Adrenal medullary hyperplasia - what is it???

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04-2015
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MEIR MEDICAL CENTER,
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Case presentation

- 54 year old, male. S/P smoker.
- Diabetes mellitus type 2 – Januet
- Hypertension (5 years) – Lotan
- Dyslipidemia – Simovil

- No family history of malignancy.

- Month of Rt thigh pain.
- CT – susp metastases in Rt femur (10 cm).
- CT chest-abdoman-pelvic: Rt kidney mass 8*10*10 cm, Lt adrenal mass 20*10 mm, 27 HU. Susp metastases in T8.
Case presentation

- **Adrenal mass – DD:**
  - metastases VS. adrenal neoplasm.

- **DST – normal.**

- **Renin, aldosterone – normal.**
## Urine collection 24 hours

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reference Range</th>
<th>03/07/2014 08:49</th>
<th>14/08/2013 08:02</th>
<th>08/05/2013 09:27</th>
<th>30/05/2011 08:21</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREATININE- U 24h</td>
<td>800 - 2000 mg/24h</td>
<td>1651</td>
<td></td>
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<tr>
<td>CREATININE- U SAMPLE</td>
<td>mg/dl</td>
<td>45.9</td>
<td>66.4</td>
<td>68.1</td>
<td>218.6</td>
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<tr>
<td>METANEPHRINE/CREA</td>
<td>10 - 319 µg/gr crea</td>
<td>218</td>
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<tr>
<td>NORMETANEPHRINE/CREA</td>
<td>96 - 452 µg/gr crea</td>
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<td>1785*</td>
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<tr>
<td>CH3-0-TYRAMIN/CREA</td>
<td>10 - 300 µg/gr crea</td>
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<td>74</td>
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<td>EPINEPHRINE/CREA</td>
<td>0 - 20 µg/gr crea</td>
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<tr>
<td>NOREPI/CREA</td>
<td>10 - 75 µg/gr crea</td>
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<tr>
<td>DOPAMINE/CREA</td>
<td>10 - 400 µg/gr crea</td>
<td>144</td>
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<tr>
<td>EPINEPHRINE- U 24h</td>
<td>0 - 20 µg/24hr</td>
<td>4</td>
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<tr>
<td>NOREPI- URINE 24h</td>
<td>10 - 75 µg/24hr</td>
<td>36</td>
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<tr>
<td>DOPAMINE- URINE 24h</td>
<td>10 - 400 µg/24hr</td>
<td>238</td>
<td></td>
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<tr>
<td>METANEPHRINE U 24h</td>
<td>10 - 300 µg/24hr</td>
<td>288</td>
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<tr>
<td>NORMETANEPH- U 24h</td>
<td>90 - 450 µg/24hr</td>
<td>2948*</td>
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<tr>
<td>CH3-0-TYRAMIN U 24h</td>
<td>40 - 300 µg/24hr</td>
<td>122</td>
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</tbody>
</table>
Case presentation

- Anamnesis – 5 years of hypertension 150/95.
- 2 years ago – admitted to ER with palpitations and weakness.
- Sweating attacks.

- Vital signs –
- Blood pressure 150/100, pulse 100 regular, temp 36.6°C

- Susp pheochromocytoma.
• Dibenyline 10mg X3/D – > 20mg X3/D.
• Saline.

• After 12 days...
The surgery

- 20/7/ 2014 –
- Total nephrectomy Rt
- Paraortic LN dissection.
- Lt adrenalectomy – macroscopic RCC metastases.

- Frozen section – no pheochromocytoma!!!!
- but RCC metastases!!!!
Post – operation

- Blood pressure - 110/70
- Pulse 70 regular
- no treatment!!

- Pheochromocytoma or not????
Pathology

- Metastatic Renal cell carcinoma of Rt kidney (metastate to LT adrenal gland).
- 5/8 LN are involved by metastatic RCC.
- Adrenal medullary hyperplasia.
The topics

- Adrenal medullary hyperplasia –
  - What is it? History...
  - Diagnosis.
  - Treatment.
  - Genetics.
Attempts to establish as clinically pathologic process - since **1933**.

**1952** – Schwab and Denninger: a woman with symptoms of pheochromocytoma with out tumor, but marked medullary hyperplasia.

