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“Glandular intoxication” following emergent tracheotomy during transsphenoidal surgery for acromegaly: Cushing’s 1910 unrecognized case of thyroid storm?

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Abstract

Harvey Cushing’s monograph *The Pituitary Body and Its Disorders* describes Case XXXVIII, H. M. B., a 33 year-old man who presented with acromegaly in 1910. The detailed operative note reports an emergency tracheotomy performed following induction of anesthesia, and immediately prior to a naso-labial approach to a suspected sellar lesion. Cushing’s post-operative notes document a significant increase in temperature prior to the patient’s death. Cushing offered an explanation for the patient’s symptoms immediately pre-mortem, which is largely unsatisfying. Following institutional review board approval, and through the courtesy of the Alan Mason Chesney Archives, the surgical records from the Johns Hopkins Hospital, 1896–1912, were reviewed. A review of the original surgical file revealed a more extensive description of the emergent tracheotomy required following induction of anesthesia, and provided additional information regarding the patient’s symptoms in the immediate pre-mortem period. Namely, the urgent tracheotomy transected the thyroid gland, and post-operatively the patient experienced significant tachycardia and hyperthermia, consistent with thyroid storm. The new information regarding the hospital course of H. M. B. offers insight into the previously incompletely described circumstances surrounding his emergent tracheotomy, and subsequent death. Additionally, the case underscores the clinical importance of recognizing and appropriately treating thyroid storm.

Keywords

Cushing; Thyroid storm; Acromegaly

Introduction

In his 1912 monograph *The Pituitary Body and Its Disorders*, Harvey Cushing described Case XXXVIII, a 33 year-old man who presented with acromegaly in 1910. In the detailed explanation of the naso-labial approach for a suspected sellar lesion and post-operative course, Cushing offered hints at complications and unforeseen outcome, saying: “an

emergency tracheotomy, with transverse tracheal incision, was performed” and later, “an elevation of temperature to 107.2° per rectum preceded death” [1]. Although Cushing proffers an explanation for the symptoms preceding the patient’s death, namely that the patient suffered symptoms similar to those seen in canine models of anterior pituitary resection, the explanation remains largely unsatisfactory.

A review of the Johns Hopkins Hospital surgical records recovered the original file for H. M. B., and provided new information which offers insight into his post-operative course, and a likely cause of death. Here we offer a summary of H. M. B.’s stay at the Johns Hopkins Hospital, taken from the original hospital records, and a thorough explanation of the circumstances surrounding his operative intervention and death.

Methods

Following institutional review board approval, and through the courtesy of the Alan Mason Chesney Archives, the surgical records from the Johns Hopkins Hospital, 1896–1912, were reviewed. The file for H. M. B., Case XXXVIII, was selected and is described here.

Case report

On April 25, 1910, a 33 year-old chemist (Fig. 1) presented to the Johns Hopkins Hospital complaining of frontal headaches, dizziness, and “unsteadiness on feet”. Although the admission exam documents enlargement of his facial features and extremities, the patient himself was unaware of the change:

Brother thinks face has gotten larger during past year; espec. noticeable change in size and shape of nose. The pt. has noted no great change in his general appearance or in the size of his hands, face or feet; although says he wears a half size larger hat and shoes than he did 3 years ago...tongue at times feels very large and thick...The change in face, hands and feet has been so gradual that he never noticed any great change until attention was called to it here. Says his dentist called his attention to the spreading of his teeth about 6 months ago.

During his admission, the patient was treated with subcutaneous injections of “2 cc 5% ant. lobe (ox)” extract, given at midnight. The following morning the patient “suddenly became very pale, complained of dizziness and nausea, was covered with a profuse sweat. Evidently lost consciousness for a few seconds. Was gotten into bed and had typical projectile vomiting. Rapid fall in pulse rate—from 84–88 to 60”.

Four days following the anterior lobe extract administration, Cushing documented that the patient had lost 6.25 lbs since the treatment.

Cushing brought the patient to the operating room for a labio-nasal approach to the pituitary gland on May 10, 1910. The operative note documents the administration of anesthesia, and the subsequent approach:

Patient an hour before operation was given 1/150 scopolamin and 1/16 of morphia. Very quiet before administration of general anaesthesia which probably led to the

upset to be described, owing to its administration as though no primary anesthetic had been administered.

