Chapter 34

Two Patients with Headache and Hyperprolactinemia

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Case History I

The patient is a 35-year-old working woman, who did not drink or smoke and led a normal life. She had no history of significant illness, except that at the age of 16 years, she suffered a bout of weight increase (putting on 20 kg in a few months) associated with reduced menstrual cycle frequency and flow. She managed to regain her previous weight after about a year without dieting or therapy. However, the menstrual cycle alteration persisted, and at the age of 30 years, she developed oligomenorrhea, which was treated with combination estrogen–progesterone. The patient discontinued the medication on her own initiative after 6 months, and amenorrhea and headache appeared within a month; there was no galactorrhea.

The headaches were mild, seemed like a weight on the head involving the entire cranium, without autonomic signs, lasting 4 to 5 hours, and resolved without the use of analgesics. After about a year, they were occurring every day, with more or less the same characteristics, but with periods of intense head pain resembling migraine attacks, associated with nausea, photophobia, and phonophobia. The patient started taking analgesics (indomethacin and ibuprofen) for the intense episodes. Initially, these reduced the pain, but never completely resolved it. Eventually, she was taking analgesics daily and at this point decided to consult a neurologist, who advised hospital admission for further examination.

On admission, the patient's clinical examination was normal, her blood pressure was 135/85, and her heart rate was 68 bpm; routine blood tests and a neurologic examination were all normal. An eye examination revealed normal fundi and visual fields. A head radiograph revealed an enlarged sella turcica, prompting a sellar region computed tomography (CT) study with contrast, which revealed an area of hypodensity at the media-paramedian base of the hypophysis, compatible with microadenoma. Magnetic resonance imaging (MRI) with and without gadolinium-pentetic acid showed a rounded, hyperdense (compared to the gland) lesion in the hypophysis of about 8×10 mm, compatible with hypophyseal adenoma (Figure 34-1). Given the high prolactin (PRL) level (180 ng/mL; normal level is 5 to 20 ng/mL) and normal thyroid-

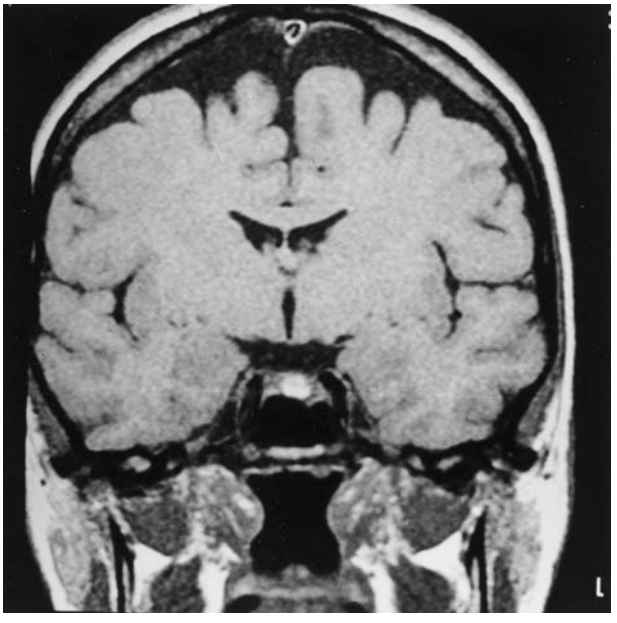

Figure 34-1. Case I: Coronal section of a T1-weighted magnetic resonance image.

stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), adrenocorticotropic hormone (ACTH), cortisol, growth hormone (GRH), follicle-stimulating hormone, and luteinizing hormone levels, the patient was started on the dopamine agonist cabergoline (0.5 mg per week), resulting in amelioration and eventual disappearance of the headache, with return of the menstrual cycle and prolactin levels to normal (15.6 ng/mL) after about 4 months. An MRI performed after a year of cabergoline therapy revealed a modest reduction in the volume of the lesion and the absence of intralesional or intrasellar hemorrhage (Figure 34-2). The patient remains asymptomatic and continues therapy with cabergoline.

