Bilateral pheochromocytomas in Von Hippel Lindau (VHL) disease

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Patient profile

• 6-year-old boy with history withheld
Our patient: Ultrasound-1

A 3 cm well-circumscribed mass medial and superior to kidney.
Our patient: Ultrasound-2

- A well-circumscribed mass medial or attached to kidney

Transverse view of R’t kidney, US
The possible origin of the masses

- Adrenal gland
- Kidney itself
- Vessels lesion
After US, 
What’s the next imaging modality you want to obtain?
Our patient: serial CT images-1

Axial, C+ abdominal CT
PACS, CHB
Our patient: serial CT images-2

Axial, C+ abdominal CT
PACS, CHB
Our patient: serial CT images-3

Axial, C+ abdominal CT
PACS, CHB

L’t adrenal mass
Our patient: serial CT images-4

Axial, C+ abdominal CT PACS, CHB

Bilateral enhancing adrenal masses
Our patient: serial CT images-5

Bilateral enhancing adrenal masses

Axial, C+ abdominal CT
PACS, CHB
Our patient: serial CT images-6

- No vessel infiltration or encasement
Our patient: CT C+
Coronal reconstruction

1. Bilateral well-circumscribed adrenal masses
2. Two masses are enhanced heterogeneously with a peripheral zone of intense enhancement
Differential diagnosis

• Pheochromocytoma (adrenal medulla)
• Neuroblastoma
• Adrenal cortical adenomas, carcinoma.
• Metastases from an unidentified primary
After the CT, what’s the next imaging modality you want to obtain?
I-123 MIBG (MetaiodoBenzy1 guanidie) SPECT Scan

- Expected physiological accumulation is seen in the salivary glands and bladder.
- Abnormally bilaterally increased suprarenal uptake
What is I-123 MIBG scan?
Let’s see!
MIBG (MetaiodoBenzylguanidine) Scan

- MIBG is a guanidine derivative that resembles norepinephrine and selectively accumulates in catecholamine-secreting cells.
- Useful in evaluation pheochromocytoma, neuroblastoma, carcinoid, and medullary carcinoma of thyroid.
Can you narrow down the DDx now?
If not, hope the patient’s complete info will help you.
Complete Patient Information

- 6-year-old boy with episodes of sweating, tachycardia, and hypertension that have occurred frequently (50-100 times) over the past several months.
- The attacks occur mostly in the night. Hypertension was noted during the attack.
- No history of headaches, weight loss, weight gain, blurry vision, or feminization.
- He takes no medications and has no known drug allergies.
Final diagnosis

• Pheochromocytoma!!
Management

• Bilateral laparoscopic total adrenalectomies
• Post-op, the endocrinology team followed the patient and initiated stress dose adrenal replacement therapy.
• He was gradually weaned off pressors.
Our patient: one year follow up MRI

Axial, T2 weighted image, MRI
Now, we’ve known the diagnosis. Let’s learn something about Neuroblastoma which is the most important DDx in this case.
Neuroblastoma-1

• The most common extracranial solid tumor in pediatrics. ---2-4 yrs, 90%<5 years old
• the most common abdominal tumor to demonstrate calcifications (50%)
Neuroblastoma-2
(similar points with Pheo.)

- 65% p’ts are abdominal in location
  - 2/3 adrenal gland
- Arising from neuroblasts (pluripotent sympathetic cells).
- I123/131 -MIBG accumulates in catecholaminergic cells
The embryogenesis

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Sympathetic chain

**Left:** Anatomic distribution of extra-adrenal chromaffin tissue in the newborn.

**Right:** Locations of extra-adrenal pheochromocytomas reported before 1965.

(Reproduced, with permission, from Coupland R: *The Natural History of the Chromaffin Cell*. Longmans, Green, 1965.)

**Source:** Greenspan's Basic & Clinical Endocrinology > Chapter 12. Adrenal Medulla & Paraganglia > Pheochromocytoma > Pathology of Pheochromocytomas & Related Tumors >
Pheochromocytoma-1

• a **catecholamine**-secreting **tumor** derived from **chromaffin cells** of adrenal medulla or extra-adrenal ectopic tissues.