Primary anaesthesia with gas switched off to ether. The operator had decided to attempt to conduct the operation without tracheotomy and preparations had been made to administer ether through a large tube introduced into the pharynx. Before this could be arranged the patient became bluer and bluer in spite of the drawing out of the large tongue which had evidently closed the glottis. Finally the cyanosis reached such an extreme degree as to cause great anxiety and the patient ceased breathing. The heart kept on for a few minutes and a tracheotomy was performed cutting through the large middle lobe of the thyroid which bled black blood profusely. Doubtless this had something to do with emptying the heart but which may have saved the patient's life, for the heart had ceased to beat. The tube was finally introduced through a transverse incision and by cardiac massage the spontaneous heart beat was resumed. It was a very close call.

The advisability of continuing the operation seemed questionable but the patient's condition soon became so good that the operator determined to proceed. The usual incision in the lip was made and the mucous membrane stripped from the septum...

During the last hour of the operation no anaesthesia was necessary. The patient moved his hands about and was semi-conscious but when questioned at the end of the operation said he had no discomforts.

On post-operative day three, the patient developed a fever to 107 Fahrenheit, and the autopsy documents that "just before death pulse was also rapid and weak up to 150–160". Cushing's note adds that "the terminal symptoms were so similar to those which occurred after the anterior lobe injection, and were so promptly recognized by his wife, who had seen the patient go through similar severe attacks at home, that it seems quite probable that they must have been due to an extensive anterior lobe (?) intoxication". Cushing had originally suspected a surgical site infection as the root cause of the patient's death: "I had supposed that they [symptoms] must be due to some post-operative complication and feared either an infection or something else of this kind, thinking little of the possibility of a glandular intoxication". Following the autopsy, Cushing remarked that "it is possible that the secretion which may have been let loose was an active anterior lobe secretion or else that a sudden release from pressure allowed a pronounced absorption of retained secretion of pars anterior or of pars intermedia, which caused the great intoxication". The autopsy report further notes that, although no sellar lesion was resected during the operation, "the operation had been considerably misjudged as to its direction. The anterior wall instead of the base of the sella turcica has been removed and the stalk of the hypophysis cleanly divided...shows almost complete degeneration of the anterior lobe obviously from having its circulation shut off by baring the base of the gland and dividing its stalk. Posterior lobe normal".

Discussion

Interestingly, Cushing offers a very different explanation for H. M. B.'s terminal symptoms in *The Pituitary Body and Its Disorders* than in his unvarnished chart documentation. Although the surgical records reflect Cushing's initial impression that the symptoms were

due to hypersecretion of anterior pituitary hormones, his monograph offers the observation that “the patient’s terminal symptoms, barring the high temperature, were very much akin to those of acute experimental cachexia hypophyseopriva, such as follow total anterior lobe removal in the canine” [1].

Although Cushing originally attributed the patient’s post-operative decline to an overdose of anterior pituitary secretions, the intra-operative thyroid trauma offers an alternative etiology: iatrogenic thyroid storm.

Based on the surgical record, the patient receives the highest possible scores on the Burch and Wartofsky diagnostic criteria for thyroid storm [2, 3] in the categories of thermoregulation (30 points) and tachycardia (25 points), as well as 10 points for gastrointestinal-hepatic dysfunction. The surgical record does not provide information regarding symptoms of congestive heart failure, atrial fibrillation, or central nervous system effects. However, from the available information, the patient has a total score of 65 using the Burch and Wartofsky criteria, which is highly suggestive of thyroid storm [2, 3].

Although rare, there are case reports of thyroid storm induced by trauma, including percutaneous tracheotomy [4], strangulation [5], blunt force trauma [6, 7], and penetrating trauma [8]. In many of these cases, there was only a brief delay between injury and onset of thyroid storm; the patient described here developed a fever to 103 on post-operative day one, and 104 on post-operative day two. Without any intervention, his hyperthermia reached an extreme of 107 on post-operative day three, immediately prior to death. Furthermore, thyrotoxicosis has been demonstrated to have an adverse affect on the cardiovascular system of patients with underlying acromegaly [9].

