DIAGNOSIS OF ENDOCRINE DISEASE

Expanding the cause of hypopituitarism

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Abstract

Hypopituitarism is defined as one or more pituitary hormone deficits due to a lesion in the hypothalamic–pituitary region. By far, the most common cause of hypopituitarism associated with a sellar mass is a pituitary adenoma. A high index of suspicion is required for diagnosing hypopituitarism in several other conditions such as other masses in the sellar and parasellar region, brain damage caused by radiation and by traumatic brain injury, vascular lesions, infiltrative/immunological/inflammatory diseases (lymphocytic hypophysitis, sarcoidosis and hemochromatosis), infectious diseases and genetic disorders. Hypopituitarism may be permanent and progressive with sequential pattern of hormone deficiencies (radiation-induced hypopituitarism) or transient after traumatic brain injury with possible recovery occurring years from the initial event. In recent years, there is increased reporting of less common and less reported causes of hypopituitarism with its delayed diagnosis. The aim of this review is to summarize the published data and to allow earlier identification of populations at risk of hypopituitarism as optimal hormonal replacement may significantly improve their quality of life and life expectancy.

Introduction

Hypopituitarism is an uncommon condition with a prevalence of ~46 per 100,000 (1). It is defined as one or more anterior pituitary hormone deficiencies caused by a variety of structural lesions or trauma in the hypothalamic–pituitary region. The diversity of underlying etiology of hypopituitarism is the challenge. The most common cause of hypopituitarism associated with a sellar mass is nonfunctioning pituitary macroadenoma. Hypopituitarism may occur as a consequence of treatment of pituitary adenomas with...
pituitary surgery and/or radiotherapy. Other less prevalent causes of hypopituitarism such as radiation-induced and traumatic brain injury-induced hypopituitarism have been studied more extensively in the recent years. More rarely, vascular causes (pituitary apoplexy, Sheehan’s syndrome, subarachnoid hemorrhage and aneurysm), infiltrative/immune/inflammatory processes such as lymphocytic hypophysitis, sarcoidosis, hemochromatosis and infectious diseases have been associated with hypopituitarism (Table 1).

Whatever the cause, hypopituitary patients usually exhibit nonspecific symptoms/signs. For the clinician, it remains challenging to ascribe specific features for each pituitary hormone deficiency. The recently published guidelines on hormonal replacement in hypopituitarism in adults discuss in great detail the diagnosis and management of hypopituitarism (2).

Hypopituitarism is associated with increased mortality (3). Highest mortality is among younger patients, women and patients with diabetes insipidus (4). A recent study from Sweden shows a decline in mortality in patients optimally replaced including GH replacement therapy (5).

Given the complexity of hypopituitarism, its insidious onset with a delay in the diagnosis by decades, here we review contemporary studies on the less common/unusual causes of hypopituitarism in adults.

### Neoplastic lesions in the sellar and suprasellar region

Hypopituitarism may be the consequence of many sellar and parasellar masses that include meningioma, germinoma, glioma, astrocytoma, chordoma, ganglioneuroma, pituicytoma, pituitary lymphoma, plasmacytoma and metastases (6).

### Pituitary lymphoma

Recently published systematic review of primary sellar lymphoma reported a total of 33 cases of this isolated localization of lymphoma in the sella (7). The vast majority of CNS lymphomas are non-Hodgkin B-cell lymphomas. T-cell lymphoma and NK/T-cell lymphoma are much more rare. Patients do not have systemic lymphoma or other brain lesions. Even rarer is an intravascular large B-cell lymphoma characterized by massive proliferation of lymphoid cells within the small and medium blood vessels. We reported a rare case of hypopituitarism in a patient with intravascular large B-cell lymphoma who after complete hematological remission, reversed hypopituitarism after more than two years (8). Anterior pituitary deficiencies are present in 70% of cases (most have panhypopituitarism), diabetes insipidus is frequent (in 36% of cases), unlike in pituitary adenomas (7). MRI usually shows diffusely enlarged pituitary gland with invasion of both cavernous sinuses mimicking a pituitary adenoma. Usually a preoperative presumptive diagnosis of pituitary adenoma is made and only pathologic evaluation reveals the diagnosis of the pituitary lymphoma. Invasive sellar mass with rapid growth pattern and cranial nerve palsies in an elderly patient (60–70 years) may be discriminative and suggestive of lymphoma.

