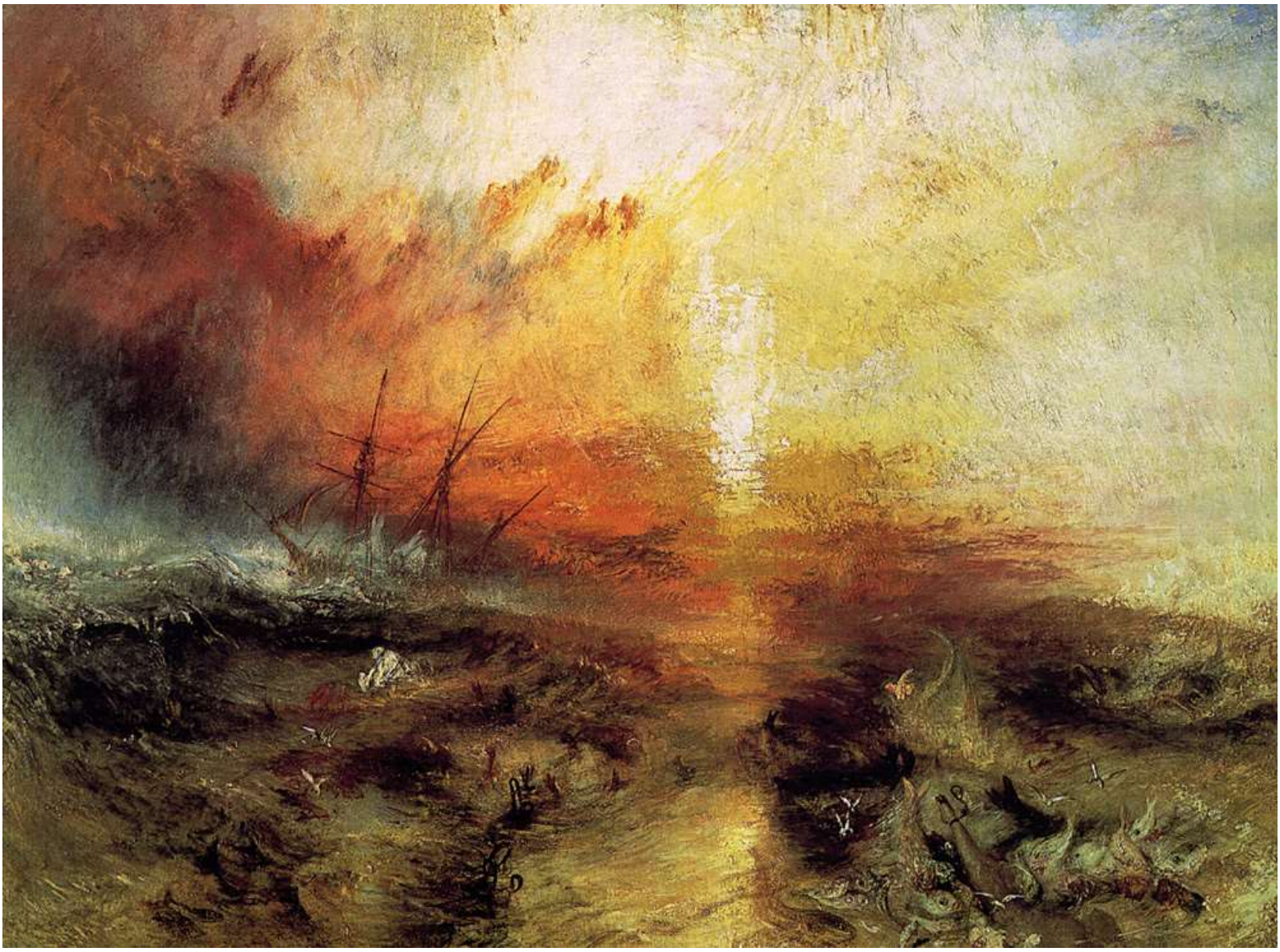
THE NORTHERN HOSPITAL

PHAEOCHROMOCYTOMA



"Slavers, Slave Ship Throwing Over the Dead and Dying, Typhoon Coming On" oil on canvas, 1840 J.M.W Turner, Museum of Fine Arts, Boston.

