Why did Harvey Cushing misdiagnose Cushing’s disease? The enigma of endocrinological diagnoses

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The case of Minnie G

Minnie G’s menses started at the age of 14 and were regular for two years and then suddenly ceased. She began to grow stout and in two years her weight had increased from 112 to 137 pounds. She suffered a great deal from headaches, nausea and vomiting. She complained also of aching pains in the eyes which latterly had become prominent, and there had been occasional periods of seeing double. Other noteworthy symptoms were insomnia, tinnitus, extreme dryness of the skin, frequent sore throats, shortness of breath, palpitation, purpuric outbreaks, recurring nosebleeds, and marked constipation. A definite growth of hair had appeared on the face with thinning of hair on the scalp. She had become increasingly round-shouldered. Muscular weakness had become extreme and there was constant complain of backache and epigastric pains.1

Case discussion

This case represents the original words of Harvey Cushing in describing Case XLV, a woman who came to be known in the literature as Minnie G or MG.1 The description appeared in Cushing’s seminal work, The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations in 1932. Cushing first saw MG in 1910 and originally attributed the complaints of obesity, diabetes, hirsutism, and adrenal hyperplasia to myxedema.2 He then changed his differential to “pituitary, adrenal, or ovary?”3 Over the next 20 years, Cushing saw MG twice more and began an extensive review of the literature. His previous work on acromegaly led him to postulate that if acidophilia could lead to growth hormone excess, then perhaps basophilia could lead to cortisol excess.3 An 1898 case description by Cushing’s mentor, Sir William Osler, helped Cushing to finally determine in 1932 that MG’s symptoms were the result of a cortisol secreting pituitary adenoma.

The case of Minnie G illustrates a common diagnostic challenge in endocrinology: endocrine conditions often are associated with a non-specific symptom set, which combined with individual variability can have the result that some patients go undiagnosed or are misdiagnosed. If even Harvey Cushing struggled with the diagnosis of Cushing’s disease, what hope is there for humble endocrinologists and general practitioners? This article will use Cushing’s disease as a prototype to explore how and why symptoms are grouped into diagnoses, and the associated perils and advantages of this practice.

The diagnostic approach to Cushing’s Disease

Cushing’s disease is one form of Cushing’s syndrome, a group of symptoms that result from hypercortisolism. Diagnosis of Cushing’s disease depends on clinical, laboratory, and imaging modalities. For instance, a diagnosis of Cushing’s disease requires evidence of hypercortisolism; the excess cortisol must be the result of high ACTH levels; and the high ACTH must be the product of a pituitary adenoma.

The following algorithm aims to fulfill those three criteria:4,5

1. Does the patient exhibit symptoms of cortisol excess?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing’s syndrome</th>
</tr>
</thead>
</table>
| Observation | Truncal obesity  
Facial plethora  
Hirsutism  
Acne  
Skin bruising  
Edema  
Muscle weakness  
Hypertension |
| History | Mood disorders  
Polyuria  
Polydypsia |
| Laboratory testing | Glucose intolerance |

2. Is there actually cortisol excess?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11pm salivary cortisol</td>
<td>&gt;4x increase</td>
</tr>
<tr>
<td>Serum cortisol after low dose dexamethasone suppression test</td>
<td>&gt;54nmol/L</td>
</tr>
<tr>
<td>24 hour urine free cortisol</td>
<td>&gt;250nmol/day</td>
</tr>
</tbody>
</table>
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3. Is the cortisol excess ACTH-dependent?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ACTH</td>
<td>&gt;40 pmol/L</td>
</tr>
</tbody>
</table>

4. Is the excess ACTH from the pituitary?

<table>
<thead>
<tr>
<th>Test</th>
<th>Results suggestive of Cushing’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Petrosal venous sampling</td>
<td>High ACTH levels in the region of the pituitary</td>
</tr>
</tbody>
</table>

Why do we define disease?

Because the symptoms that make up a syndrome are so variable, it is perhaps appropriate that they are named after the people who first described them. Diseases are, in essence, a human creation. They are an attempt to impose order and allow parsimonious treatment. Cushing argued that defining disease was important because “a peculiar clinical syndrome has first been described by someone with a clarity sufficient to make it easily recognizable to others.” 1 It is only by having an accurate definition that different physicians are able to make the same diagnosis.

If a collection of symptoms has a common cause, it is easier to treat the cause than it is to treat each individual symptom. Consider the example of Cushing’s disease:

Figure 1. Pathogenesis of Cushing’s disease and diagnostic tests for each level.

Note that the diagnostic tests described above detect only by the clinical manifestations of hypertension, obesity, and glucose intolerance and by laboratory abnormalities.

