A 23-year-old patient who was examined in 1910 by Harvey Cushing triggered his lifelong interest in the syndrome that bears his name. "Minnie G.," as she became historically known, presented with a "... syndrome of painful obesity, hypertrichosis, and amenorrhea with overdevelopment of secondary sexual characteristics accompanying a low grade of hydrocephalus and increased cerebral tension." This case stimulated Harvey Cushing's inquisitive mind and sparked an interest that 20 years later culminated in his seminal report, "The basophil adenomas of the pituitary gland and their clinical manifestations (pituitary basophilism)." In this classic work, Cushing reported in detail the cases of two patients encountered from his own practice and 10 similar cases collected from the literature. Minnie G. was the first case that Cushing reported. The clinical course of that case is briefly reviewed in this article.

**Key Words** - Harvey Cushing • pituitary adenoma • Cushing syndrome • neurosurgical history • primary pigmented nodular adrenal disease

In his original monograph, *The Pituitary Body and its Disorders: Clinical States Produced by Disorders of the Hypophysis Cerebri*, Cushing divided pituitary lesions into six groups according to the most striking clinical manifestations of the diseases. Group 1 included those cases "... in which both neighborhood" (that is, symptoms of mass effect such as visual failure and cavernous sinus syndrome) "... and glandular symptoms are outspoken;" Group 2 comprised those lesions with "... pronounced neighborhood but inconspicuous glandular symptoms;" Group 3 encompassed tumors "... with pronounced glandular manifestations but inconspicuous neighborhood disturbances;" Group 4 included those cases presenting with signs and symptoms of hydrocephalus; Group 5 consisted of distant lesions not necessarily involving the pituitary gland, but causing hypopituitarism; and Group 6 (which included Minnie G.) [Case XLV] included cases demonstrating "... a pluriglandular syndrome." In introducing Minnie G. and subsequent cases, Cushing stated that the intracranial symptoms were sufficiently definite to lay the burden of responsibility upon the hypophyseal or pineal gland, and yet in all, the glandular manifestations were so bizarre, so unlike those presented by the cases which have been recorded in the preceding groups, that they have been placed apart in this group of cases with a pluriglandular syndrome.
A 23-year-old woman, was referred from New York by Dr. DeWitt Stetton and was evaluated for the first time by Cushing in December 1910 at the Johns Hopkins Hospital. Her numerous symptoms included a 7-year history of amenorrhea, which appeared together with headache, back pain, and swelling of the feet. At the same time her vision “began to fail” and she complained of intermittent diplopia. Other striking features included a 20-lb weight gain over a 2-year period, . . . insomnia, tinnitus, extreme dryness of skin, frequent sore throat, shortness of breath, palpitation, purpuric outbreaks, marked constipation, sudden attacks of dizziness with falling, a definite growth of hair and mustache during the past few years with marked falling out of the hair of the scalp. . . . Muscular weakness was . . . extreme and there is much complaint of backache and epigastric pains.4

On physical examination, Cushing noted that this patient’s face was “. . . dusky and cyanosed and covered with a fine growth of hair, which is particularly noticeable on forehead and upper lip.” There was also

. . . a definite tendency toward hemophilia. The skin bruises easily and large spontaneous ecchymoses occur frequently. Epistaxis is almost a daily occurrence . . . Adiposity, particularly limited to the abdomen, is marked and of recent origin. It is very painful and tender (adiposis dolorosa).

Plain x-ray films of the sella turcica revealed a “somewhat thinned-out sella of normal configuration, but of small size.”

A subtemporal decompression was considered and, ultimately, performed because some of the symptoms were possibly referable to increased intracranial pressure. A month following the procedure, the patient’s headaches had resolved, her blood pressure had improved, and she had lost 12 lbs.

In commenting upon the case of Minnie G., Cushing observed that the patient displayed signs and symptoms similar to those observed with “hypophyseal deficiency” (amenorrhea, adiposity, and short stature). Instead of the “sexual infantilism of reversion type,” which had been associated with cases of hypopituitarism observed by Cushing before that time, however, Minnie G. exhibited “the secondary sexual development, mammary and genital, of a multipara, with unusual and recently acquired hirsuties.”4

Follow-Up Consultations

Minnie G. was readmitted to the Peter Bent Brigham Hospital in 1912. At that time her general condition and symptoms were unchanged. Polycythemia and hypertension were present.2 Notes obtained at the time of an addi-
Cushing’s Case XLV: Minnie G.