Case History II

The patient, a 47-year-old male lorry driver, led a normal life, did not drink alcohol, and smoked no more than 6 cigarettes a day. He was single with no children. The clinical history revealed no significant illnesses apart from an appendectomy and tonsillectomy. There was no family history of any endocrine disorders or headaches.

The patient presented to Accidents and Emergencies with an intensely painful headache which had begun 3 days previously and was resistant to the analgesics taken (ibuprofen 400 mg and nimesulide 200 mg). For about 3 months, the patient had been complaining of headaches. Initially, the headaches had a low frequency and were of mild intensity, often occurring early in the morning, together with symptoms of confusion. At the beginning, the attacks lasted from several minutes to several hours; however, the headache frequency progressively increased, and during the last month, the patient had almost daily headaches. The headaches were normally accompanied by nausea. The patient usually did not take any medication for the attacks.

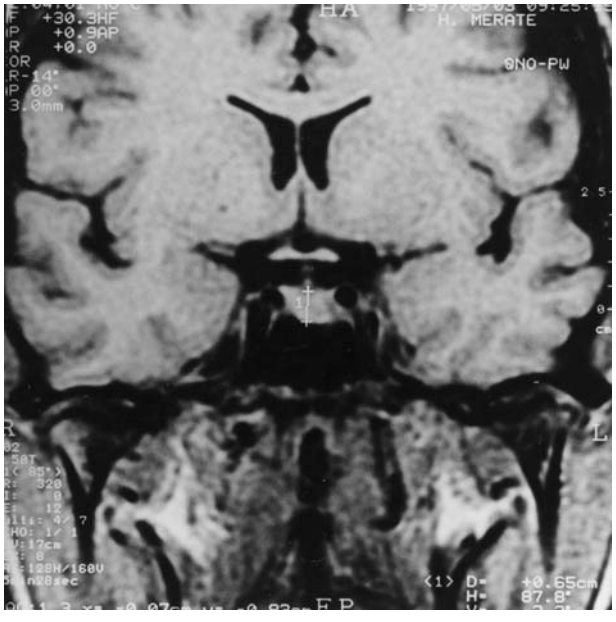

Figure 34-2. Case I: Coronal section of a T1-weighted magnetic resonance image showing a dense pituitary microadenoma after 12 months of cabergoline therapy.

The patient was admitted into hospital. His clinical examination on admission was within the normal range, blood pressure was 130/80, with a heart rate of 72 bpm. The neurologic examination was normal and the eye examination revealed normal fundi.

The visual field examination (measured using Goldmann-Friedmann perimetry) was within the normal range.

During the hospital stay, the patient underwent a cerebral CT scan with and without contrast; extensive lesions were found at the cranial base.

MRI showed extensive lesions in the sellar region, with suprasellar involvement and the beginnings of infiltration into the optic canal and the sinus cavernosus, with deformation of the carotid arteries, without stenosis (Figure 34-3).

With a suspected hypophyseal adenoma, the patient had blood levels of FT3, FT4, TSH, ACTH, free and combined cortisol, GRH, testosterone, and serum prolactin, all of which were within normal values except for PRL. The PRL base level was 7,843.0 ng/mL (normal values of 5 to 20 ng/mL), and after a saline infusion for an hour, the level was 7,478.2 ng/mL.

The patient was then treated with cabergoline 0.5 mg at night for 7 days, which resulted in a significant reduction in the PRL levels to 650 ng/mL. The dose of cabergoline was then reduced to 0.5 mg three times a week. After almost a month from the start of the treatment, the patient had noted rhinorrhea, which after thorough examination, was found to be rhinorrhea of the cerebrospinal fluid (CSF). After consultation with our neurosurgical colleagues, the dose of cabergoline was reduced to 0.5 mg per week, which resulted in the disappearance of the rhinorrhea. Currently, 5 months from the start of treatment, the patient continues to have attacks of headaches on the crown of the head, which are worst mostly in the morning on wakening and occur without any autonomic signs. The duration of the headache varies from 2 hours to an entire day, and is of medium intensity without any symptomatic treatment. The headache diary revealed that the headaches occur 3 to 4 times per month.