In the late 1830's one issue galvanized British moral outrage more than any other. Slavery. Britain had outlawed slavery throughout the empire, but in the Hispanic empires and the United States it not only survived, but thrived. In 1840 in London, an international convention of the great and good was planned to express righteous indignation of this fact. Turner, initiated into the cause so many years ago by his patron, Walter Fawkes, wanted to have his say, in paint. And how does he do it? By being a thorn

in the side of self-congratulation. Turner reaches back 60 years to resurrect one of the most shameful episodes in the history of the British Empire. 1781, the British slaver, the Zong, was off the coast of Jamaica after a routinely profitable journey from Africa. But deep below decks there was trouble. Slaves were dying, at more than the usual rate, and the ship's master, Luke Collingwood, suddenly had a business disaster on his hands. His human cargo was insured, but the underwriters would only pay up if the casualties could be accounted for as losses at sea, not dead on arrival. So Captain Collingwood went below decks and began the merciless business of selecting which slaves he would swiftly turn into losses at sea. One hundred and thirty two Africans - men, women, and children, their hands and feet fettered, were thrown overboard into the shark-infested waters of the Caribbean. The moral horror of the case of the Zong was the moment when thousands of Britons abandoned their indifference and became campaigners against the slave trade. One hundred and thirty two Africans perished horribly, but a mass movement was born from their martyrdom.

Turner's approach to this appalling tragedy was not that of a literal historical illustrator. What the great enchanter of the canvas wanted was, Prospero-like, to summon an apocalypse, a typhoon. The slave ship pitches us into the midst of a feverish dream of catastrophe and terror, sin and retribution. The silhouetted ship almost engulfed in the erupting spray is both a real vessel and something cursed and haunted, like the ship of the ancient Mariner. Waves, seethed with monsters, a kind of obscene, piranha-like nibbling and gobbling, and the oncoming fishy monster is not to be caught off the coast of Jamaica, but off the canvas of Hieronymus Bosch, Hell in High Water. Of course, it has its imperfections, all that flailing, flurry of action in the foreground, the mysteriously floating iron fetters, the flung limb that may or may not be detached from its torso. All the frantic fishy action could seem too fussily staged. In the end, there's only one test that matters.

You come into the room, you fix it in your sights. Does it, or does it not attack you in the guts?

It does.

Does your heart jump?

Do your eyes widen?

Does your pulse race?

Do your feet get a bad attack of lead boots, you're so struck down by it?

They do. For Turner has drowned you in this moment, pulled you into this terrifying chasm in the ocean, drenched you in his bloody light, exactly the hue you sense on your blood-filled optic nerves when you close your eyes in blinding sunlight. Though almost all of his critics believe that the slavers represented an all-time low in Turner's reckless disregard for the rules of art, it was in fact his greatest triumph in the sculptural carving of space. For none of the stormy atmospherics, the great pinwheel fury of reds and golds would have the impact they did were it not for that deep trough Turner has cut in the

ocean. Which at the center of the painting makes the blackly heaving swells stand still as though the wrathful hand of Jehovah has suddenly passed over the boiling waters. For this is a day of martyrdom, retribution, and judgment, but also a scene, Turner must have optimistically thought, of vindication. It would be a sin redeemed. Slavery would be defeated. There is, after all, a patch of clearing blue at the top right corner of the painting. The critics went to town. Turner became the butt of jokes, a crackpot, old loon lost in the tempest, with his ridiculous painting, and it's even more ridiculous full title. "Slavers, Slave Ship Throwing Over the Dead and Dying, Typhoon Coming On" Punch magazine joined in the chorus of catcalls, lampooning Turner by inventing a painting with the title, "A Typhoon Bursting a Samoon over a Whirlpool Maelstrom, Norway, a Ship on Fire, an Eclipse with the Effect of a Lunar Rainbow". But Punch and all the other high hat critics missed the one overwhelming point which makes this the greatest British picture of the 19th Century. The perfect match between message and form. The payoff of the slaves' martyrdom would in the end be freedom. So Turner has given himself glorious freedom with his brush and with his color, and with his imagery to convey the power of the sacred moment.

Two years after the debacle of the Slave Ship, a young Scottish admirer, William Leighton Leitch, visited Turner's house in Queen Anne's Street. He'd heard that the Turner Gallery was in disrepair, but nothing could possibly have prepared Leitch for the squalor. "I walked backwards and forwards in the gallery feeling cold and uncomfortable. There was no sound to be heard, but the rain splashing through the broken windows upon the floor". Leitch stood in the evil-smelling gloom and as he peered at Turner's most recent work, among which was hanging somewhere the scarlet explosion that was the unsold, unwanted, unloved Slave Ship, he felt more and more depressed. But this was the moment when the country's favorite painter once revered as the patriarch of British art was written off as a senile lunatic.