### Intrasellar plasmacytoma

Intrasellar plasma cell tumors are rare, may mimic nonfunctioning pituitary tumors and may present as the first manifestation of multiple myeloma (9). The radiological and clinical features of sellar plasmacytoma are nonspecific. Cranial nerve affection and intact pituitary function are usually present. The diagnosis is made histologically. The diagnosis of intrasellar plasmacytoma should be suspected in patients with invasive sellar mass, intact anterior pituitary function and cranial nerve palsies in the presence of significant sellar destruction (Fig. 1).

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Pituitary metastasis

Metastatic tumors represent a small fraction of sellar masses. A rise in incidence is due to longer life expectancy in patients with malignant disease and advances in diagnostic imaging. In most cases, the nature of a metastasis to the sellar region is suggested by the primary tumor, but when the primary tumor is unknown, sellar metastasis is diagnosed postmortem. Breast and lung cancers are the most common sources of metastases (10, 11). Pituitary metastases of prostate, renal cell, gastrointestinal, thyroid and pancreatic cancers are far less common. Sudden onset of diabetes insipidus (DI) or rapid deterioration of visual fields, severe headache and acute onset hypopituitarism in a patient aged more than 50 years of age are hallmarks of metastatic pituitary disease. DI is prevalent and the predilection for the posterior lobe involvement is thought to be due to the direct arterial supply. Rapidity of symptom development is a consequence of rapid tumor growth. Pituitary metastases are most often identified in the late stage of the malignant disease, although cases presenting with sellar masses as the first manifestation of malignancy have also been reported (Fig. 2).

Langerhans cell histiocytosis: a neoplastic disease?

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder of unknown etiology characterized by monoclonal proliferation of Langerhans cells derived from myeloid progenitor cells that express CD34 surface antigen. Recently, somatic oncogenic BRAF(V600E) mutations were detected in 25–60% of LCH patients, suggesting that LCH is likely a neoplastic disorder (12). Positive response to a BRAF inhibitor vemurafenib in patients with BRAF(V600E)-mutated LCH is described (13). Central nervous system is affected in 6% of patients with LHC, mostly the hypothalamopituitary region and pineal gland, cerebellum and basal ganglia (14). Patients present with central DI and pituitary stalk thickening. This may be a diagnostic challenge with broad differential diagnosis. Nowadays, fluorodeoxyglucose-positron emission tomography scanning (FDG-PET) is used as a potentially better imaging modality in patients presenting with central DI when the cause is unclear and when pituitary stalk biopsy carries a significant risk. FDG-PET scanning is used for assessing the extent of LHC, its progression and the response to treatment (15). There are reports suggesting the use of chemotherapy as a first-line treatment for these patients after biopsy confirmation of the diagnosis. LCH is rare among the adult population and is most commonly diagnosed in children (Fig. 3).
multipotent hematological precursors or local tissue histiocytes (16). In a recent large French study involving 64 patients with ECD, central diabetes insipidus was reported in 33% of patients with a high percentage of concomitant pituitary involvement (91% of patients had partial anterior pituitary failure) (17). In that study, anterior pituitary dysfunction was more frequent than pituitary MRI anomalies (pituitary stalk thickening). Recently, FDG-PET/CT has been shown to be helpful for locating the pituitary lesion (elevated metabolic activity) and for discovering the multisystem involvement.

