomas (most VHL patients will develop these)
        - Cerebellum most common
            - May be bilateral
            - Usually in posterior fossa off of midline
        - Can be retinal (aka retinal angioma)
        - Most common in cerebellum>retina>spinal cord>brain stem
        - On imaging a hemangioblastoma looks like a cyst with a soft tissue mural nodule
            - The soft tissue component is fluid secreting, hence the cystic appearance
            - These tend not to calcify
            - Nodule tends to be very vascular
        - Adult with infratentorial cystic mass with enhancing nodule think hemangioblastoma and VHL (especially if multiple)
            - Child with infratentorial cystic mass with enhancing nodule think pilocytic astrocytoma
        - Spinal cord hemangioblastomas are most common in thoracic cord, classic look is a widened spinal cord with edema, serpiginous draining meningeal varices, flow voids
    - Cysts of pancreas, kidneys, liver
    - Renal malignancies
        - Typically, clear cell renal cell carcinoma
        - May be multiple and bilateral
            - Think VHL if they show you multiple or bilateral RCCs
        - Treatment is surgical resection

        - Renal angiomyolipomas also associated with VHL but know that the classic renal manifestation of VHL is bilateral renal cell carcinomas
    - Pheochromocytomas
    - Paraganglioma
        - Paragangliomas are extra-adrenal pheochromocytomas
        - VHL: pheochromocytoma more common than paraganglioma
        - Multiple paragangliomas may be seen in MEN2 or VHL
    - Cystadenomas of epididymis or round ligament
    - Pancreas
        - Pancreatic cysts are very common in VHL and very rare in practice so if you see multiple pancreatic cysts consider possibility of VHL
        - Neuroendocrine islet cell tumors may also arise
            - About 10% of VHL patients get these, may be multiple
            - Hypervascular tumors with arterial enhancement
                - Associated with VHL and MEN1
        - Pancreatic serious cystadenoma
            - These are microcystic and may show calcification with stellate scar
        - Pancreatic adenocarcinoma is typically not associated with VHL
    - Adrenal gland
        - Pheochromocytoma
            - 20% of all pheochromocytomas arise with VHL
            - Bilateral pheochromocytomas think VHL
            - Remember workup can include VMA and norepinephrine levels, nuclear MIBG scan
    - Endolymphatic sac tumor
        - Locally aggressive permeative tumor with risk of hearing loss
            - Often present with hearing loss and tinnitus
        - Occur in about 15% of VHL patients
        - Bilateral endolymphatic sac tumors is pathognomonic for VHL
        - Look for erosion of the petrous apex with “moth eaten” pattern on CT with associated enhancing mass
        - May be cystic with peripheral vascular mass
            - May see flow voids and tumor blush on angiography
        - CT typically shows internal calcifications
        - Treat with surgical excision
    - Epididymis
        - Cysts
        - Papillary cystadenomas
            - Cystic lesion with vascular mural nodule(s)
            - May be bilateral

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- Key things to remember with VHL
  - Hemangioblastomas
  - Cysts of many organs (liver, kidney, pancreas, epididymis)
  - Tumors tend to be cystic with vascular mural nodules
  - Tumors tend to be multiple and bilateral
  - Tumors tend to be CNS and abdominal
  - Retinal angioma = VHL
  - Multiple hemangioblastomas = VHL
  - Endolymphatic sac tumor = VHL
  - Multiple renal cell carcinomas = VHL
  - Bilateral pheochromocytomas = VHL

- You actually often screen patients with known VHL or family history starting as a teenager
    - Most VHL lesions are treatable so screening makes sense
    - However, prognosis is poor and many VHL patients do not survive past 50s
    - NIH has recommended MRI screening of head and abdomen for individuals in VHL families after 10 years of age every 2 years

- Tip: On board exams any time they show you bilateral tumors, or a single organ with multiple non-metastatic tumors, they are probably showing you a disease process with a genetic abnormality

- VHL mnemonic is HIPPEL
  - H: hemangioblastoma
  - I: increased risk of renal cell cancers (kind of stupid that I=RCC)
  - P: pheochromocytoma
  - P: pancreatic lesions
  - E: eye (retinal) hemangioblastoma
  - L: liver cysts