A control MRI of the brain performed 5 months after starting treatment showed a significant reduction of the tumor size (Figure 34-4).

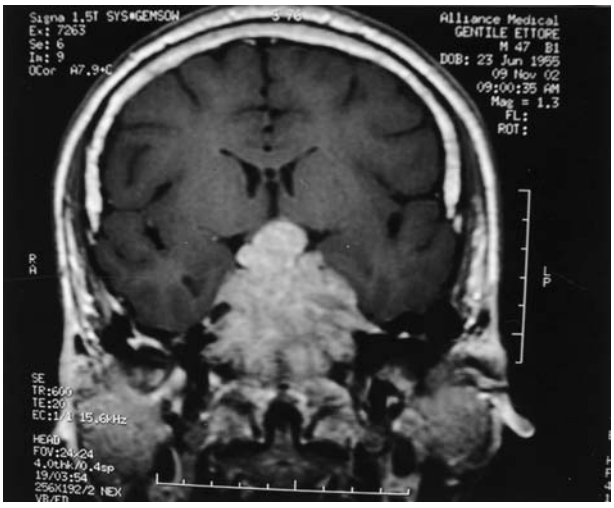

Figure 34-3. Case II: Coronal section of a T1-weighted magnetic resonance image showing a pituitary macroadenoma.

The PRL levels taken at 3 months and 5 months were 200 ng/mL and 60 ng/mL, respectively. The patient continues therapy with cabergoline.

Questions on the Cases

Please read the questions, try to answer them, and reflect on your answers before reading the authors' discussion.

- Is headache a prominent symptom of hypophyseal adenoma?
- What type of headache is typical of prolactinoma?
- What causes the headache-increased PRL levels or prolactinoma?
- What are the possible pathogenetic mechanisms of this type of headache?
- What are the therapeutic possibilities for PRL-secreting hypophyseal tumors?
- Does the headache improve in response to therapy?

Case Discussion

The female patient discussed in Case I presented with a history of worsening tension-type headache, interspersed with rare episodes of migrainous headache. There was an extensive history of menstrual cycle alterations, culminating in hyperprolactinemia-induced amenorrhea. Neuroradiologic investigations led to the diagnosis of a PRL-secreting hypophyseal microadenoma.

The male patient discussed in Case II presented with a recently emerged headache, which normally occurred on wakening and was of a tension-type nature that rapidly worsened, increasing in frequency.

The neurologic studies and the PRL levels supported a diagnosis of a PRL-secreting hypophyseal macroadenoma, otherwise known as a "giant prolactinoma." According to the literature, the term "giant prolactinoma" is used to define prolactinomas that are extremely large, or when a pituitary tumor becomes larger than 4 cm in diameter. Recently, with the increase in the number of reports of invasive adenomas, the term "giant prolactinoma" has been applied to macroprolactinomas associated with serum PRL levels of greater than 3,000 ng/mL, or where there is invasive growth.

Prolactinomas are the most common type of pituitary adenomas. They are relatively rare in men: more than 70% of cases occur in females. In clinical practice, macroadenomas occur less frequently than microadenomas, and macrolactinomas and giant prolactinomas are more commonly found in men whereas microprolactinomas are more common in women. It is unclear if these findings simply reflect a delay in the diagnosis or if they are due to gender-specific differences in tumor pathogenesis. Cannavo and colleagues found