**Radiotherapy and traumatic brain injury**

**Cranial irradiation**

Patients treated with cranial irradiation for head and neck tumors, pituitary or hypothalamic tumors, for brain tumors or children who received prophylactic cranial irradiation (childhood cancer survivors) and those who received total body irradiation for various malignancies are at risk of hypopituitarism many years after radiotherapy. There are still controversies about the site and pathophysiology of radiation damage. Radiation-induced damage is primarily hypothalamic and mechanisms include direct injury to hypothalamic neurons, vascular damage with reduction of cerebral flow and fibrosis and altered neurotransmitter input to the hypothalamus from other brain centers (18). The risk of hypopituitarism is time and dose dependent with sequential pattern of hormonal deficiencies. GH deficiency is the most common pituitary hormone deficiency and occurs in 50% of childhood cancer survivors treated with cranial irradiation (19). Why is GH the first pituitary hormone to become deficient after cranial irradiation remains unclear. Lengthy follow-up is needed. Hypopituitarism after cranial radiation is progressive and irreversible and periodical testings of the hypothalamo–pituitary axes are mandatory. Special attention is payed to the excess of second malignant neoplasm after all childhood cancers (20). There is a concern that GH treatment has a causal role in the development of subsequent neoplasms in the CNS in childhood cancer survivors. However, this is a group already at increased risk of malignancy and cranial radiation therapy may be the culprit (Fig. 4).

**Traumatic brain injury (TBI)**

A great number of people are subjected to traumatic brain injury (TBI) worldwide every day. With improvements in emergency and neurosurgical care, there are more TBI survivors nowadays. Traffic injuries are the most prevalent cause of TBI; however, sports-related chronic repetitive head trauma of low intensity (boxing, kickboxing, football and ice hockey) and blast-related mild TBI
among soldiers in military operations are more and more prevalent (21). The greatest challenge in individuals with TBI is early recognition of subtle clinical manifestations of hypopituitarism. The reality may be that TBI is a common cause of hypopituitarism nowadays.

That TBI is underdiagnosed is demonstrated by evidence of postmortem findings in fatal cases. First reports of hypopituitarism caused by TBI were described more than a century ago as case or autopsy reports. Autopsy studies in fatal TBI demonstrated a fairly high prevalence of hypothalamic lesions (22).

Data emerging since 2000 demonstrate the importance of traumatic brain injury (TBI) as a cause of hypopituitarism, but the prevalence varies widely (15–90%) (23, 24) (Fig. 5). TBI is a very common public health problem worldwide, and recent studies have shown that partial hypopituitarism in particular is not rare among TBI victims. Since a great number of people are subjected to TBI around the world every day, even low rates of hypopituitarism mean a very high number of patients with TBI might have hypopituitarism (21).

Studies are heterogeneous regarding TBI severity, preselection procedures for testing, optimal timing after TBI, the diagnostic tests used and the prevalence of hypopituitarism after TBI. Diabetes insipidus occurs particularly in the acute phase of TBI and usually is reversible, whereas partial or complete hypopituitarism may develop during an acute phase or months and years after TBI (21). Recently published analysis of 16 studies with 1291 TBI patients reported the frequency of posttraumatic hypopituitarism in the chronic phase between 15% and 50%, with the decrease to 12% if repeated testing is applied (25). Growth hormone deficiency was found to be the most common deficit (9%), followed by ACTH (6%), LH/FSH (5%) and TSH (1%) deficiencies (25).

Several mechanisms have been suggested to play a role in the development of neuroendocrine abnormalities in TBI: focal shear injury lesions (severed axons), vascular/hypoxic insult and inflammatory changes with activation of the immune system (autoimmunity). Vascular damage (infarctions and hemorrhages) in the hypothalamus is the most likely explanation of acute neuroendocrine dysfunction after TBI. The spreading of proinflammatory response initiated by TBI and axonal injury (diffuse and focal shear) that induces degenerative processes in distant brain regions (progressive demyelination) may explain the evolution of posttraumatic hypopituitarism with time (26).

