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A Case Report from the Ancient Past

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Patient: —
Final Diagnosis: **Pituitary apoplexy with hypothyroidism**
Symptoms: —
Medication: —
Clinical Procedure: —
Specialty: **Endocrinology and Metabolic**

Objective: **Educational purpose**
Background: Standard translations of Hippocratic works are sometimes misleading because the translators knew less about their subject than did the ancient authors.
Case Report: A new translation and explication of a chapter from a Hippocratic work of the fifth century before the Common Era (BCE), *Diseases II*, describes patients with pituitary apoplexy and subsequent myxedema, the 2 events separated by as much as 14 years.
Conclusions: The association of myxedema with an intracranial event that occurred years earlier predates by 2400 years the causal association of a pituitary adenoma with hormonal deficiency.

MeSH Keywords: **Hippocrates • History, Ancient • Myxedema • Pituitary Apoplexy**

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Background

Many clinical works attributed to Hippocrates (460–380 BCE), venerated for over 2 thousand years, are now all but forgotten. Popular textual references on clinical content have been to classic translations from the Greek, most notably by Dr. Emile Littre (1801–1881) in France and Dr. Francis Adams (1796–1861) in Scotland [1,2]. Both were trained in medicine and both published in the mid-nineteenth century when scientific truths were beginning to flood the medical world, but their translations retained many elements of medieval interpretation and vocabulary. Some recent translations of Hippocratic passages by medical specialists suggest, however, that ancient Hippocratic physicians were more observant and prescient than were their translators until well into the twentieth century [3–6].

This paper presents a new translation of a single short chapter selected from the Hippocratic treatise, *Diseases II*, a work that, focusing on internal medicine, contains much that, on cursory reading, seems to elude common sense. Chapter 12 of *Diseases II* shares that shortcoming, but when parsed more carefully reveals a syndrome associated with pituitary tumors. Validity of the present translation is supported by a recent neurosurgical interpretation of chapters 14 and 15 of *Diseases II* as representing a credible diagnosis and surgical management of an otitis-related brain abscess [7,8].

Case Report

(As translated by the author from the Greek of the 1538 Froben edition of the works of Hippocrates [see Appendix]).

Diseases that develop from the head

Whenever it becomes full and it happens that it becomes heated from something, hypesthesia grips the head, and the patient must urinate all the time. Otherwise he suffers as if he had strangury. After 9 days of these symptoms, should something like water or dribble drain from the nose or ears he will recover from the disease and the strangury ceases. By day 20 he then will urinate a lot without difficulty and the urine will be pale. And the distress emanating from the head then remits, but should the eyes be looked into, the gleam [of the eyes, glint] is absent and the patient sees faces from only one side. By 40 days he becomes completely healthy.

In many the disease sometimes gradually recurs 7 to 14 years later; the skin of the head is thicker and exhibits edema. Despite little food the skin appears soft and of a good complexion, but auditory acuity is decreased.

Whenever you come across a patient with these problems early in the course of the disease before there is watery drainage down from the nose and/or ears, and if there is the same discomfort [of the head], it is necessary to shave the head and then tie a leather flask filled with water as hot as tolerable to the forehead, refilling the flask when it cools down. But if the patient becomes too weak, leave off for a while but do it to him [continue it] until the tenderness eases. If the patient is constipated, use an enema and hydrate him ... [remainder of paragraph irrelevant].

And during that time if there is watery drainage from the nose and the urine is concentrated [viscous] but the discomfort [of the head] is easing, the flask on the head is no longer needed, but [have him] drink the well-washed and warmed diuretic with diluted honey. ... [remainder of the paragraph irrelevant].

Should the disease recur, give the patient a vapor bath and in the morning give him some hellebore to drink; and after an interval of whatever you think might be the [right] time, cleansing the head, give a lower medicine [probably a laxative], and scarify the head in 8 places, 2 near the ear, 2 on the forehead, and 2 posteriorly on the head on each side over the occiput, and 2 by the nose near the inner canthus of the eye. Then burn [to seal] the blood vessels near the ears until the pulsations stop; do this with wedged hot irons, to cauterize across the vessels. In doing this the patient becomes healthy.