**1961** – Bialestock: the first case in the *pediatric* age (5 and 11 years old).
Bilateral Adrenal Medullary Hyperplasia in Multiple Endocrine Neoplasia, Type 2

The Precursor of Bilateral Pheochromocytoma

An asymptomatic 12-year-old girl with multiple endocrine neoplasia, type 2, had high urinary levels of vanillylmandelic acid that suggested pheochromocytoma; she also had bilateral medullary thyroid carcinoma and hyperparathyroidism. Her mother and maternal aunt and uncle had bilateral pheochromocytoma (metastatic in the former two). Bilateral adrenalectomy was performed. Diffuse, non-nodular adrenal medullary hyperplasia was present. This hyperplasia was characterized by increased medullary mitotic activity, decreased corticomedullary ratio, increased total adrenal weight, and increased total catecholamine content (left adrenal). The results in this case suggest that diffuse hyperplasia of the adrenal medulla may be the precursor of pheochromocytoma in patients with this syndrome.

The association between thyroid carcinoma and pheochromocytoma was emphasized by Sipple in 1961. Since then, more than 200 affected patients in multiple families have been recognized. This commonly familial association is part of the syndrome of multiple endocrine neoplasia syndrome type 2 (MEN type 2). In these cases there is a spectrum of involvement of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism.
Sporadic Unilateral Adrenomedullary Hyperplasia with Hypertension Cured by Adrenalectomy

Henning Drale, M.D., Sören Schröder, M.D., Klaus F. Gratz, M.D., Reinhard Grote, M.D., Barbara Padberg, M.D., and Rolf D. Hesch, M.D.

Klinik für Abdominal- und Transplantationschirurgie, Medizinische Hochschule Hannover, Hannover; Institut für Pathologie, Universitätskliniken Hamburg-Eppendorf, Hamburg; Abteilung Nuklearmedizin und Spezielle Biophysik, Medizinische Hochschule Hannover, Hannover; Abteilung Diagnostische Radiologie I, Medizinische Hochschule Hannover, Hannover; and Abteilung Klinische Endokrinologie, Medizinische Hochschule Hannover, Hannover, Federal Republic of Germany

Adrenomedullary hyperplasia (AMH) with increased urinary excretion of epinephrine is regarded as the earliest adrenal manifestation in familial pheochromocytoma; however, pathogenetic mechanisms and morphogenesis involved in the development of sporadic adrenomedullary diseases are unknown as yet. We present 4 patients with clinical, biochemical, imaging, and morphological findings of sporadic unilateral adrenomedullary hyperplasia cured by unilateral adrenalectomy. All patients were hypertensive with intermittent hypertensive crises, and with increased catecholamine concentrations in urine and serum. Correct unilateral localization was achieved by 123-I-BG-scan (planar and SPECT) (n = 2) or cavouenous blood sampling with selective catheterization of both suprarenal veins (n = 2). Histomorphometric analyses revealed diffuse adrenomedullary hyperplasia in all 4 specimens with significant increase of relative volume to 17.6% (controls, 8.7%), and of estimated medullary development of pheochromocytoma is largely unknown [6–8]. From clinicomorphological studies, pheochromocytoma in familial and MEN 2-associated adrenal medullary diseases is regarded as the neoplastic endstage of a stepwise development beginning with hypertrophy and hyperplasia of the medullary cells [8–10]; however, aside from this conclusive pathogenetic hypothesis concerning familial pheochromocytoma, frequency and clinical significance of preneoplastic forms of sporadic pheochromocytoma are as yet unknown. To our knowledge, there are only few communications from the earlier literature describing the existence of sporadic adrenal medullary hyperplasia (AMH) [11–14].
Diagnosis

- Anamnesis and physical examination.
- Urine collection/plasma sample of catecholamines and metanephrines.
- Imaging studies – no tumor.
- MIBG scan.
- Definitive diagnosis is provided by histological study.
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Bilateral Adrenal Medullary Hyperplasia Associated With an SDHB Mutation
Grogan RH et al. Journal of Clinical Oncology, Vol 29, No 8 (March 10), 2011
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Bilateral Adrenal Medullary Hyperplasia Associated With an SDHB Mutation
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treatment
Five patients underwent adrenal exploration because of clinical and biochemical findings compatible with PC.