The TBI severity does not seem to correlate with the prevalence of hypopituitarism (isolated deficiency or panhypopituitarism). Pituitary functions generally improve with time as shown when repeated confirmatory testing was applied (24). In a few cases, new pituitary deficiencies (mainly in the somatotropic and gonadotropic axis) may develop during the follow-up.

Screening is costly and logistically difficult but still remains a great challenge! The most appropriate time for endocrine assessment is 1 year after TBI (21). Any unexplained onset of malaise and generally decreased vital signs with associated stagnation of rehabilitation progress should prompt the clinician to suspect the presence of hypopituitarism (24). We should bear in mind that pituitary dysfunction is an important and modifiable determinant of poor functional outcome after TBI.

**Vascular causes of hypopituitarism are rare**

** Intracranial aneurysm **

Intracranial aneurysms localized predominantly in the internal carotid artery and anterior or posterior communicating artery are rare causes of space-occupying lesions in sellar and suprasellar region, some of them causing hypopituitarism as an acute or chronic complication (27, 28). Aneurysms may present as primary disease or as a complication of pituitary surgery and radiotherapy i.e. traumatic aneurysm. A large retrospective study reported a very low prevalence of intrasellar aneurysm as a cause of hypopituitarism (0.17%) (29). These patients have anterior pituitary
hormone abnormalities and hyperprolactinemia, whereas diabetes insipidus is not reported. Sometimes syndrome of inadequate ADH secretion occurs (27) (Fig. 6).

Subarachnoid hemorrhage (SAH)

Subarachnoid hemorrhage (SAH) is an important cause of morbidity and mortality, and there is evidence that SAH may adversely affect pituitary function in both the acute and chronic phases (30, 31). The prevalence of endocrine dysfunction caused by SAH ranges from 0 to 55% (31, 32). Isolated pituitary hormone deficiencies are more frequently found than multiple. Currently, there is not enough evidence to recommend routine endocrinological evaluation in patients after SAH.

Pituitary apoplexy (PA)

Between 2% and 12% of patients with pituitary adenomas experience clinically manifest apoplexy. PA is a clinical syndrome characterized by sudden onset of acute severe headache accompanied by vomiting, ocular palsies, reduced visual acuity and impaired visual fields with reduced consciousness, all caused by hemorrhage and/or infarction of the pituitary tumor. The diagnosis of apoplexy is delayed because 3 of 4 patients do not have a previous history of pituitary adenoma. Frequently, pituitary apoplexy is subclinical (asymptomatic), is diagnosed on MRI imaging as hemorrhagic or necrotic areas in the pituitary tumor and resolves spontaneously. Precipitating factors for pituitary apoplexy can be identified in about 40% of patients and include major surgery (cardiac and orthopedic), dynamic pituitary tests, anticoagulation treatment, coagulopathies, head injury, dopamine agonists, acute systemic illness, pregnancy and oral contraceptives (33). Hypopituitarism is frequent with the the most crucial deficit of corticotrophin (ACTH) reported in 70% of patients. Apoplexy is a medical emergency requiring prompt commencement of corticosteroid therapy. Further management (conservative or surgical) is recently proposed by the UK guidelines for the management of PA (34).

Sheehan’s syndrome – the postpartum pituitary necrosis

Sheehan’s syndrome or the postpartum pituitary necrosis is the leading cause of hypopituitarism in underdeveloped and developing countries, but it is rare and has become a neglected cause of hypopituitarism in Western society (35). Sheehan’s syndrome is caused by infarction in the pituitary precipitated by massive uterine hemorrhage during the peripartum period or postpartum. Necrotized areas of the pituitary form a fibrous scar. Mechanisms of Sheehan syndrome include autoimmunity and a genetic predisposition. Predisposing factors for postpartum pituitary necrosis or Sheehan’s syndrome are for women who delivered at home, women with severe postpartum hemorrhage who are given a blood transfusion, women with higher number of pregnancies and deliveries, those with genetic factors involved in the coagulation cascade and those with small sella size (35, 36).