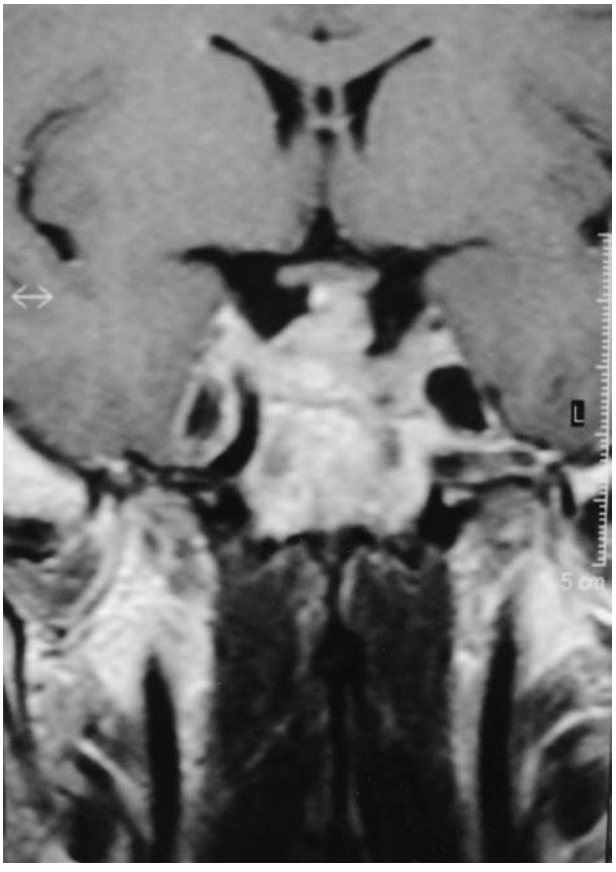

Figure 34-4. Case II: Coronal section of a T1-weighted magnetic resonance image showing macroadenoma after 5 months of cabergoline therapy.

that the most common symptoms of onset of prolactinoma in female adolescents with microadenoma were oligomenorrhea (58%), galactorrhea (58%), or headache (17%). In young men with macroprolactinoma, the most common symptoms of onset were headache (50%), visual impairment (39%), or short stature (16%).

Data obtained from the literature show that headaches are present at onset in 12 to 60% of prolactinomas.

Which is the primary cause of the headache: the hyperprolactinemia or the intracranial tumor with mass effect?

In both cases presented, the headaches resembled tension-type headaches with no prodromal symptoms and became worse over time. In a study by Strebel and colleagues of a group of women with secondary amenorrhea and/or galactorrhea, headache was four times more frequent in patients with prolactinoma than in those without, and tended not to disappear when PRL levels were restored to normal. The hyperprolactinemia was only associated with headaches in the presence of a prolactinoma, and after the regression of the prolactinoma, neither high nor intermediate PRL levels were associated with headache.

These findings would suggest that the mass effect of the prolactinoma is responsible for the headache in women with nonpuerperal hyperprolactinemia. Thus, in spite of its nonspecific nature, headache may indicate the presence of occult prolactinoma in women with secondary amenorrhea and/or galactorrhea. This is further supported by the fact that nonsecreting hypophyseal adenomas producing compressive signs are associated with headache in 70 to 80% of cases.

It is hypothesized that hypophyseal adenoma (and principally the macroadenomas) may give rise to headache through the compression of the sellar diaphragm, or torsion of the cranial and dural blood vessels, with activation of blood vessel nociceptors and stimulation of the meningeal nociceptors. These events could trigger headaches in genetically predisposed patients characterized by a low pain threshold.

In conclusion, a strong association between persistent, apparently tension-type headaches and prolactinoma suggests that headaches are an indicator of prolactinoma and not hyperprolactinemia. Prolactinoma is only rarely associated with migraine-like headache (without aura), and is extremely rare, with a cluster headache-like syndrome.

Management Strategies

Administration of drugs with dopamine agonist activity is the current first-line treatment for both micro- and macroprolactinomas.

The treatment objectives for these tumors are the control of the PRL hypersecretion with return to a normal gonadal state, reduction of the tumor size and any pressure effects, preservation or restoration of other anterior pituitary functions, and prevention of any recurrence or progression of the disease.

In the last two decades, extensive experience has been accumulated using bromocriptine treatment. The use of bromocriptine at its maximum dose of 10 to 20 mg per day allows us to normalize PRL levels in 70 to 80% of cases, to obtain normal ovulatory menses in 80 to 90% of cases, and to reduce tumor size by > 30% in 70 to 80% of cases. The most significant adverse events noted with the use of bromocriptine are digestive disturbances (nausea and vomiting) and orthostatic hypotension, which are often so significant as to require treatment suspension.