Yet the effects of the critical onslaught is to make it more, not less brave. He's off on his own now, the solitary mariner on a completely uncharted ocean, of pure painting. Alongside all these scenes of oceanic turmoil, Turner was still capable of painting images of exquisite liquid calm, but you have the feeling he could do those in his sleep. It's when his whirlpool of paint resolves itself in something weightier and mightier than the entertainment of the senses, when he reaches towards the truths of history and eternity, that I think Turner is at his greatest. That's when he changes not just British art, but all of art, most completely.

And you know, this is why Turner still matters to us, and always will. That old cockney geezer in his battered hat and filthy coat transports us somewhere where the slick conformist would never dare to go - into the eye of history's storm, into the ocean of light.

Simon Schama, The Power of Art, BBC Television, 2010.

Does your heart jump? Do your eyes widen? Does your pulse race? Do your feet get a bad attack of lead boots, you're so struck down by it? If so there are two possibilities - you are looking into JMW Turner's "Slave Ship"…or you have a phaeochromocytoma!

PHAEOCHROMOCYTOMA

Introduction

Pheochromocytoma is a rare neoplasm of the adrenal medulla or of the sympathetic nervous system.

It is a rare cause of secondary hypertension, probably occurring in less than 0.2 percent of patients with hypertension.

Diagnosis is particularly challenging, as symptoms are variable and non-specific and the condition is rare.

Diagnosis is important as the condition is potentially fatal, but also potentially curable.

Pathophysiology

Phaeochromocytomas arise from the chromaffin cells derived from the embryonic neural crest.

They can be derived from:

- The **adrenal medulla**, (the majority of cases will be single adrenal medulla tumors), about 90%.

- **Extra-adrenal sympathetic nervous system**, (within the neck, thorax, abdomen or pelvis), about 10%. These are sometimes also referred to as catecholamine-secreting paragangliomas.

They produce excess catecholamines, (adrenaline, noradrenaline and dopamine) that give rise to the clinical and biochemical features that are seen.

Malignant phaeochromocytomas appear histologically and biochemically the same as benign ones.

The only reliable clue to the presence of a malignant phaeochromocytoma is local invasion or distant metastases, which may occur as long as 15 years after resection.

Approximately 10% of adrenal pheochromocytomas and 35% of extra-adrenal pheochromocytomas are malignant.

Catecholamine metabolites:

Metanephrine and normetanephrine are metabolites of adrenaline and noradrenaline respectively.

Of all the biogenic amines, plasma free metanephrines (and urinary metanephrines) are the most sensitive tests for diagnosis of phaeochromocytoma and are the most suitable for its reliable exclusion.

Genetic predispositions:

The majority of cases are sporadic, however about 30% of pheochromocytomas occur as part of hereditary syndromes.

Pheochromocytoma has classically been associated with 3 syndromes:

- Von Hippel-Lindau (VHL) syndrome
- Multiple endocrine neoplasia type 2 (MEN 2)
- Neurofibromatosis type 1 (NF1)

It is now known, however, that there are now as many as 10 genes that have been identified as sites of mutations that may lead to lead to pheochromocytoma. These different genes produce tumors with different ages of onset, secretory profiles, locations, and potential for malignancy

Clinical Features

1. The classically described triad of symptoms in patients with a pheochromocytoma consists of *episodic* periods of:
    - Headache.
    - Sweating / pallor / flushing
    - Tachycardia / palpitations
2. Hypertension:
    - This may be labile, (ie episodic) or sustained.
3. CNS features:
    - Anxiety symptoms or other psychiatric disorders.
4. GIT:
    - Nausea, vomiting
    - Weight loss.

- Abdominal pain (predominantly epigastric) can also be a prominent feature.

5. Orthostatic hypotension may occur:

    - This may reflect a low plasma volume.

The condition however is not commonly diagnosed according to "classic" presentations.

Among patients *suspected* to have a phaeochromocytoma, the diagnosis is rarely confirmed.

Not all patients have the three classic symptoms and patients with essential hypertension may have these same symptoms.

It may otherwise present in a number of ways, including:

- In at least 10 percent of patients the tumor is discovered incidentally during CT or MRI of the abdomen for unrelated symptoms or at surgery for removal of an adrenal mass not identified preoperatively as being a phaeochromocytoma. These patients may have few or no symptoms.