Recent Turkish study showed that Sheehan’s syndrome was present in 13.8% of patients with hypopituitarism, compared with 3.1% in developed countries (37, 38). The onset of hypopituitarism is usually insidious, and there is often a delay in diagnosis of several decades (a median delay is 10 years). Patients can present with a wide variety of symptoms (failure to lactate and to resume menses) (39, 40). Most symptoms are nonspecific, that is, patients feel generally unwell and patients are managed by symptoms (secondary amenorrhoea). Appropriate guidance is not provided after an eventful delivery. Hypopituitarism is
progressive, with no recovery of the pituitary function. MRI of the sella reveals partial or complete empty sella in the chronic phase (35).

Glomangioma

There are only a few case reports on glomangioma tumor in the sellar region (41, 42). This is a benign vascular tumor that originates from gomitoli of the hypophyseal portal vessels. Patients present with sellar mass effects (visual field disturbances) and hypopituitarism. Sellar MRI reveals a large contrast-enhancing mass, hyperintense on T1-weighted MRI scans. Pathology evaluation of the surgical specimen reveals that the mass represents glomangioma (Fig. 7).

Snakebite

Snakebites are important health problem in the tropics with significant mortality rate. Hypopituitarism is a rare complication after snakebite. Isolated case reports and small series of patients with acute or chronic hypopituitarism as a complication of snakebite have been published (43, 44).

Immunological/infiltrative/inflammatory diseases

Primary hypophysitis

Primary hypophysitis can be classified into several histologic types: lymphocytic, granulomatous, plasmacytic (immunoglobulin G4 related), necrotizing, xanthomatous and mixed forms (45). The incidence of hypophysitis is 1/10 million per year, and lymphocytic hypophysitis (LH) is the most common form of the disease. It represents less than 1% of sellar lesions and presents with symptoms similar to those seen in patients with pituitary adenoma (46). However, unlike in patients with pituitary adenoma, the early loss of ACTH secretion in lymphocytic hypophysitis is intriguing and remains unexplained. LH predominantly affects females frequently associated with pregnancy and other autoimmune diseases, with spontaneous resolution. Hypophysitis presents on MRI as a symmetric pituitary gland enlargement with homogenous enhancement of the pituitary mass, thickened pituitary stalk and with appearance of dural tail (contrast enhancement of dura adjacent to the pituitary) (47). Empty sella is seen as a characteristic finding on MRI in the late stage of autoimmune hypophysitis (48). Pathogenetic mechanism in primary hypophysitis involves lymphocytic infiltration and autoimmunity, with detected autoantibodies specific for pituitary autoantigens. The disease may resolve spontaneously or rarely be severe with invasion of the cavernous sinus causing ocular nerve palsies. Then, transsphenoidal decompression is needed for diagnostic and therapeutic purposes. In difficult cases when glucocorticoids and surgery fail, immunosuppressive drugs such as azathioprine, methotrexate, cyclosporin A and/or radiotherapy/radiosurgery have been used (49).

Secondary hypophysitis

Secondary hypophysitis is diagnosed in cases of preexisting tumors (germinoma, Rathke's cleft cyst and meningioma) or systemic disease (sarcoidosis, tuberculosis, histiocytosis and Wegener’s granulomatosis) or it can be induced by drugs (CTLA-4 blocking antibodies, anti-PD-1 antibodies and interferon-α) (49) (Fig. 8).

Iplilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, a IgG1 monoclonal antibody against CTLA-4, used for unresectable or metastatic melanoma. CTLA-4 inhibitors (iplilimumab) increase T-cell proliferation and activity. Recently, it was reported that 10–15% of patients treated with ipilimumab may develop hypophysitis as a consequence of immune activation (50). Its pathogenesis is unkonwn. Recently at autopsy, the pituitary glands of six cancer patients who were treated with monoclonal antibody blocking CTLA-4 were analyzed. CTLA-4 antigen was expressed by pituitary endocrine cells with the highest levels found in patients with severe hypophysitis. In patients
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with severe hypophysitis, immune reactions induced aggressive necrotizing form with extensive destruction of the adenohypophyseal architecture (51). Pituitary autoantibodies against thyrotrophs, corticotrophs and gonadotrophs were identified in the sera of patients who developed hypophysitis (52). Ipilimumab-induced hypophysitis appears more frequently in men, in older patients, with higher dose of ipilimumab (50). Pituitary enlargement is usually mild and patients present with headache and fatigue, very rare with visual field defects. Hypopituitarism is diagnosed 2–3 months or later after the initiation of ipilimumab, and most patients have multiple pituitary hormone deficiencies. Central hypothyroidism is the most frequent abnormality, followed by central hypocorticism and hypogonadism. Pituitary enlargement is transient and resolves within 3–8 weeks after the diagnosis of hypophysitis. Hypopituitarism persists and patients must be replaced with glucocorticoid, thyroid hormones and later with sex steroid hormones. Hypopituitarism is a rare complication (1% of patients) of novel family of immune-checkpoint inhibitors, anti-PD-1 monoclonal antibodies (anti-programmed cell death protein 1) (nivolumab and pembrolizumab) used in several malignancies, including melanoma (53, 54).

Other autoimmune forms of hypopituitarism

Recently, a novel clinical entity of acquired combined pituitary hormone deficiencies named ‘anti-PIT-1 antibody syndrome’ was described (55, 56). An autoantibody against pituitary transcription factor PIT-1 (POU1F1) was detected in patients with adult-onset combined GH, PRL and TSH deficiencies.

Sarcoidosis

Sarcoidosis is a chronic multisystemic disorder of unknown etiology characterized by a deposition of epithelioid granulomas without caseation necrosis (57). Central nervous system is affected in 5–15% of cases, and neurosarcoidosis may be the first presenting feature of these systemic diseases (57). Lesions of sarcoidosis in the sellar region are found in the hypothalamus, the stalk and pituitary gland; are rare and account for 1% of sellar masses (58). The classic MRI feature is thickening of the stalk. A large French study on 24 patients with hypothalamo-pituitary sarcoidosis showed that 22/24 patients had anterior pituitary deficiencies, whereas 10 patients had diabetes insipidus (59). Results of this large study analyzed with other 4 studies showed that central hypogonadism was the most common neuroendocrine abnormality (87.5–89%), followed by central hypothyroidism (56%), central hypocorticism (37%) and GH deficiency (30%). One third of patients had panhypopituitarism. With treatment, infiltrative lesions dissapeared, but hypopituitarism persisted (59).

Hemochromatosis and hemosiderosis iron overload

Hereditary hemochromatosis is a genetic disorder of iron overload and organ damage, whereas hemosiderosis may develop as a complication of frequent blood transfusions for severe congenital or acquired anemia. Iron overload presents with two endocrinopathies: central hypogonadism (pituitary) and diabetes mellitus (pancreas) (60). The most common pituitary manifestation of iron overload is hypogonadotropic hypogonadism. The reason why gonadotropes are most sensitive to iron overload is not known (61). Pituitary function can improve after iron depletion therapy.

Wegener’s granulomatosis

Wegener’s granulomatosis is a multisystemic autoimmune disease characterized by inflammation of small-to-medium vesells (necrotizing granulomatous vasculitis), which typically affects the upper respiratory tract, lungs, kidney and skin. Pituitary involvement is a late manifestation of

Figure 8
(A and B) A 12-year-old girl presenting with diabetes insipidus. Sellar MRI scan (A sagittal and B coronal views) shows intense diffuse and homogenous enhancement of sellar mass and stalk thickening. Biopsy revealed hypophysitis secondary to a germinoma.
Wegener granulomatosis (62). Contiguous propagation of the granulomatous inflammatory lesion from the sinuses or orbits appears years after the primary diagnosis. In two recent studies, diabetes insipidus and gonadotropin deficiency were the most common presenting features including moderate hyperprolactinaemia (63, 64). After remission of the Wegener’s granulomatosis, the majority of patients had permanent hypopituitarism, whereas very few recovered pituitary function.

