Post-induction Hemodynamic Crisis: Undiagnosed Pheochromocytoma

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Case Presentation

• 44 year old male ASA 3 with spinal tumors & myelopathy
• Procedure: C1-4 laminectomy and resection of large intradural tumors
• PMH: Type I Neurofibromatosis
Anesthetic Technique #1

- Pre-op arterial line, GA ETT, asleep
  2nd large bore IV
- Neurological monitoring: SSEP, EMG
- Isoflurane at 0.5% and Propofol infusion
- Sufentanil infusion; ketamine bolus; MgSO4; clonidine
Surgical Course

Uneventful
Anesthetic Technique #2
(7 days following preceding case)

- GA ETT, asleep 2nd large bore IV and Aline
- Neurological monitoring: SSEP, EMG, and MEP
Surgical Course

Hemodynamic crisis following intubation
Rest of the Operation

- Case cancelation discussed but patient stable
- Surgery performed
- Uneventful extubation and PACU recovery
The Culprit?
Pheochromocytoma Overview

- **Background**
  - Varied presentation
  - Associated hereditary disorders
- **Preoperative preparation**
- **Intraoperative management**
Historical Perspective

- Early mortality rates > 50%
- Modern mortality rates 0-3%

Ludwig Pick
Background

- Pheochromocytoma (80-85%)
  - Neuroendocrine tumor
  - Arising from adrenal medulla
- Paraganglioma (15-20%)
  - Arise from extra-adrenal chromaffin tissue; “extra-adrenal pheochromocytoma”
  - Head & neck tumors
Pheochromocytoma

- **Incidence**
  - Rare
  - 500-1,600 cases per year
- **Prevalence:** 0.2-0.6% in patients with HTN
- Up to 50% of cases diagnosed only during postmortem exam
Clinical Presentation: Catecholamine Secretion

Direct Action
- HTN
- Tachycardia
- Pallor
- Headache
- Anxiety
- Nausea
- Fever
- Flushing

Metabolic Effects
- Hyperglycemia
- Lactic acidosis
- Weight loss

Classic triad:
1) Headache
2) Diaphoresis
3) Palpitations
## Frequency of signs & Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>60-90%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5-70%</td>
</tr>
<tr>
<td>Sweating</td>
<td>55-75%</td>
</tr>
<tr>
<td>Sustained Hypertension</td>
<td>50-60%</td>
</tr>
<tr>
<td>Pallor</td>
<td>40-45%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>20-40%</td>
</tr>
<tr>
<td>Anxiety/ Panic</td>
<td>20-40%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>40%</td>
</tr>
<tr>
<td>Paroxysmal Hypertension</td>
<td>30%</td>
</tr>
<tr>
<td>Nausea</td>
<td>20-40%</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>10-50%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10-20%</td>
</tr>
</tbody>
</table>
Adrenal Incidentaloma

- 2-3% of patients undergoing abdominal CT have an incidentaloma
  - 5% are clinically silent pheos!!!
  - Check labs!!!
Case Report: Pheochromocytoma Detected During Anesthesia Induction
Pheochromocytoma Detected During Anesthesia Induction
“Pheochromocytoma Multisystem Crisis”

- Tetrad of symptoms
  1) Multiple organ failure
  2) Encephalopathy
  3) High fever
  4) Severe BP derangements

- 50% perioperative mortality
Case Report: Catastrophic Cardiac Hypokinesis and Multiple-Organ Failure After Surgery

- Undiagnosed pheochromocytoma
- Incidental surgery
  - Intraop: Hypertensive crisis & pulmonary edema
  - Postop: refractory multiple-organ failure
- “Emergency” tumor excision
  - Expedited preoperative pharmacologic blockade
  - Rapid resolution after pheochromocytoma excision
Challenging the “Rule of 10”

- **Bilateral**: > 10%
- **Extra-adrenal**: up to 20%
- **Hereditary**: 25%
- **Malignant**: 33%+
Pheochromocytoma

**Hereditary**
- Earlier diagnosis
- Multifocal
- Extra-adrenal tumors
- Association
  - MENII
  - Von Hippel-Lindau Syndrome
  - Neurofibromatosis I
  - Familial paragangliomas

**Sporadic**
- Diagnosed aged 40-50 years
Von Hippel-Lindau Syndrome (VHL Gene)

- Type 1 (no pheochromocytoma)
- Type 2 (pheochromocytoma)
  - A: Retinal and CNS hemangioblastomas
  - B: Renal-cell cysts and carcinomas
  - C: Pheochromocytomas only
- Pheo presentation: Norepinephrine, bilateral, multifocal
Multiple Endocrine Neoplasia Type 2 (RET Gene)

- **MEN IIA**
  - Pheochromocytoma
  - Medullary thyroid cancer, hyperparathyroidism, cutaneous lichen amyloidosis