Four had asymmetrical positive MIBG scans.
- Unilateral adrenalectomy - diffuse AMH

Followed for 19 (5-27) years with normal clinical and biochemical findings.
Treatment of bilateral pheochromocytoma and adrenal medullary hyperplasia.

• In this rare condition removal of the largest adrenal seems adequate.
Laparoscopic Adrenalectomy for Nonfamilial Adrenal Medullary Hyperplasia

Miguel Ruiz Marín, Maria Fe Candel Arenas, MD Francisco Miguel González Valverde, MD
Emilio Terol Garaulet, María Maestre Maderuelo, Amparo Meoro Avilés,
Francisco Pastor Quirante, MD Antonio Albarracín Marín Blázquez, MD

JSLS (2013)17:433–439

General and Digestive Surgery Department, General University “Reina Sofía” Hospital, Murcia, Spain
A retrospective review of the medical records of patients operated on between 2007 and 2011 at Reina Sofia University General Hospital, Murcia, Spain, with a diagnosis of AMH.

### Table 1.
Epidemiologic, Medical History, Symptomatology, and Biochemical Data

<table>
<thead>
<tr>
<th>Patient No./Age (y)/Sex</th>
<th>Medical History</th>
<th>Symptomatology</th>
<th>Biochemical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/57/M</td>
<td>DM-II, HT, hyperuricemia, overweight, chronic atrial fibrillation, dyslipidemia</td>
<td>HT, adrenergic crises</td>
<td>uTC, 820 µg/24 h; uE, 370 µg/24 h; uNE, 226 µg/24 h; uMN, 4 450 µg/24 h; uNM, 680 µg/24 h; uVMA, 18 mg/24 h</td>
</tr>
<tr>
<td>2/36/F</td>
<td>HT</td>
<td>HT, adrenergic crises</td>
<td>uTC, 560 µg/24 h; uE, 433 µg/24 h</td>
</tr>
<tr>
<td>3/21/M</td>
<td>Allergic rhinitis, HT</td>
<td>HT</td>
<td>uTC, 247 µg/24 h; uE, 312 µg/24 h; uDA, 644 µg/24 h</td>
</tr>
<tr>
<td>4/49/F</td>
<td>β-Lactam antibiotic and metamizol allergy, seborrheic dermatitis, HT</td>
<td>HT, adrenergic crises</td>
<td>Before first surgery: uTC, 385 µg/24 h; uNE, 372 µg/24 h; uVMA, 21 mg/24 h; uDA, 692 µg/24 h; Before second surgery: uTC, 141 µg/24 h; uNE, 165 µg/24 h</td>
</tr>
<tr>
<td>5/51/F</td>
<td>Fallopian tubes ligation, urinary incontinence surgery, HT</td>
<td>HT, adrenergic crises</td>
<td>uTC, 926 µg/24 h; uE, 99 µg/24 h; uMN, 148 µg/24 h</td>
</tr>
<tr>
<td>6/42/M</td>
<td>HT, thyroidectomy due to Graves-Basedow disease, groin hernioplasty</td>
<td>HT, adrenergic crises</td>
<td>uTC, 193 µg/24 h; uE, 47 µg/24 h; uNE, 103 µg/24 h</td>
</tr>
<tr>
<td>7/53/F</td>
<td>Obesity, OSAS, HT, appendectomy</td>
<td>HT, adrenergic crises</td>
<td>uTC, 1 169 µg/24 h; uNE, 183 µg/24 h; uNM, 1 017 µg/24 h; uVMA, 16 mg/24 h</td>
</tr>
<tr>
<td>Patient No.</td>
<td>CT</td>
<td>MRI</td>
<td>PET</td>
</tr>
<tr>
<td>------------</td>
<td>----</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>N</td>
<td>N</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

DOPA = dihydroxyphenylalanine; N = normal; SPECT = single photon emission computed tomography.
Complete disappearance of symptoms, as well as the reduction or abstention of antihypertensive treatment, leads to normalization of catecholamine hypersecretion.
Recent advances in diagnostic and surgical methods have changed the management and outcome of this unusual disease.

Laparoscopic adrenalectomy may be recommended as the gold standard in the treatment of this entity.