Other dopamine agonists that have been studied in recent years are quinagolide and cabergoline. At present, cabergoline is the most frequently used drug, although bromocriptine and quinagolide are effective alternatives. Cabergoline, a selective, long-lasting D2-dopamine agonist, is characterized by an extremely long duration of PRL-lowering action after oral administration. It is administrated at a dose of 0.5 to 1.5 mg, once or twice weekly. It is known that cabergoline is effective at normalizing PRL levels and inducing tumor shrinkage in micro- and macroprolactinomas. Cabergoline is also very well tolerated and can also improve gonadal function and fertility. Ferrari and colleagues reported that treatment with cabergoline for 1 year, in patients with microprolactinomas, resulted in tumor shrinkage in 74% of patients, and resulted in a complete disappearance of the tumor in 37% of cases. In the case of macroprolactinomas, it has been demonstrated that 12 to 24 months of cabergoline treatment induced marked tumor shrinkage, with complete disappearance of the tumor in 26.1 to 36.4% of patients. In one comparative study, Webster and colleagues demonstrated that cabergoline was significantly more effective than bromocriptine at suppressing PRL secretion and at restoring gonadal function, and that cabergoline was also the better tolerated of the two drugs. The evidence available also suggests that tumor shrinkage (92.3%) and tumor disappearance (61.5%) are greater in patients who have not previously been treated with any other dopamine agonists prior to cabergoline use.

An uncommon complication of dopamine agonist treatment of invasive prolactinomas is CSF rhinorrhea as a result of the subsequent shrinking of the tumor. Some prolactinomas are highly sensitive to dopamine agonists, and tumor shrinkage may be quite considerable over a short period. In giant prolactinomas that

invade the skull base, it is therefore wise to begin therapy with the lowest effective dose. In all cases of CSF rhinorrhea, the leakage should be surgically repaired as soon as possible, due to the risk of meningitis. If the patient is unsuitable for surgery, then a complete withdrawal or reduction of the dose of cabergoline could be useful in order to allow tumor re-expansion and to stop the effusion of the CSF.

With the availability of these highly effective treatments, the following include the current indications for surgical intervention:

- Urgent cases of acute chiasmatic compression due to a primary necrosis of the tumor or a secondary necrosis as a result of dopamine agonists treatment
- Women with micro- or macroprolactinomas who wish to become pregnant, in order to reduce the risks of tumor growth
- Patients who are intolerant or resistant to drug treatment (in the literature, 5 to 20% of prolactinomas are reported to be resistant to dopamine treatment)
- A fistula with effusion of CSF, to close the breach

Case Summaries

Two case studies have been presented. The first case is a 35-year-old woman suffering from chronic tension-type headache interspersed with occasional episodes of migraine without aura. The patient had also suffered menstrual cycle alterations since the age of 16 years. At the age of 30 years, she developed amenorrhea with hyperprolactinemia. CT and MRI scans revealed a median-left intrasellar mass of about 8×10 mm.

Treatment with cabergoline resulted in complete resolution of both types of headache and the menstrual cycle and PRL levels returned to normal. The therapy also reduced the volume of the tumor.

The second case is a 47-year-old male who had been suffering from tension-type headaches for almost 3 months which, in the last month prior to recovery, had degenerated to almost daily attacks. The patient had never previously suffered from headaches.

CT and MRI scans showed a large sellar and suprasellar lesion of about 4 cm in diameter with raised serum PRL levels. Treatment with cabergoline had significantly reduced the PRL levels and had also improved the patient's headaches.

The clinical characteristics of the headache–hyperprolactinemia–hypophyseal-adenoma association are discussed, the various diagnostic and treatment possibilities are explored, and the etiology of the headache is considered in the light of several pathogenetic possibilities.