- **MEN IIB**
  - Pheochromocytoma
  - Medullary thyroid cancer, multiple neuromas, marfanoid habitus

- Pheo characteristics: epi & norepi secretion, bilateral
Neurofibromatosis Type 1 (NF-1 Gene)

- Multiple fibromas on skin and mucosae, “café au lait” skin spots, iris hamartomas, bony abnormalities, CNS gliomas, macrocephaly, cognitive deficits

- Pheochromocytomas
  - Relatively rare (5% prevalence)
  - Secrete both epinephrine & norepinephrine
Succinate Dehydrogenase Gene Mutations

- SDHD and SDHB
- Pheochromocytomas
  - Mainly occur as paragangliomas
  - Predominantly norepinephrine secreting
  - High rate of malignancy
Biochemical Testing

- Not indicated in asymptomatic patients with HTN
- Groups to test
  - Paroxysmal sign/Sx (including paradoxical BP response during anesthesia/ surgery)
  - Hereditary predisposition
  - Adrenal incidentaloma
## Biochemical Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-free metanephrines</td>
<td>99%</td>
<td>89%</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td>Urinary catecholamines</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>Urinary-fractionated metanephrines</td>
<td>97%</td>
<td>69%</td>
</tr>
<tr>
<td>Urinary total metanephrines</td>
<td>77%</td>
<td>93%</td>
</tr>
<tr>
<td>VMA</td>
<td>64%</td>
<td>95%</td>
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## Values of Catecholamines in Urine

<table>
<thead>
<tr>
<th>Presence of Pheochromocytoma</th>
<th>Unlikely</th>
<th>Possible</th>
<th>Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (nmol/ 24 h)</td>
<td>&lt;500</td>
<td>500-1180</td>
<td>&gt;1180</td>
</tr>
<tr>
<td>Epinephrine (nmol/ 24 h)</td>
<td>&lt;100</td>
<td>100-170</td>
<td>&gt;170</td>
</tr>
<tr>
<td>Normetanephrine (nmol/ 24 h)</td>
<td>&lt;3000</td>
<td>3000-6550</td>
<td>&gt;6550</td>
</tr>
<tr>
<td>Metanephrine (nmol/ 24 h)</td>
<td>&lt;1000</td>
<td>1000-2880</td>
<td>&gt;2880</td>
</tr>
<tr>
<td>VMA (μmol/ 24 h)</td>
<td>&lt;40</td>
<td>40-55</td>
<td>&gt;55</td>
</tr>
</tbody>
</table>

### Urine Chemistry Results

<table>
<thead>
<tr>
<th>Date</th>
<th>Creatinine, Urine</th>
<th>Epinephrine, Urine</th>
<th>Metanephrine, Urine</th>
<th>Norepinephrine, Urine</th>
<th>Normetanephrines, ...</th>
<th>Sodium Urine Random</th>
<th>URINE TOTAL VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/23/2015 0115</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>4/26/2015 2250</td>
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<td>2246</td>
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<tr>
<td>5/7/2015 1330</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>676</td>
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</tbody>
</table>
# Values of Catecholamines in Plasma

<table>
<thead>
<tr>
<th>Presence of Pheochromocytoma</th>
<th>Unlikely</th>
<th>Possible</th>
<th>Likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline (nmol/L)</td>
<td>&lt;3.0</td>
<td>3.0- 7.7</td>
<td>&gt;7.7</td>
</tr>
<tr>
<td>Adrenaline (nmol/L)</td>
<td>&lt;0.45</td>
<td>0.45- 1.2</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>Normetanephrine (nmol/L)</td>
<td>&lt;0.6</td>
<td>0.6- 1.4</td>
<td>&gt;1.4</td>
</tr>
<tr>
<td>Metanephrine (nmol/L)</td>
<td>&lt;0.3</td>
<td>0.3- 0.42</td>
<td>&gt;0.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/25/2015</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>METANEPHRINE, FREE</td>
</tr>
<tr>
<td>NORMETANEPHRINE, FREE</td>
</tr>
</tbody>
</table>
Preoperative Management

- **Goal**: prevent catecholamine-induced complications during surgery
- **Recommended for ALL patients**

![Diagram showing preoperative preparation steps]

- Normalization of hematocrit
- Symptom control
- Reduce intraoperative hemodynamic crises
- Attenuation of vasoconstriction
- Reverse myocardial ischemia

Restitution of vascular volume
Correct RWMA
Alpha Blockers = 1st line

- Phenoxybenzamine
  - Long acting, non-competitive, non-selective α-blocker
  - Hypotension after tumor removal
  - Rebound tachycardia
- Doxazosin, prazosin, terazosin
  - Short-acting, competitive selective, α-1 antagonist
  - Dose day of surgery