By his own admission, Cushing was not the first one to describe the syndrome that bears his name: “... other cases with precisely the same syndrome have been recorded in the past. ...” The previous six cases alluded to in his monograph were reported between 1903 and 1910, and were all associated with adrenal disease. In some respect, therefore, Minnie G. was not unique in being the first reported case of hypercortisolism, which we now appreciate to be the immediate cause of Cushing syndrome. We are also now aware that approximately 80% of cases of spontaneously occurring Cushing syndrome are due to adrenocorticotrophic hormone–secreting pituitary adenomas, which cause bilateral adrenocortical hyperplasia (Cushing disease). Cushing initially thought that the clinical picture of Case XLV resembled that observed in some cases of adrenal tumors. For some time he had been aware that the anterior pituitary contained at least three types of cells: 1) neutrophil or chromophobe cells, which are difficult to stain and commonly give rise to tumors that tend to destroy other cells; 2) acidophil cells, which have an affinity for acid dyes and which in excessive amounts cause gigantism and acromegaly; and 3) basophil cells, which attract the basic dyes. Until 1924, the only basophil adenomas of which Cushing was aware were associated with two cases reported by Erdheim in 1903, and both of these were clinically silent. When Cushing published his monograph in 1912, he had changed his opinion regarding Minnie G. He hypothesized that if acromegaly was due to acidophil hyperpituitarism, there must be another form of dyspituitarism caused by an excess of basophil cells and involving sexual dysfunction (amenorrhea in women and impotence in males). Cushing hypothesized this as early as 1912 and, therefore, included Minnie G. in his monograph on the pituitary body. He appreciated and catalogued the entity as a “pluriglandular syndrome,” a result of changes caused by a primary basophilic pituitary adenoma, without ever making the connection with a corticotrophic factor such as adrenocorticotrophic hormone. Despite Cushing’s research at the Hunterian Laboratory on basophilic staining of normal pituitary cells, much of the experimental evidence and subsequent case reports that he integrated only came to light 6 years before publication of his paper on pituitary basophilism in 1932, 20 years after The Pituitary Body and its Disorders was published. This makes Cushing’s conviction about the cause of the syndrome even more remarkable, and sets him apart from other persons evaluating the syndrome.

The natural history of Cushing disease is still relatively unknown because most afflicted patients receive treatment. Among the 12 patients described by Cushing in his monograph, eight (67%) died within a few years after the presentation; Minnie G. was unique because she survived longer than 40 years. It was this survival that intrigued Carney, who speculated that perhaps Minnie G. suffered from the Carney complex or PPNAD. In rare cases, this disorder can undergo spontaneous regression. Carney also appreciated the fact that, statistically, the most likely explanation perhaps was that Minnie G. harbored a basophil adenoma that underwent partial infarction. One can only wonder how neurosurgical history would have been altered if an autopsy had been performed in the case of Minnie G.—whatever results were disclosed.

Dr. Carney’s Search for Minnie G. and Her Family

In 1985, Dr. J. Aidan Carney, a surgical pathologist, and his colleagues at the Mayo Clinic described a complex consisting of PPNAD associated with Cushing syndrome, which became known as the Carney complex. When associated with PPNAD, Cushing syndrome can infrequently undergo spontaneous regression. Carney, intrigued by the fact that Minnie G. had lived for many years without receiving any treatment directly targeted to a possible pituitary tumor, hypothesized that she might have suffered from PPNAD. To gain more information on the original case, he undertook a methodical search for further information regarding Minnie G. and her family. This led to an article published in 1995, ‘The search for Harvey Cushing’s patient, Minnie G., and the cause of her hypercortisolism.” Following his quest, Carney gathered additional clinical history, postdating Cushing’s last contact with this patient in 1932.

In June 1933, Minnie G. was admitted to Lenox Hill Hospital in New York for investigation of a bowel disorder. The clinical notes associated with this admission list her weight as 122 lbs (down from a maximum of 155 lbs) and stipulate that her weight had been fairly constant for several years. These notes confirm that her amenorrhea had resolved. Hypertension, however, persisted. Interestingly, the records from Lenox Hill Hospital indicated that Minnie G. left against medical advice. Through conversations with family members, Dr. Carney was able to ascertain that she “ran out of the hospital” after being shown pictures in a book. These pictures were most likely photographs of the patient that were contained in Cushing’s The Pituitary Body and its Disorders (Fig. 1). The monograph and Minnie G.’s relation to it were indeed mentioned in the medical record of her 1933 admission to Lenox Hill Hospital.