Overview of Headache Associated with Endocranial Tumors

For cerebral tumors in general, headache is the presenting symptom in around 20% of patients, and appears during the course of the disease in about 90% of cases. The head pain in brain tumor is generally deep, more diffuse than pulsating, and becomes progressively more intense. It may be exacerbated by coughing, effort, and sometimes, by standing up. A slow-growing tumor may produce recurring headache over a period of months or even years, when the patient may otherwise be clinically normal.

Typically, tumor headache presents at the beginning of the early stages of the disease: the patient may wake with headache that passes after some minutes or perhaps an hour or so. As the tumor grows, the ventricles may be compressed leading to increased endocranial pressure, so that the headache becomes progressively more intense. At this stage, an attack often begins suddenly, increases rapidly in intensity, and disappears within a few minutes. At height of crisis, the patient often becomes confused. The increased pressure may provoke tonsillar herniation, which is evident as an intense neck-muscle spasm. There may be other, more specific characteristics of the headache, depending on the exact location of the tumor.

Overview of the Problem of Pituitary Tumors

Hypophyseal tumors are relatively common, constituting 6 to 18% of endocranial neoplasms. Small asymptomatic hypophyseal tumors are identified incidentally in 1.5 to 27% of autopsies or from MRI or CT scans, and are called "incidentalomas." It is estimated that asymptomatic microhypophyseal adenomas are present in 10 to 20% of the adult population. These benign tumors can originate from any of the adenohypophyseal cells in the form of prolactinomas (52%), somatotropinomas (27%), or corticotropin-secreting tumors (20%); there are also the very rare TSH-omas and gonadotropinomas.

There are also nonfunctional or nonsecreting hypophyseal tumors, which are classified according to their neuroradiologic characteristics. Macroadenomas have a diameter greater than 10 mm, and the sella turcica is altered when viewed on a radiograph; they may cause neurologic manifestations due to expansion. Microadenomas have a diameter less than 10 mm and are visible only on MRI and high-resolution CT with contrast.

Craniopharyngiomas must also be classified among the hypophyseal tumors. They constitute about 3% of all parasellar tumors, and are congenital neoplasms derived

from remnants of Rathke's pouch. They take the form of encapsulated nodules that often contain cysts that arise from tissue degeneration and contain cholesterol crystals. They are located typically in the hypophyseal stalk and tend to expand toward the hypothalamus. They are nonsecreting, but may give rise to delayed growth and hypogonadism, following disruption of hypothalamic–hypophyseal connections.

Although virtually all hypophyseal adenomas are histologically benign, some present histologic features (increased mitotic figures, cellular pleomorphism, nuclear hyperchromatism, and an increased nucleus–cytoplasm ratio) suggesting malignancy. Such cytologic features are not specific, and only the presence of distant metastases (rare) can be accepted as a criterion of malignancy. However, hypophyseal tumors are more frequently "locally malignant," in the sense that they give rise to mass effects that seriously compromise vital structures such as the optic chiasm and the hypothalamus itself.

In addition to headache, the neurologic manifestations of prolactinomas include bilateral disturbances of vision, and visual field defects in particular; the latter most commonly (60 to 70% of cases) takes the form of bitemporal hemianopsia. Typically, this will begin in the upper quadrants (due to initial compression of the central part of the chiasm). It will extend to the inferior quadrants and eventually involve central vision. When the tumor develops unusually, visual field defects can take a very different course. Although the fundus may appear normal initially, primary optic atrophy may develop (pallid disc with distinct margins) as the tumor expands. In around 5% of cases, eye motility is compromised.