<table>
<thead>
<tr>
<th>α1</th>
<th>Vasoconstriction, sweating, decreased insulin release</th>
</tr>
</thead>
<tbody>
<tr>
<td>α2</td>
<td>Inhibition of further NE release</td>
</tr>
</tbody>
</table>
Beta Blockers

- **Indication:** tachycardia 2/2 α-blockade
- **Do not initiate prior to α-blockade**

<table>
<thead>
<tr>
<th>β1</th>
<th>Chronotropy, inotropy, arrhythmogenicity, renin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>β2</td>
<td>Smooth muscle relaxation in bronchi/vascular wall/uterus, insulin &amp; glucagon secretion</td>
</tr>
</tbody>
</table>
Calcium Channel Blockers

- 1st line for patients who don’t tolerate α-blockade or normotensive patients
- Nicardipine, amlodipine, verapamil, nifedipine
Metirosine (A-Methyl Para Tyrosine)

- Interrupts catecholamine synthesis
- Refractory HTN
  - In combination with α-blockers
  - Short interval before surgery
Adequate Preoperative Preparation

- Endocrine Society Target:
  - BP <130/80, HR 60-80
  - Modified for age and CV disease
- “Test” stimulus (SBP < 160)
- Roizen’s Criteria
- CANCEL IF POOR BLOCKADE
## Medications That Can Precipitate a Crisis

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2 receptor antagonists</td>
<td>Metoclopramide, droperidol, chlorpromazine, prochlorperazine</td>
</tr>
<tr>
<td>B- Blockers Sympathomimetics</td>
<td>Labetalol, propanolol, Ephedrine, pseudoephdehrine</td>
</tr>
<tr>
<td>Opioids</td>
<td>Morphine, tramadol</td>
</tr>
<tr>
<td>Norepinephrine reuptake inhibitors</td>
<td>Amitriptyline, imipramine</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td>Paroxetine, fluoxetine</td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors</td>
<td>Phnelzine, moclobemide</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone, prednisone, hydrocortisone, betamethasone</td>
</tr>
<tr>
<td>Peptides</td>
<td>Glucagon, ACTH</td>
</tr>
<tr>
<td>Neuromuscular blocking agents</td>
<td>Succinylcholine, atracurium, tubocurarine</td>
</tr>
</tbody>
</table>
Remaining Preoperative Assessment

End-organ manifestations

- Metabolic panel
- EKG
- Consider echo
Surgical Treatment

- Minimally invasive adrenalectomy preferred
- Open resection preferred for paragangliomas
- Partial adrenalectomy for selected patients
“A conscientious, attentive anesthetic in a well-prepared patient is almost certainly more important than which drug or drug combination is selected.”

“Equal parts art and science when it comes to the intraoperative anesthetic…”
Premedication

- No metoclopramide
- Short-acting α-blockers (‘-zosins’) should be taken day of surgery
Monitors

- Arterial line pre-induction
- Central venous access
  - Volume expansion and pressors after tumor removal
  - “Test” stimulus versus post-induction
Induction

- No ketamine, everything else okay
- Relaxant: no succinylcholine
Maintenance

- Inhalation agent: no desflurane
- Regional okay
- No morphine
Intraoperative Management

Hypertension & acute catecholamine excess before tumor removal

--------- Clamping adrenal vein ---------

Hypotension & acute catecholamine deficiency after tumor removal

Good communication with surgeon!
Magnesium Sulfate

- Hemodynamic control before tumor resection
- 2g bolus, 1-2 g/h infusion
- Unique MOA
  - direct vasodilation
  - inhibits catecholamine release
  - blocks catecholamine receptors
- Stop with adrenal vein ligation
- Potentiates NMB
Clevidipine (Cleviprex)

- Ultra-short acting, selective calcium channel blocker
- “Esmolol” of CCBs
- Hemodynamic control before tumor resection
- Fast onset & off-set, rapidly titratable
Post Tumor Excision Hypotension

- Residual α-blockade
- Residual action of vasodilators
- Hypovolemia
- Catecholamine withdrawal
- α-adrenoreceptor down-regulation
- GIVE FLUIDS AND PRESSORS!
Vasopressin

- **Mechanism**
  - Increases water reabsorption
  - Causes systemic vasoconstriction
  - Acts via vasopressin 1 receptors
Postoperative Management

- ICU or intermediate care unit
- Immediate postop period
  - Hypotension
  - Severe hypoglycemia
Surveillance

- Recurrence rate 17%
- Life-long, annual biochemical testing
Endocrinology Consult: Suspected Pheochromocytoma

- Labs
- Imaging: CTA & MIBG scan
Endocrinology Consultation: Pheochromocytoma

- Surgical resection
- Premedication with nicardipine
References

Questions?