Patients should be followed up because of the metachronous nature of the adrenomedullary lesions.
Clinical Study

Diagnosis and Treatment of Adrenal Medullary Hyperplasia: Experience from 12 Cases

Lu Yang,¹ Liang Gao,¹ Xiao Lv,¹ Shengqiang Qian,¹ Siyuan Bu,¹ Qiang Wei,¹ Jiuhong Yuan,¹ and Tianyong Fan²

¹ Department of Urology, West China Hospital, Sichuan University, No. 37 Guoxue Xiang, Chengdu 610041, China
² Department of Urology, People's Hospital of Deyang City, Deyang 618000, China

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**Table 1: Clinical characteristics of patients.**

<table>
<thead>
<tr>
<th></th>
<th>Male number of patients</th>
<th>Female number of patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Medium age (range)</td>
<td>47 (39–71)</td>
<td>33.5 (27–45)</td>
<td>41.5 (27–71)</td>
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<tr>
<td>Symptoms</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Heart anomalies</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Operation</td>
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<td>Laparoscopic</td>
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<tr>
<td>Lesions</td>
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<tr>
<td>Hyperplasia only</td>
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<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Mass only</td>
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<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hyperplasia and mass</td>
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<td>0</td>
<td>3</td>
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<tr>
<td>Size of mass (cm)</td>
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<tr>
<td>Medium</td>
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<td>0.5</td>
<td>0.5</td>
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<tr>
<td>Range</td>
<td>0.2–1.5</td>
<td>—</td>
<td>0.2–1.5</td>
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<tr>
<td>Follow-up (yr)</td>
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<tr>
<td>Medium</td>
<td>6.5</td>
<td>4.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Range</td>
<td>2–14</td>
<td>1–9</td>
<td>1–14</td>
</tr>
</tbody>
</table>
To prevent severe complications caused by AMH, surgery is still the most effective choice.

From our experience, patients with AMH should undergo a similar preoperative preparation with pheochromocytoma; then an adrenalectomy (partial or total) could be carried out at the evident side. If the symptoms could not be relieved, contralateral partial adrenalectomy should be taken into consideration.
Pheochromocytoma

identical clinical symptoms and biochemical findings.

Adrenal medullary hyperplasia
## Pheochromocytoma VS AMH

<table>
<thead>
<tr>
<th>Macroscopic features</th>
<th>Pheochromocytoma</th>
<th>Adrenal medullary hyperplasia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Enlarged adrenal nodule</td>
<td>No adrenal nodule</td>
</tr>
<tr>
<td>Cortex to medulla ratio (Picture 3)</td>
<td>compress the remaining adrenal tissue</td>
<td>&lt;10:1</td>
</tr>
<tr>
<td>Microscopic features</td>
<td>Nests of cytologically atypical polygonal cells (Zellballen)</td>
<td>Normal cellular architecture</td>
</tr>
<tr>
<td>Imaging studies for diagnosis</td>
<td>CT, MRI, MIBG scintigraphy, PET-FDG</td>
<td>sometimes can be detected by MIBG scintigraphy</td>
</tr>
</tbody>
</table>
**Genetics**

- **RET** - Multiple endocrine neoplasm (MEN) type 2a 2b
- **VHL** - Von-Hippel Lindau disease
- **NF1** - Recklinghausen disease = type 1 neurofibromatosis
- Somatostatin-rich duodenal carcinoid
- Beckwith-Wiedemann syndrome

- **SDHD, SDHC, SDHB** (genes for succinate dehydrogenase subunits D,C,B)
Genetics

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- **SDHD, SDHC, SDHB** (genes for succinate dehydrogenase subunits D,C,B)
Back to our patient

- Two month after surgery:
- Blood pressure - 122/88.
- Pulse – 80.
- Tx – sutent (Sunitinib).
- *Normal urine collection.*
Take home messages

- Pheochromocytoma and AMH - identical clinical symptoms and biochemical findings.

- No discreet tumor nodule.

- Lateralization (MIBG scintigraphy, PET-CT).

- Adrenalectomy.

- AMH can be included in the differential diagnosis in a patient with symptomatic pheochromocytoma-like syndrome and no evidence of discreet tumor.