Family members who were contacted agreed that Minnie G. looked different from her sisters and some remembered her facial hirsutism. All remembered her odd personality and behavior, which was described at times as “psychotic” or “paranoid.” The woman was definitely prone to emotional outbursts and these symptoms persisted, despite resolution of some features typical of hypercortisolism. According to Carney, this might have made Cushing assert that some features of her disease still persisted in 1932.

From his reconstruction of the events, Carney was able to conclude that Minnie G. died in 1958, 48 years after her initial consultation with Cushing. Her death certificate cited atherosclerotic heart disease and no mention was made of Cushing syndrome. In accordance with Jewish custom, at the time of Minnie G.’s death an autopsy was refused by her sister. Thus, Carney was unable to verify the possible cause of the woman’s symptoms.

Discussion

By his own admission, Cushing was not the first one to describe the syndrome that bears his name: “... other cases with precisely the same syndrome have been recorded in the past. ...” The previous six cases alluded to in his monograph were reported between 1903 and 1910, and were all associated with adrenal disease. In some respect, therefore, Minnie G. was not unique in being the first reported case of hypercortisolism, which we now appreciate to be the immediate cause of Cushing syndrome. We are also now aware that approximately 80% of cases of spontaneously occurring Cushing syndrome are due to adrenocorticotrophic hormone–secreting pituitary adenomas, which cause bilateral adrenocortical hyperplasia (Cushing disease). Cushing initially thought that the clinical picture of Case XLV resembled that observed in some cases of adrenal tumors. For some time he had been aware that the anterior pituitary contained at least three types of cells: 1) neutrophil or chromophobe cells, which are difficult to stain and commonly give rise to tumors that tend to destroy other cells; 2) acidophil cells, which have an affinity for acid dyes and which in excessive amounts cause gigantism and acromegaly; and 3) basophil cells, which attract the basic dyes. Until 1924, the only basophil adenomas of which Cushing was aware were associated with two cases reported by Erdheim in 1903, and both of these were clinically silent. When Cushing published his monograph in 1912, he had changed his opinion regarding Minnie G. He hypothesized that if acromegaly was due to acidophil hyperpituitarism, there must be another form of dyspituitarism caused by an excess of basophil cells and involving sexual dysfunction (amenorrhea in women and impotence in males). Cushing hypothesized this as early as 1912 and, therefore, included Minnie G. in his monograph on the pituitary body. He appreciated and catalogued the entity as a “pluriglandular syndrome,” a result of changes caused by a primary basophilic pituitary adenoma, without ever making the connection with a corticotrophic factor such as adrenocorticotrophic hormone. Despite Cushing’s research at the Hunterian Laboratory on basophilic staining of normal pituitary cells, much of the experimental evidence and subsequent case reports that he integrated only came to light 6 years before publication of his paper on pituitary basophilism in 1932, 20 years after The Pituitary Body and its Disorders was published. This makes Cushing’s conviction about the cause of the syndrome even more remarkable, and sets him apart from other persons evaluating the syndrome.

The natural history of Cushing disease is still relatively unknown because most afflicted patients receive treatment. Among the 12 patients described by Cushing in his monograph, eight (67%) died within a few years after the presentation; Minnie G. was unique because she survived longer than 40 years. It was this survival that intrigued Carney, who speculated that perhaps Minnie G. suffered from the Carney complex or PPNAD. In rare cases, this disorder can undergo spontaneous regression. Carney also appreciated the fact that, statistically, the most likely explanation perhaps was that Minnie G. harbored a basophil adenoma that underwent partial infarction. One can only wonder how neurosurgical history would have been altered if an autopsy had been performed in the case of Minnie G.—whatever results were disclosed.
Conclusions

The case of Minnie G. triggered Cushing’s life-long interest in pituitary basophilism, culminating in his seminal article, published in 1932, and the disease that now bears his name. Yet, the primary cause of her Cushing syndrome remains unknown. It can be speculated that Minnie G. might have harbored a pituitary adenoma that spontaneously infarcted, leading to partial regression of her symptoms. It is also possible that she had PPNAD. Direct proof of either cause in this historical case is still lacking. Regardless, Minnie G.’s unique place in medical history remains assured.

References


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