The endocrine symptoms provoked by hypophyseal tumors may be of two types: the first is hyperfunction arising from the pathologically high secretory activity of the tumor cells, and the second is hypopituitarism following destruction of the tissue surrounding the tumor. The symptom of hyperprolactinemia is always to be considered pathologic, except in pregnancy and lactation and when due to medications. It causes galactorrhea, oligomenorrhea, and lack of ovulation in 30 to 80% of women. Although prolactinomas (generally microprolactinomas) are the most frequent cause of hyperprolactinemia, it is important to remember that many other conditions can give rise to high circulating PRL levels, including tumors or lesions that disconnect the hypothalamus from the pituitary, systemic conditions such as chronic renal insufficiency, severe liver disease, primitive hypothyroidism, chest wall lesions, and a polycystic ovary. A mechanism for hyperprolactinemia may be obstruction of the capillaries of the hypophyseal stalk, so that release of hypophyseal dopamine is blocked, in turn resulting in excess PRL secretion by lactotropic cells of the adenohypophysis. Also important are drug-induced prolactinemias, which are most frequently caused by phenothiazines, sulpiride, and neuroleptics in general, but also cimetidine and other H_2 receptor antagonists, estrogenics, and opioids. The idiopathic form called functional hyperprolactinemia is not rare. Prolactinomas are much less common in men than in women. In men, the high PRL levels they produce result in depressed libido, impotence, and more rarely, gynecomastia and galactorrhea.

The diagnosis of prolactinoma is not difficult. It is suspected when there is hyperprolactinemia (more than 100 to 200 ng/mL) in patients with galactorrhea, amenorrhea/oligomenorrhea, gonadal disturbances, or any combination thereof. Other causes of hyperprolactinemia must, however, be excluded (Table 34-1).

It is important to emphasize that blood PRL levels in excess of 200 ng/mL are characteristic of prolactinomas (but also of chronic renal insufficiency and therapy with drugs that affect the dopaminergic pathways, such as benzamides and neuroleptics). By contrast, voluminous sellar lesions (eg, craniopharyngiomas, nonsecreting macroadenomas, and meningiomas) typically induce only moderate prolactinemia (less than 200 ng/mL) by virtue of their interference with hypophyseal-stalk function. To distinguish prolactinoma-induced from drug-induced hyperprolactinemia, it is often useful to test the PRL response to thyrotropin-releasing hormone challenge. There is usually no PRL response in the former, but a strong PRL surge typically occurs in drug-induced hyperprolactinemias. High-resolution CT, with and without contrast, or MRI is necessary to visualize microprolactinomas (and other sellar lesions) and confirm the diagnosis. CT or MRI scan will also reveal the volume of the lesion and any expansion outside the sella turcica. For all hypophyseal adenomas, the key radiologic element is alteration of the sella turcica with asymmetry. Macroadenomas generally destroy the dorsum sellae and enlarge the sella craniocaudally; there may also be calcifications.

Table 34-1. Main Causes of Hyperprolactinemia

Hypophyseal conditions: prolactinomas, acromegaly, Cushing's disease, dissection of the pituitary stalk
Hypothalamic conditions: craniopharyngiomas, meningiomas, dysgerminomas and other tumors, sarcoidosis, histiocytosis X, radiotherapy to neuraxis, vascular lesions
Neurogenic causes: lesions of the thoracic wall or spinal cord, breast stimulation
Drugs: neuroleptics such as phenothiazine, butyrophenones, monoamine oxidase inhibitors, tricyclic antidepressants, reserpine, methyldopa, metoclopramide, verapamil, cocaine
Other: pregnancy, hypothyroidism, renal insufficiency, liver cirrhosis
Idiopathic

Recent studies in diagnostic neuroradiology have shown that MRI, particularly in association with gadolinium contrast, is superior to CT for identifying suspected microadenomas and for assessing the extent of hypophyseal and parahypophyseal lesions in general. An MRI has now become the first-choice modality for diagnosis and treatment planning of these lesions.

Macroadenomas compress the hypophysis, confining it generally to the cranioposterior periphery of the sella. Further growth modifies the form and structure of the bony walls of the sella; eventually, the sella diaphragm yields and the tumor impinges on the chiasm and optic nerves. In the absence of therapy, the tumor expands mainly in the direction of the hypothalamus, raising the floor of the third ventricle, occluding the foramen of Monro, thereby causing endocranial hypertension and hydrocephalus.