Pituitary infections

Pituitary infections are rare disorders caused by bacteria, tuberculosis, viruses, fungal and parasitic infections (65). They occur by hematogenous spread in immuno-compromised hosts or by contiguous extension from adjacent anatomical sites (meningeal infection, sphenoid sinus, cavernous sinus and skull) or from previous infectious diseases of the CNS of different etiologies and by iatrogenic inoculation during trans-sphenoidal adenoma resection. Risk factors for pituitary infections are diabetes mellitus, tuberculosis, organ transplantation, human immunodeficiency virus (HIV) infection, non-Hodgkin lymphoma, chemotherapy and Cushing’s syndrome. Patients may present with hyponatremia, partial or complete hypopituitarism, hyperprolactinaemia or central diabetes insipidus. Hypopituitarism may occur early in the acute phase of infection or at a late stage as a sequela of infection (66, 67).

Pituitary abscess

Pituitary abscesses are uncommon. About 200 cases are reported. The diagnosis is difficult as symptoms can be unspecific without signs of systemic infection. Very few are diagnosed preoperatively. The most common clinical signs and symptoms are headache, hypopituitarism and diabetes insipidus. Pituitary abscess may develop as a complication; e.g., infection of Rathke’s cleft cyst (68). MRI image suggestive of a pituitary abscess is ring-enhancing cystic sellar/suprasellar mass (69). Surgery is diagnostic, and microbiological cultures are frequently negative (in 50% of cases). The chance of complete hormonal recovery is unlikely and requires continued follow-up.

Tuberculosis

The incidence of tuberculosis is rising both in the developing and developed countries (due to spreading of HIV infection). Incidence and prevalence of intrasellar tuberculosis are expected to grow, given the increasing level of population migration and multi-ethnic nature of societies. Tuberculous meningitis is not rare and tubercular abscess of the brain has been reported (70, 71). Tuberculous lesion may affect the hypothalamus, the pituitary or infundibulum. MRI scan shows thickening of the pituitary stalk or pituitary tuberculoma, which may mimic pituitary adenoma. Previous history of systemic tuberculosis should prompt the diagnosis of pituitary tuberculosis (Fig. 9).

In an Indian study, multiple pituitary hormone deficiency was reported in 29.3% of cases, and no patient had evidence of diabetes insipidus (72). After treatment with antituberculous drugs, the pituitary tuberculoma may disappear with the reversal of hypopituitarism in some cases (71).

Syphilis

The incidence of syphilis has been increasing in Western countries. Neurosyphilis is a rare cause of hypopituitarism that occurs either during acute phase of the disease or as a chronic complication. Recently, the first case of HIV-positive patient with acute neurosyphilis, hypophysitis and hypopituitarism was published (73). The patient was successfully treated with ceftriaxone and replaced with levothyroxine and hydrocortisone. Another case of acute syphilitic hypophysitis and partially reversible

Figure 9

(A and B) A 62-year-old male presenting with systemic tuberculosis. Sellar MRI scan (A sagittal and B coronal views) enlargement of the pituitary and stalk thickening due to tubercular hypophysitis. (C) Computed tomography of the thorax shows pulmonary tuberculosis (TB caverna and pleural effusion).
hypopituitarism in a non-HIV-infected patient was described (74). There is only one publication on chronic *Treponema pallidum* infection, psychosis and hypopituitarism as a late complication of this infection (75).