Discussion

The patient proposed by the examiner presents with facial numbness and headache and might have had a purulent sinusitis or otitis media eased by spontaneous drainage of pus. But the problem is more complex. The facial numbness (anesthesia or hypesthesia) suggests cranial nerve V involvement and, because of urinating “very much” and “much and easily,” the patient may have had antidiuretic hormone (ADH) deficiency. Strangury is mentioned, but, in contrast to polyuria, strangury is associated with voiding of small amounts of urine. It is likely that the term “strangury” was used here by the examiner because the patient had a feeling of urgency to urinate caused by frequent bladder distention rather than bladder or urethral irritation associated with the hesitancy, sense of incomplete voiding, and straining at urination that defines strangury. A week or so later such a patient can have a watery trickle from the nose or ear, not descriptions that would suggest purulent drainage. The facial numbness and headache then disappear, but the urine remains plentiful and pale (of low specific gravity), suggesting ongoing diuresis of a hypotonic urine, but urinary urgency has ceased. At this point the patient is developing a cranial nerve palsy, for on looking into the eyes the normal positioning of the corneal light reflex

apparently is not seen by the examiner, indicating asymmetry of gaze has now developed. Concurrently the patient has developed a visual field defect. Diagnostic visual field testing was yet to be invented, and the description that such a patient might see only one-half of faces is probably an incorrect interpretation by the examiner. Visual field cuts are common with pituitary tumors. They tend, however, to be bitemporal hemianopias, and a homonymous hemianopia is possible but rare. Central scotomas, however, are frequent. These might have produced an image interpreted as “half a face” [9]. Despite these symptoms the patient was judged healthy a month or so later.

Years later some symptoms described might recur, but now such a patient can have thickened skin of the face that compresses with fingertip pressure. It is proposed that the patient has developed myxedema. Along with the skin changes, his hearing is diminished and there is a decrease in caloric requirements, both often present in advanced hypothyroidism. A “good” complexion is not how modern physicians would describe the advanced hypothyroidism facies, for the skin tends to be dry and some sallow pallor is often present, but in older textbooks the classical description of hypothyroidism can include a “peaches and cream” complexion. Furthermore, pallor may have seemed less obvious in a Mediterranean population. Hypothyroidism is more likely than anasarca to explain the skin changes, for edema is not described as pitting (a distinction made in another Hippocratic work), and dependent edema, ascites, and generalized tissue edema are not described¹. There is a suggestion of chronicity as weakness developed in the intervening years, a vague symptom, but one consistent with hypothyroidism and not attributed to a new problem. Years later, should the proposed patient have another exacerbation, the recommendation is scarification and cautery of superficial vessels of the head, thus following the usual Hippocratic practice of surgery as a last resort.

The probable cause of such a relatively acute clinical sequence in an adult is pituitary apoplexy. Hormones that might be affected include ADH, oxytocin, and any or all of the anterior pituitary hormones such as thyroid-stimulating hormone and adrenocorticotrophic hormone. The role of ADH is postulated as follows: when first seen, the patient’s pituitary tumor was impairing ADH release from the posterior pituitary, which explains the increased urination. Nine days later (after consulting the physician?) a cerebrospinal fluid (CSF) leak occurred, one consequence being a decrease in intracranial pressure either generally or locally, and this, perhaps with a decrease in tumor size from infarction, led to cessation of the headache and a concurrent decrease in pressure on the hypothalamus or posterior pituitary that permitted a correction of the impaired

ADH release. Urine output, therefore, could have transiently decreased, presumably for a few days, and been viewed as normalized by day 9. Alternatively, the syndrome of inappropriate ADH secretion (SIADH) or an element of adrenal or thyroid insufficiency might have masked ADH deficiency, thus mimicking an improved ADH status [10]. Once the CSF leak spontaneously ceased, which often occurs, the effect of local pressure on the mechanism of ADH release returned, for 11 days later there is extraocular muscle impairment, a visual field defect, and resumption of diuresis. Although tumor effects reappeared, the discomfort of the head did not.

Hippocratic treatment is given in 3 phases. In phase 1, prior to the nasal drainage, the symptoms of headache, hypesthesia, constipation, and polyuria are treated with local heat, hydration, and laxatives. Application of localized heat to the head may have been prescribed to promote drainage and ease pain, just as hot compresses were thought to do when applied to abscesses. Fortuitously, nasal drainage appeared and some symptoms abated. The alternative of ear drainage is inconsistent here and may have been merely inferred by the examiner from experience with trauma-induced CSF leaks. In phase 2, therefore, hot compresses were discontinued, and mild cathartics started. In phase 3, efforts now shift to scarification and cautery, presumably because it has been decided that no medicinal therapies are effective against the late manifestations of the underlying problem, which, quite remarkably, is still considered to be in the head.