The various other complications that arise, particularly when the tumor is not diagnosed or treated sufficiently early, are as follows:

- Blindness, if the tumor attains a large volume within the cranium (giant adenoma)
- Diabetes insipidus, as a result of compression of the hypothalamus
- Jacksonian (partial) epilepsy, if the tumor expands toward the temporal lobe
- Endocranial hypertension with papilledema, following occlusion of the third ventricle
- Generalized epilepsy and psychiatric disturbances, if the tumor expands frontally
- Intratumoral hemorrhage, with abrupt and violent headache, rapid deterioration of sight, ocular paralysis, confusional state, blunting of consciousness, and sometimes, nuchal rigidity; in some patients, tumor can provoke hypophyseal apoplexy, followed by death within hours or days
- Invasion of the surrounding structures, with rapid loss of sight and appearance of signs of invasion of the sinus cavernosus

Overview of Empty Sella Syndrome

This is a condition in which an arachnoid diverticulum expands into the sellar cavity, either because of a primary defect in the sellar diaphragm or as a result of alterations secondary to a hypophyseal tumor, or other pathologic or iatrogenic processes (surgery or radiotherapy) involving the hypothalamohypophyseal region. The presence of CSF within the sella results in remodeling of the walls, and sometimes enlargement of the sellar cavity and compression of the hypophysis. The condition is associated with headache, obesity, and a variety of endocrine manifestations, including hyperprolactinemia, hypopituitarism, and diabetes insipidus.

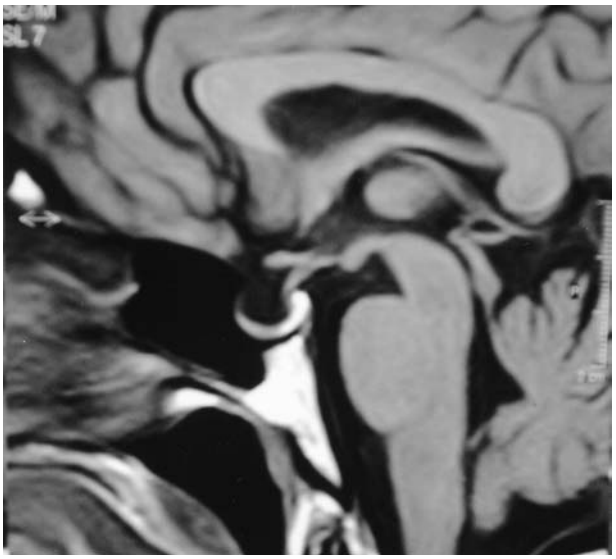

Figure 34-5. Sagittal section of a T1-weighted magnetic resonance image showing an empty sella.

In the absence of specific clinical indications or hormonal alterations, diagnosis depends on radiologic investigation. Radiography may reveal an enlarged sella, but only CT or MRI can demonstrate the presence of CSF within it.

Primary empty sella (Figure 34-5) is benign and does not require therapy. However, the patient should be followed to ensure the early treatment of any deficit arising in the various adenohypophyseal axes.

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Editorial Comments

The cases presented by Drs. Bussone and Moschiano illustrate the neurologic problems encountered in dealing with patients who harbor lesions in the region of the pituitary gland and its proximal structures. Many anatomic and neuroendocrine functions are located in these areas, and thus any direct or indirect disturbance of these structures or perturbations of function can lead to diverse symptoms and signs, as well as abnormal biochemical alterations, such as elevated PRL levels. The associated headaches may be nondescript, or mimic primary headache disorders such as tension-type headache. This is a potentially difficult area for neurologists from both the diagnostic and management points of view; however, guided by reasonable suspicion and careful historic and clinical examinations, along with appropriate neuroimaging, these cases are solvable and ultimately treatable. The editors are grateful to the authors for offering up these cases and for their indepth and erudite overview of these topics. We are sure all experienced neurologists have been involved in the diagnosis and management of such cases, and that these case examples will go a long way to ensuring that such cases continue to be recognized, especially those presenting with headache.

Final diagnosis:

Pituitary adenoma and headache