In defining disease, establishing criteria for a syndrome is perhaps the most difficult task. Syndromes are collections of symptoms, signs, and investigational results that have a similar course and response to treatment. However, syndromes are made up of sufficient rather than necessary elements. That is, the symptoms make the diagnosis more likely, but there is no one symptom that will absolutely rule in or out the diagnosis. Endocrinology is fraught with vague symptoms, largely because the definition of normal is elusive. Hormone levels fluctuate throughout the day, with age, with environment, with diet, and between individuals. It is incredibly difficult to define ‘normal’ for a measurement that is not only inconsistent between but also within individuals.
the disease at different levels of disease progression. Therefore, the test that is chosen will have an impact on the part of the disease that is observed. If an MRI reveals an adenoma, this is not sufficient to make a diagnosis of Cushing's disease. While it is high on the etiologic pathway, the possibility of a non-secreting and therefore asymptomatic incidentaloma remains.

Conversely, symptoms of obesity and hirsutism could suggest Cushing's disease, but without the MRI and ACTH tests, we are not justifiably in applying that label. These two instances have treatment implications: the first requires no treatment if it is truly an incidentaloma. The second requires treatment, but without knowing the cause of the symptoms, our ability to intervene is limited to symptomatic relief.

The elusive diagnosis

According to Gross et al., "Although the initial presentation of a patient with such a constellation of symptoms is suggestive of Cushing Syndrome, most symptoms characteristic of the disease are nonspecific, resting the burden of an accurate diagnosis on an appropriate diagnostic workup." The diagnosis of Cushing's is fraught with perils at multiple levels:

1. **The Disease**
   - Atypical presentation
   - Interstitial hypercortisolism
   - Pituitary incidentalomas
   - Adrenal incidentalomas
   - Rare forms
   - Macronodular adrenal hyperplasia
   - Abnormal sensitivity to glucocorticoids
   - Phaeochromocytoma
   - Pseudo Cushing's
   - Obesity
   - Amenorrhea
   - Alcohol
   - Depression

2. **The Tests**
   - The definition of 'normal' is not absolute
   - Timing: Symptoms require long-term glucocorticoid excess, and levels of cortisol vary throughout the day
   - Imperfect lab tests, none are 100% sensitive or specific
   - Tests require patient compliance (e.g., 24-hour urine collection)

3. **The Patient**
   - Symptoms are interpreted in light of education, culture, relationships, etc.
   - Comorbidities
   - Subpopulations present differently: pregnant women, children
   - Lifestyle effects (diet, exercise, exogenous hormones)

4. **The Physician**
   - Rare disease, may not consider it

5. **The Medical System**
   - Imperfect communication between specialists
   - Ignoring parsimony: diagnosing the symptoms instead of the syndrome
   - Specialty-specific care

![Figure 2. Complicating factors in the diagnosis of Cushing's disease.](image)

As seen in Figure 1, the first step in the diagnosis of Cushing's disease is the recognition of clinical symptoms. However, when viewed in isolation, these symptoms can be characteristic of numerous diseases. Many patients who are ultimately diagnosed with Cushing's disease find themselves passed between specialties before an astute physician finally integrates the symptoms into a whole. For instance, Evans et al. describe a woman who saw a dermatologist, cardiologist, orthopaedic surgeon, and psychiatrist before ultimately diagnosing herself from information in the lay press. This illustrates a fundamental flaw with the current medical system - subspecialisation ensures expert care of specific symptoms, but it may neglect to view the patient as a complete person. Diagnostic re-evaluation is needed as time and symptoms evolve and an astute physician looking at the entire person may be seminal in putting the pieces together. Optimal communication is required between specialists to ensure that a common cause of symptoms can be found if it exists.

Finally, note in Figure 1 that the final arrow in the pathway is bidirectional. The effects of symptoms in turn impact the patient's experience of the disease. This is particularly true in Cushing's disease, as stress is an additional cause of hypercortisolism. Therefore, worsening symptoms can impact a patient's functioning, which in turn increases stress levels which ultimately serve to worsen symptoms. Therefore, the final step in any diagnostic pathway must include an exploration of the context in which the patient experiences symptoms.

Conclusions

The diagnosis of Cushing's disease can be enigmatic and elusive, but, as evidenced by the following letter from Minnie G to Cushing, ultimately rewarding:

"Dear Sir: Of course, I am very sorry to trouble you again with letters, but I am taking advantage of your own words. The great pains my body is forced to bear can be honestly compared to the modern German artillery... And now I have told you most all. I do believe sufficient amount and I ask you again, what can you do? There must be some palliation in my letters for I regard you as my best friend and doctor. Yours sincerely, Minnie G."

Cushing may have originally misdiagnosed the disease that bears his name, but he was a brilliant physician who was a friend to his patients. His devotion was such that he actually resided in the hospital to better care for his patients.

The case of Minnie G thus highlights a number of the vital components of endocrinological diagnosis:

- A high index of suspicion.
- Careful vigilance and reassessment of diagnostic assumptions.
- Communication between specialists.
- Thorough histories, physicals, and diagnostic
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- An exceptional physician-patient relationship.

Grouping of symptoms into a diagnosis is not an exact science but rather requires some of the art of medicine which can recognize variableness of disease presentation within a population of interest. Harvey Cushing's recognition of these lessons warrants remembrance of his name not only in the context of hypercortisolism, but as an example of how we should strive to practice medicine.

References