Of the more than 70 works listed under the sobriquet of “Hippocrates,” most were written between 450–350 BCE. Many are notable for their brevity and sparse commentary, more like quick clinical notes than prolix sophism of the philosophers. In the words of Dr. W. H. S. Jones, translator of the first 4 volumes of the *Loeb Classical Library* series on the works of Hippocrates, “Not a word is thrown away” [11]. There is no unanimity of opinion that a medical personage now hailed as Hippocrates ever existed, and scholars are convinced that the Hippocratic works are the product of many authors. The clinical case presently under discussion nonetheless inhabits a niche in history to which its credibility can be appended, namely, confidence in the approximate dates of its production, mid-fifth century BCE, and confidence that its authors were clinicians that as a group can be designated “Hippocratic.”

The final diagnosis of the present case report is postulated to have been a nonfunctioning pituitary tumor with infarction or hemorrhage, still quaintly termed “pituitary apoplexy,” and subsequent hypothyroidism. But the correctness of the diagnosis is of less interest than the implication that the same patient,

¹ Different types of edema are described in standard sections of the following Hippocratic works: pitting edema – Internal Affections, section 44; dependent edema – Epidemics III, section 12 under “Constitution;” anasarca – Aphorisms VII, p.

or perhaps 2 or 3 patients from whom the clinical sequence was put together, was under medical observation for as long as 14 years, thus allowing what likely was advanced hypothyroidism to be postulated as a consequence of the much earlier event affecting the head. If true, the continued personal involvement of one or more local physicians with one or more patients over such a long time suggests a stability of Hippocratic medical practice, a continuity of care, and a method of data collection/preservation that would seem without parallel in ancient times. Support for this inference is provided by other Hippocratic works describing situations where acute events and later, seemingly unrelated, phenomena were considered one illness, such as diphtheria and its paralytic effects, relapsing spirochetal fevers, and the association of “critical days” with physiological responses to pathogens [12].

Seemingly healthy after a month and a half, the patient was assessed as “cured,” just as he was following cautery and scarification. Yet when reassessed 7 years later, primary hypothyroidism was developing. It does underscore the fact that many of the patients identified in Hippocratic clinical works who are claimed to have been “cured” were, in fact, not cured. Their later consequences may not have been known to the initial physician because of the peripatetic nature of his practice or because the patient died or moved from the region prior to the arrival of a subsequent physician who would be unaware of the ultimate outcome. In the present case, continuity of care appears to have covered as much as 14 years, although one might suppose that the physician who scarified and cauterized the patient’s head promptly left town after pronouncing the patient as cured.

The question remains, how could the course of such a protracted illness be described in terms that suggest similar illnesses had been seen by Hippocratic physicians, thus allowing for a filling in, over time, of clinical events covering 14 years? The prevalence of “clinically relevant” pituitary tumors in Belgium has been reported to be 1 per 1000 persons² [13,14]. About one-half were nonfunctioning. If an ancient

Greek city-state contained 10 000 persons who might have been visited by Hippocratic physicians (excluding slaves and foreigners who would not have been their patients), several nonfunctioning pituitary adenomas might have been present at any given time if the epidemiology of pituitary disease were similar to the present day, and, as there was no effective treatment, that number, because of case accumulation, may have been even higher. The prevalence of pituitary apoplexy in a defined population in southern England was about 6 cases per 100 000 population, or somewhat less than 1 patient per year at any given time in the proposed city-state [15,16]. If classical pituitary apoplexy and hypothyroidism are both to be included, the situation is even more uncommon. On the other hand, if mild forms of pituitary apoplexy are included, such cases would be more common, although it is uncertain as to what degree [17]. Assuming a standardized incidence ratio approaching 2 patients with pituitary apoplexy per 100 000 population per year, of whom half become hypothyroid, this would equate to a case of hypothyroidism following pituitary apoplexy every 10 years. Given this statistical background, if a small group of medical professionals, perhaps 4 or 5 practitioners, periodically pooled their knowledge and experience over a generation, the assertions of Chapter 12 of *Diseases II* could claim epidemiological plausibility. Furthermore, it has been proposed that Hippocratic physicians could communicate with one another even though geographically dispersed [18].