**Fungal infections**

Fungal infections of the pituitary region are extremely rare, and they usually occur in immunocompromised patients. Fungal pituitary abscess must be considered in the differential diagnosis of a sellar or parasellar mass. They are caused by *Aspergillus*, *Nocardia* or *Candida albicans* and present with central diabetes insipidus, hyperprolactinemia and gonadal dysfunction (76). The posterior pituitary is more often involved because of blood supply coming directly from the systemic circulation. MRI scan shows a sellar mass (Fig. 10). Treatment consists of transsphenoidal operation, followed by antimycotics (amphotericin B, itraconazole, voriconazole and caspofungin). In very rare cases, allergic fungal sinusitis may spread from sinuses to the sellar region. This can occur in immunocompetent patients in whom the overshooting response of eosinophilic granulocytes against fungi causes chronic inflammatory infiltrate, which may erode the sellar floor, displace the pituitary and compresses the pituitary stalk (77).

**Viral hypophysitis**

Various viruses may affect the central nervous system (CNS) causing meningitis (herpes simplex, varicella and enterovirus), meningoencephalitis (herpes simplex, influenza and Coxsackie), encephalitis (tick borne, herpes simplex and cytomegalovirus) or neuroborreliosis. In some cases, partial or complete hypopituitarism may develop either during the acute phase of CNS infection or as a late complication of the infection despite good neurological recovery. A large study investigated patients two years after CNS infections, and isolated corticotroph deficiency was diagnosed in some patients (66). Hemorrhagic fever with renal syndrome (HFRS) is a viral infection caused by Hantaviruses, with acute shock, vascular leakage, thrombocytopenia, hypotension and acute renal failure. Hantaviruses are RNA viruses (serotypes Hantaan, Seul, Puumala and Dobrava–Belgrade) endemic in some parts of Europe and in the Balkans, with outbreaks during wars and with a mortality rate of 6.6%. Hantaviruses are transmitted by rodents. Especially soldiers and farmers are at risk for Hantavirus infection via aerosolized rodent urine, feces or saliva. During the acute phase of the HFRS, the virus has been demonstrated in cerebrospinal fluid with direct pituitary invasion causing viral hypophysitis (78). Viruses may infect the neuroendocrine and vascular endothelial cells of the pituitary and also may cause the pituitary ischemia/infarction with necrosis and subsequent hypopituitarism. Sporadic cases of hypopituitarism as a complication of HFRS and autopsy results are reported (78, 79). In a large retrospective study (60 adults who recovered from HFRS), high prevalence of partial or complete hypopituitarism was found in HFRS survivors (80). In a recent study, a group of patients suffering from
Puumala hantavirus infections were followed long term. Two patients had pituitary hemorrhage during the acute phase of the disease, one of them recovered within a year after the acute illness and the other patient remained hypopituitary (81).

Parasites

Toxoplasma gondii is a widespread parasite that may affect CNS causing chronic infection, in rare cases causing hypopituitarism (82, 83). Two case reports describe patients with an interesting association of prolactinomas with T. gondii infection and one case report describes a patient with nonfunctioning pituitary adenoma associated with Toxoplasma brady cysts (84, 85).

Conclusion

The less common and unusual causes of hypopituitarism are always challenging, and there is a long delay in arriving at the diagnosis. However, a high index of suspicion is needed when patients present with a history of cranial irradiation, head trauma, vascular injury, cancer treated with specific immune therapy causing hypophysitis, history of systemic diseases and bacterial, tuberculosis, viral, fungal and parasitic infections. Once suspected, the diagnosis can be confirmed with pituitary function tests and imaging. The pattern of pituitary hormone deficiencies depends on the nature of the underlying pathological process. Hypopituitarism may be permanent in some instances or transitory in other necessitating repeated assessment. It is unclear who and how often to screen, but certainly, a lengthy follow-up is needed. Some of the so-called uncommon causes of hypopituitarism, such as traumatic brain injury, may in the near future be a common cause, as the number of patients sustaining head trauma is increasing.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

Dr Pekic and Dr Popovic wrote the manuscript.

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