- Diagnosed as part of the workup of a patient with hypertension.

- May present as an acute hypertensive crisis, such as hypertensive encephalopathy.

- Phaeochromocytoma is often considered in patients with undiagnosed panic disorder, in whom many of the symptoms are due to increased sympathetic activity.

- In other patients the tumor is found only at autopsy.

Differential diagnosis:

These may include:

- Sympathomimetic drugs, including cocaine and amphetamines

- Tyramine foods in association with MAO inhibitors.

- Alcohol withdrawal symptoms.

- Severe anxiety symptoms.

- Thyroid toxicity.

Investigations

Catecholamine testing:

Two methods are available:

1. **Metanephrine (or metadrenaline) level:**

    - Plasma levels of free **metanephrines** (by liquid chromatography-tandem mass spectrometry) are the current diagnostic method of choice, (when available).

    - The advantage of assaying metanephrines is that they are produced *continuously*, resulting in steady-state levels.

      In contrast, catecholamines are released *episodically*, (hence the previously used methodology of measuring **24 hourly** urinary catecholamines and their metabolites).

    - The high sensitivity of the metanephrines has been confirmed by a number of studies, and there is growing consensus that a negative result on this *single test alone* is sufficient to exclude a diagnosis of phaeochromocytoma.

    - The test has very good sensitivity (99%) but its specificity is lower (85%), due to drug effects and congestive cardiac failure.

    - Ideally the patient should be:

        - ♥ Fasting for 12 hr prior to the test:

          *Levels may be (mildly) elevated **post prandially**, (and so may represent a possible source of a false positive result)*

        - ♥ Resting supine for 15 minutes prior to the test:

          Levels are slightly greater in the upright position, (and so again may represent a possible source of a false positive result).

    - Normal values are generally taken as: Metanephrine < 500 pmol/L and Normetanephrine < 900 pmol/L

2. 24-Hour urinary VMA/ total catecholamines:

    - 24-hour total catecholamines and vanillylmandelic acid (VMA) may be done in situations where blood metanephrine measurement is not available.

CT scan

This is s a very useful screen for detecting adrenal gland tumors.

The lesion may be picked up in particular in cases where the patient is being investigated for abdominal pain of uncertain origin, or it may be picked up as an incidental finding.

If a pheochromocytoma is being *deliberately chased*, then the scanning will need to be extended to other areas, where tumors of the sympathetic chain may be found (neck, chest and pelvis).

It also has one possible advantage in that in the right clinical setting, (i.e high clinical suspicion) it may provide (likely) diagnosis, before blood test results become available.

MRI Scan:

MRI is superior at imaging both adrenal and extra-adrenal tumors.

This modality is preferred over CT scanning in children and pregnant or lactating women.

It has a reported sensitivity of up to 100% in detecting adrenal pheochromocytomas, and so is the imaging investigation of choice, when clinical suspicion is high.

PET scanning:

This is also a newer and promising technique for detection and localization of pheochromocytomas.

Management

1. Medical management:

    - Alpha blockade:

      Preoperative patient preparation with alpha-adrenergic blockade and volume expansion have accounted for the most significant reduction in perioperative mortality.

      Pharmacotherapy to achieve alpha-adrenergic blockade, and to control hypertension, is mandatory in preparation for surgery, or where surgery is contraindicated

      This therapy minimizes the chance of intraoperative hypertensive crisis and postoperative hypotension.

      Agents used include, **phenoxybenzamine** and **prazosin.**

See latest Endocrine Therapeutic Guidelines for full prescribing details.

- Beta blockade:

  Once treatment is initiated with an alpha-blocking agent, it is then followed with a beta-blocking agent.

  The beta-adrenergic blocker should never be started first because blockade of vasodilatory *peripheral* (beta-2) beta-adrenergic receptors with unopposed alpha-adrenergic receptor stimulation can lead to a further elevation in blood pressure.

  Agents used include **atenolol, labetalol** and **propranolol.**

  See latest Endocrine Therapeutic Guidelines for full prescribing details.

2. Surgical management:

   - Surgical excision is the definitive treatment for phaeochromocytoma. It is successful in over 90% of cases.

Disposition

Initial referral should include the **Endocrinology Unit.**

Further referrals then include:

- Surgical
- Oncology, (in cases of malignancy)

References

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2. Endocrine Therapeutic Guidelines, 4th ed 2009.

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