Conclusions

While of clinical interest in itself, the 2 remarkable features of the physician’s report are 1) the association of clinical evidence of pituitary apoplexy and subsequent myxedema as manifestations of a single underlying disease process despite many years between the 2 events, and 2) the ability of early Hippocratic clinicians to maintain a written or oral record of one or perhaps several patients’ clinical history over those years that allowed them to make such an audacious assumption, one that would not be confirmed for 2400 years [19].

² The authors report an annual incidence rate of 3/100,000 in U.S., an average value that covers all age and ethnic groups.

Appendix

The Greek version of Diseases II, chapter 12, a treatise attributed to Hippocrates, is extracted from the 1538 Froben edition of the works of Hippocrates, as edited by the famed scholar and friend of Erasmus, Janus Cornarius (1500-1558). Chapter 12 is divided into five paragraphs in the Loeb Classical Library edition of Hippocrates (Harvard University Press), volume 5, as edited by Dr. Paul Potter, and is presented in English vernacular in the Case Discussion section of the attached article. The first two paragraphs in Greek with the author's interlinear literal translation are given below. It was felt important that a degree of literal translation be retained, for accuracy is preferred to literary merit that might come with a more readable translation. Words that differ between the 1538 edition and the modern Loeb Classical Library edition of Hippocrates are bolded. All five paragraphs, with some deletions considered irrelevant, are presented only in the vernacular translation in the attached article.

νοῦσοι αἱ ἀπὸ τῆς κεφαλῆς γινόμεναι· ὅταν πλήρης
diseases the **from the head to be developing**; **whenever full**
γένηται ἡ κεφαλή, καὶ τύχη ὑπό τινος
it becomes the head, and it happens from something
τούτων διαθερμανθῆναι, νάρκη ἴσχει
of them to be thoroughly heated, numbness (hypesthesia) grips
τὴν κεφαλὴν, καὶ οὐρέει **συχνα**. καὶ τὰ ἄλλα πά-
the head, and he urinates **very much. and the other** [symptoms] he
σχει ἄπερ ὑπὸ στραγγουρίης. ὁ αὐτὸς ἡμέρας ἐννέα
is affected as if from strangury. **the same** days nine
ταῦτα πάσχει, καὶ ἦν μὲν ῥαγῆ κατὰ τὰς ῥίνας,
these he suffers. and should it flow down from the nose
ἢ κατὰ τὰ ὠτα ὕδωρ καὶ **βλαίονα**, ἀπαλλάσσεται
or down from the ears water or **dribble**, he is relieved

τῆς νόσου. καὶ παύεται τῆς στραγγουρίης. οὐρέει
of the disease, and he has suppression of the strangury; he urinates
τὲ ἀπόνως. καὶ **πολυ** καὶ λευκόν, ἐς τὰς εἴκοσιν ἡμέ-
and easily. both much and pale, within twenty
ρας. καὶ ἢ ἐκ τῆς κεφαλῆς ὀδύνη ἐκλείπει, καὶ ἐκ
days. and from the head the tenderness remits, and from
τῶν ὀφθαλμῶν ἐσορῶντι κλέπτεται οἱ ἢ αὐγή.
the eyes looking into is concealed which the bright gleam [of the eyes].
καὶ δοκέει τὸ ἥμισυ τῶν προσώπων ὄραν. οὗτος
and he seems unilateral [one side] of faces to be discerning. this [patient]
τεσσερακοσταῖος ὑγιῆς **παν τελῶς** γίνεταί.
by forty days healthy completely becomes.

ἐνίοτε δὲ **πολλοῖς ὑπανέστρεψεν** ἡ νόσος ἐβδόμῳ
sometimes and in many gradually comes back the disease in seven
ἔτει, ἢ τεσσερεσκαιδεκάτῳ· καὶ τὸ δέρμα οἱ παχύ-
years or fourteen. and the skin is thickened
νεταί **τὸ** τῆς κεφαλῆς. καὶ ψαυόμενον ὑπέικει· καὶ
of the head, and being touched indents; and
ἀπ' ὀλίγων σιτίων, ἀπαλὸς καὶ εὐχρῶος φαίνεται,
from a little food soft and a good complexion it (the skin) appears,
καὶ ἀκούει οὐκ ὀξέα.
and the patient hears not acutely.