The surgical record documents that the patient experienced episodes of diaphoresis, nausea, vomiting, and headache both in the hospital following administration of anterior lobe extract, and at his home prior to admission. Many of Cushing’s patients were treated pre- and post-operatively with anterior pituitary extract, which was commercially available in injectable and oral preparations. These extracts were heterogeneous, and likely contained varying concentrations of anterior pituitary hormones, including thyroid-stimulating hormone (TSH). It is possible that H. M. B.’s pre-operative episodes were induced or exacerbated by the administration of anterior pituitary extracts with high concentrations of TSH.

Without biochemical evidence, the diagnosis of thyroid storm in this patient remains theoretical, rather than definitive. Alternate explanations for the post-operative symptoms and subsequent death would include acute adrenal insufficiency, as well as sepsis. Although Cushing’s monograph describes the patient’s symptoms as similar to those seen in canine models of hypophysectomy, presumably secondary to acute adrenal insufficiency, he remained uncertain about the explanation for the extreme hyperthermia. In fact, Cushing’s canine models experienced only mild fevers following hypophysectomy, with rapid *decreases* in temperature immediately prior to death [10]. The post-mortem examination described atrophy of the anterior lobe of the pituitary, possibly secondary to damage to the infundibular stalk intra-operatively. Therefore, adrenal insufficiency may have been present

in the patient. Indeed, the possibility of thyroid storm superimposed on iatrogenic central adrenal insufficiency remains as an explanation for the patient's rapid progression from symptom onset to death. It is well known that exogenous thyroid hormone replacement in patients with unrecognized primary adrenal insufficiency can precipitate an adrenal crisis due to enhanced renal clearance of cortisol [11-13]. Although patients with central adrenal insufficiency are usually able to maintain normovolemia due to an intact renin-angiotensin-aldosterone system, it is possible that the endogenous thyrotoxicosis in this case could have accelerated the clinical consequences of hypocortisolemia [14, 15].

On the day prior to his death, the patient had a leukocyte count of 18,000 (no units provided) and Cushing himself initially suspected an infection was the root cause of the symptoms; however, his notes explain that "the nasal cavities and the large cyst were surprisingly clean and free from any evidence of trouble whatsoever. At the autopsy there was not even any suppuration in the large traumatized turbinate region, there being no muco-purulent secretion whatsoever. The cyst infundibular cavity was perfectly free and clean". In addition, Cushing's monograph describes an episode of what might have been hypotension: "his pulse was somewhat feeble and his blood pressure registered only 90" [1]. However, while a systolic pressure of 90 mmHg may be at the low range of normal, there is no documentation of the patient's baseline blood pressure to confirm that the value indicates hypotension. The negative autopsy findings and the uncertainty about the blood pressure interpretation, coupled with the patient's extraordinary hyperthermia, makes sepsis a less likely diagnosis.

At the turn of the twentieth century the role of glands, such as the pituitary and thyroid, in both healthy and disease states, were only beginning to be understood by physicians and scientists. The intra-operative complications posed by macroglossia associated with acromegaly were only partially appreciated by surgeons of the time; Cushing's attempt to conduct a transsphenoidal operation without intubating the patient led to respiratory failure, an urgent tracheotomy, and ultimately the death of the patient. Here we present an alternative explanation for the complications of this patient and report a case of what appears to have been unrecognized thyroid storm, brought on likely by intra-operative trauma during an urgent tracheotomy, which may have led to the patient's death. Although Cushing may have been correct in his theory that "glandular intoxication" contributed to the patient's cause of death, we propose that the culprit gland in this case was the thyroid rather than the pituitary.

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Fig. 1.

Top Row (left to right): Photographs of H. M. B. showing the development of his acromegalic features over time. *Middle Row:* Photographs of the post-mortem sections demonstrating the site of operation (*far left*), and cerebellar cyst disclosed on autopsy (*middle*). Microscopic examination of the resected tissue (*far right*). *Bottom Row:* Pre-operative visual field examination (*far left*); Cushing's typed notes on the case (*middle*), and a photograph of H. M. B.'s hand, demonstrating enlargement consistent with acromegaly. Image provided courtesy of the Yale University Harvey Cushing/John Hay Whitney Medical Library and The Cushing Center