• Can be anywhere along the sympathetic chain (neck to bladder).
Pheochromocytoma-2

• The classic triad:
  – episodic headaches,
  – sweating, and
  – tachycardia,

• usually accompanied by hypertension
Rule of 10’s

- 10% extra-adrenal: Paragangliomas
- 10% bilateral, malignant & extra-abdominal
- 10% familial, pediatric, silent
- 10% have autosomal dominant transmission & associated with various other dominant conditions (ex. Von Hippel Lindau)
For children with pheochromocytomas

- Compared to adults, children have a higher incidence
  - bilateral adrenal tumors,
  - extraadrenal tumors (30-60% vs 10-15%), and
  - multiple tumors (40% vs 5-10%)

- Higher risk for malignant disease
  - 47% in children vs 10% in adults

- Higher proportion of the familial type
  - familial adrenal pheochromocytomas are more likely to be bilateral

Source: upToDate, Pheochromocytoma in children. Assessed on 2010 Oct.
Imaging of pheochromocytoma

• Well-vascularized, and high water content tumor
• CT: Well defined, round, and enhancing lesion.
• MRI
  – T1: Isointense, bright if hemorrhage.
  – T2: Hyperintense
  – C+: Salt and pepper pattern of enhancement and flow voids.
• CT and MRI are similar in sensitivity.
• T2-weighted MRI with gadolinium contrast is optimal for detecting pheochromocytomas
Companion #1

Axial, T2 weighted image w/o contrast

Hyperintense adrenal mass

Coronal, Contrast+ T2 weighted image shows bilateral adrenal masses exhibiting bright T2 signal intensity with salt-and-pepper enhancement pattern.
Imaging-Nukes

- $^{131}\text{I}$- or $^{123}\text{I}$- metaiodobenzylguanidine (MIBG)
- $^{111}\text{In}$-somatostatin analogues, or
- $^{18}\text{F}$-dopa (or dopamine) positron-emission tomography (PET).
131I- or 123I- MIBG

• 123I-MIBG is preferable, because 123I emits lower energy (159 keV) radiation than does 131I (364 keV). This results in a somewhat lower absorbed radiation dose than 131I-MIBG scanning.

• Better sensitivity (83–100% vs 77–90% ) than 131I

• Most centers still use 131I-MIBG, due to its longer half-life, lower expense, and better commercial availability
Familial pheochromocytoma

- Multiple endocrine neoplasia (MEN) 2A, 2B
  - 50% include pheo
- von Hippel-Lindau (VHL) disease
  - Type 2
  - 10-20% include pheo
- Neurofibromatosis type 1 (NF1)
  - 2% include pheo
- Genetic cause should be sought in all children with Pheochromocytoma
Our patient: Genetic testing

- heterozygous for Val166Ala variant
- testing result consistent with VHL disease.
- He underwent a brain MRI which subsequently was negative.
- further testing of his parents and further discussion of the ramifications of this result are necessary
Von Hippel Lindau

- The VHL gene is a tumor suppressor gene whose locus is 3p26-25
- type 1 VHL do not develop pheochromocytomas. They tend to have loss-of-function VHL gene mutations
- type 2 VHL mutations are prone to develop pheochromocytomas. These patients carry VHL missense mutations.
Von Hippel Lindau

• Autosomal dominant disease of benign and malignant tumor formation.
  – Hemangioblastomas of the brain (cerebellum) and spine
  – Retinal angiomas
  – Clear cell renal cell carcinomas
  – Pheochromocytomas (usually bilateral)
  – Endolymphatic sac tumors of the middle ear
  – Serous cystadenomas and neuroendocrine tumors of the pancreas
  – Papillary cystadenomas of the epididymis and broad ligament
Review of Von Hippel Lindau

Thierry Hannedouche,
Von Hippel Lindau
http://www.nephrohus.org/s/spip.php?article448
Assessed on Oct. 11, 2010
Follow up recommendation of Von Hippel Lindau


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Table 12-11. Individuals Carrying a VHL Gene Mutation Must Have Close Medical Surveillance and the Following Protocol Is Recommended.

<table>
<thead>
<tr>
<th>Protocol Details</th>
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<td>Twice yearly: physical examination with blood pressure; plasma normetanephrine levels (type 2 VHL)</td>
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<tr>
<td>Yearly: 24-hour urinary fractionated catecholamines, metanephrines, and creatinine (type 2 VHL); retinal examination</td>
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<td>Yearly: abdominal imaging (ultrasound of abdomen on alternate years from MRI or CT scanning [nonionic contrast] of the abdomen)</td>
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<td>Every 2 years: MRI scanning (with intravenous contrast) of the entire brain and spinal cord (types 2A and 2B VHL)</td>
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<td>Before major surgical procedures and pregnancy: complete biochemical screening for pheochromocytoma</td>
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<td>If abnormal biochemical screening: MRI or CT scan of the abdomen (nonionic contrast) with thin-section adrenal cuts; $^{123}$I-MIBG SPECT scan</td>
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Our patient: Follow up plan

• In regards to his pheochromocytoma, we will continue with urine test and blood pressure screening, and plan to do follow-up examinations every three months.

• Plan imaging with a repeat ophthalmologic examination.

• We will also confer with our adult colleagues for further management patients with Von Hippel Lindau.
Summary

- Pheochromocytomas and paragangliomas are rare neoplasms in children.
- Learn how to differential diagnosis by different imaging modalities
- Recognize the different features of pheochromocytoma between adults and children.
- Von Hippel Lindau disease and the follow ups
References-1

References-2


References-3


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