Hippocratic works come down to us after passing through many hands, some having been transcribed by illiterate scribes, others have been translated by scholars of other cultures such as Arabic that often had no equivalent words for Greek medical terminology. It is not a surprise, therefore, that part of the first paragraph above is duplicated by transcription error in chapter VIII of another Hippocratic work, Regimen in Health, for which see the Loeb Classical Library volume 4 of the series, Hippocrates, as edited by Dr. W. H S. Jones and published in 1967, p. 57. That

same paragraph as found in the 1538 edition of the works of Hippocrates is presented below, again with difference in wording between it and the Loeb Classical Library version being bolded:

οκόσοισι δὲ νοῦσοι ἀπὸ τὸν **ἐγκεφαλον** γίνονται, νάρκη **πρῶτον** ἴσχει τὴν κεφαλὴν, καὶ οὐρέει **θαμινά**, καὶ τ' ἄλλα πάσχει οκόσα ἐπὶ στραγγουρίῃ. οὔτος ἐφ' ἡμέρας ἔννεα οὔτος πάσχει. καὶ ἦν μὲν ῥαγῆ κατὰ τὰς ῥίνας ἢ κατὰ τὰ ὠτα ὕδωρ, ἢ βλέννα, ἀπαλλάσσεται τῆς νόσου, καὶ τῆς στραγγουρίης παύεται. οὐρέει δὲ πολὺ, καὶ ἀπόνως, καὶ λευκόν. ἕς' ἂν εἴκοσιν ἡμέρας παρέλθη καὶ ἐκ τῆς κεφαλῆς ἡ ὀδύνη ἐκλείπει τῷ ἀνθρώπῳ, ἐσορέοντι **δε** βλέπεται οἱ ἡ αὐγῆ.

(1) Note that, in this duplicate transcription, ἐγκεφαλον is used instead of κέφαλος, which changes the meaning from “head” to “brain.” This transcription, if it is closer to the correct version, implies that the writer of Diseases II, 12, considered the source of the problem being described as originating in the brain. This would fit better the present clinical interpretation.

(2) The additional word πρῶτον (“first”) is consistent with the early onset of hypesthesia of the face, and it suggests that the section ὅταν ... διαθερμανθῆναι in the 1538 version (and **bolded** in the first Greek paragraph above) is miscopied into that work, for that section implies the problem originated in the sinuses or middle ear when they became “full.” Dr. Paul Potter, in his translation of Diseases II, 12, omits ὅταν ... διαθερμανθῆναι, as does this duplicate transcription. This also strengthens the argument that the duplicate transcription is closer to the original.

(3) But even if it is not the more accurate version, διαθερμανθῆναι definitely does not mean “fever.” It means, instead, “to be heated throughout”, and is an attempt at explaining the pathophysiology underlying the liquidity of the noxious agent(s) causing the illness.

(4) Another linguistic difference is the use of θαμινά rather than συχνά. The former is translatable as “crowded” or “frequent,” whereas the latter can mean, in addition, “very much,” thus permitting a translation more consistent with both increased frequency and increased volume of urine output. A sole increase in volume of urine is not consistent with the definition of strangury, for the definition of the ancient Greek term for “strangury” is similar to its modern one. This may explain why the term is here distinguished apart from the usual (“other”) symptoms of strangury.

(5) βλαΐννα (βλέννα, πλέννα) is translated here as consistent with its use by a contemporary writer, Sophron of Syracuse, for dribble implies a more aqueous liquid rather than the usual translation (“slime”) that might imply the more viscous mucus.

(6) In the final line, δὲ (“but”) rather than καὶ (“and”) suggests the patient has not become completely healthy at twenty days despite clearing of some symptoms. This is also indicated in the text of Diseases II, chapter 12.

(7) The word ἐσορέοντι (ἐσορῶντι in the text of Diseases II, chapter 12) is translated as “looking into,” for εἰσ (εσ) has its root meaning “in” or “into,” and most words having εἰσ (εσ) as a prefix specify an action in or into. The corneal light reflex is tested not by looking through the pupil into the globe of the eye, but by merely holding a light source before the patient and noting if the reflected glint of the light visible in the pupil is normally positioned in each eye. In this sense the translation comes closer to its usual translation as “peering closely.”

(8) In contrast to the first Greek paragraph above, βλέπεται (βλάπτεται in the Loeb Classical Library series of Hippocrates) rather than κλέπτεται suggests the corneal glint was not hidden but was defective or abnormal. On the other hand, if there were sufficient exotropia of one eye, the corneal light reflex might truly have seemed to be absent in one eye. Such are the vagaries of attempts at accurate translations.

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