Endotext

INFECTIONS OF THE HYPOTHALAMIC-PITUITARY REGION

Sandra Pekic, MD, Clinic for Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Center Belgrade & School of Medicine, University of Belgrade, Belgrade, Serbia, E-mail: sanendo1@gmail.com

Dragana Miljic, MD, Clinic for Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Center Belgrade & School of Medicine, University of Belgrade, Belgrade, Serbia, E-mail: draganamiljic@yahoo.com

Vera Popovic, MD, School of Medicine, University of Belgrade, Belgrade, Serbia, Dr Subotica 8, 11000 Belgrade, Serbia, Tel: (381) 11 3636300, Fax: (381) 11 2684053, E-mail: popver@gmail.com

Updated September 26, 2024

ABSTRACT

Infections of the hypothalamic-pituitary region are rare lesions, accounting for less than 1% of all pituitary lesions. The clinical diagnosis of these infections can be difficult due to the nonspecific nature of the disease (in many patients without symptoms of infection) and may be misdiagnosed as other pituitary lesions. The risk factors for infections of the hypothalamic-pituitary region are meningitis, paranasal sinusitis, head surgery, and immunocompromised host (diabetes mellitus, Cushing's syndrome, HIV infections, solid organ transplantation, malignancy). Infections can develop in a normal pituitary gland or in pre-existing pituitary lesions (adenoma, Rathke´s cleft cyst, craniopharyngioma). There are several modes of dissemination of the infection to the hypothalamic-pituitary region: hematogenous, iatrogenic (after neurosurgical procedures), and spread from paranasal or nasal cavity (through venous channels of the sphenoid bone). Hypothalamic-pituitary infections most commonly present with visual disturbances and headache, in some cases with fever and leukocytosis. A significant proportion of patients develop hypothalamic-pituitary dysfunction during the acute phase of the disease or months and years after successful antimicrobial therapy. Diagnosis can be challenging and the hypothalamic-pituitary infection with formation of abscess or granuloma may be misdiagnosed as a pituitary tumor. Transsphenoidal drainage followed by antibiotics, antimycotics, or anti-tuberculous drugs are usually efficient in successful treatment of these patients.

INTRODUCTION

Infections of the hypothalamic-pituitary region are rare and commonly described in case reports or small case series. These infections include bacterial infections (pituitary abscess), tuberculosis, fungal, viral, and parasitic infections (Table 1). An infection in the hypothalamic-pituitary region may present as a sella/suprasellar mass and may be misinterpreted as a pituitary tumor. Also, these infections may cause hypopituitarism and be misdiagnosed as post-encephalitic syndrome (1-4).

Table 1. Infectious Agents which Cause Hypothalamic-Pituitary infections
BACTERIA
Gram-positive cocci (Staphylococcus, Streptococcus)
Gram-negative cocci (Neisseria, Esherichia coli , Pseudomonas, Brucella)
Spirochete (Treponema pallidum, Leptospira Interrogans)
Mycobacteria (M. Tuberculosis)
VIRUS
Herpes simplex virus
Varicella zoster virus
Cytomegalovirus
Tick-borne
Hantaan (Hantan) virus
Enterovirus
Neuroborreliosis
SARS-CoV-2 virus
FUNGI
Candida
Aspergillus
PARASITES
Toxoplasma gondii, Echinococcus, Taenia solium

Infections of the hypothalamic-pituitary region may be primary (without an identifiable source) or secondary in origin (3, 5). The more common is a primary pituitary infection, which occurs in previously healthy normal pituitary glands. Secondary pituitary infections occur in patients with a pre-existing lesion in the pituitary region (pituitary adenoma, Rathke´s cleft cyst, craniopharyngioma, or prior pituitary surgery).

There are several sources of infections in the hypothalamic-pituitary region (Table 2). Dissemination from the sphenoid sinus to the pituitary is possible by direct contact and through shared venous drainage.

Table 2. Sources of Infections Spreading to the Hypothalamic-Pituitary Region	
Spread	**Comments**
Hematogenous spread	In immunocompromised host
Direct extension from adjacent anatomical sites	Meningeal infection, sphenoid sinus, cavernous sinus, skull
Previous infectious diseases of the CNS	
Iatrogenic	Surgical intervention in sellar and suprasellar region, tooth extraction

Infections in the hypothalamic-pituitary region are rare and several predisposing factors have been identified (2) (Table 3).

Table 3. Predisposing Factors for Hypothalamic-Pituitary Infections
Diabetes mellitus
Tuberculosis
Solid organ transplantation (renal, liver, etc.)
Human immunodeficiency virus (HIV) infection
Non-Hodgkin lymphoma
Chemotherapy
Cushing´s syndrome
Previous pituitary surgery
Immunosuppressive therapy

Infections of the hypothalamic-pituitary region may present with neurological signs and symptoms and signs of neuroendocrine dysfunction (Table 4).

Table 4. Clinical Features of Hypothalamic-Pituitary Infections	
NEUROLOGICAL SYMPTOMS	**ENDOCRINE DYSFUNCTION**
Headache	Hyponatremia
Visual disturbances	Hypopituitarism
Cranial neuropathy (III, IV, VI)	Hypogonadotropic hypogonadism
	Isolated ACTH deficiency
	Hyperprolactinemia
	Central diabetes insipidus

HYPOTHALAMIC-PITUITARY BACTERIAL INFECTIONS

Pituitary Abscess

Pituitary abscesses are rare pituitary lesions accounting for less than 1% of all pituitary lesions (6, 7). The first case of a pituitary abscess was described in 1848 and since then it has been mostly described in case reports or small series. In two-thirds of patients, pituitary abscesses occur in previously healthy normal glands (primary pituitary abscess) (8). In other patients, there is a preexisting lesion in the pituitary region, such as a pituitary adenoma, Rathke´s cleft cyst, granulomatous hypophysitis, or craniopharyngioma or prior pituitary surgery (secondary pituitary abscess) (5, 9-12). The infection can be caused by hematogenous dissemination or by direct extension from surrounding structures (meningitis, sphenoid sinusitis, cavernous sinus thrombophlebitis) (Table 2). Pituitary surgery and immunocompromised condition are also risk factors for pituitary abscesses (Table 3).

According to the clinical presentation and duration of the disease, pituitary abscesses can be acute, subacute (the disease course less than 1 month), or chronic (disease course longer than 1 month) (13). Infective manifestations (fever, leukocytosis, meningism) have been reported in patients with acute and subacute pituitary abscesses, while chronic pituitary abscesses have a more indolent course.

Many patients with pituitary abscess were misdiagnosed as having a pituitary adenoma, pituitary adenoma with apoplexy, or Rathke´s cleft cyst prior to surgery (14). The diagnosis of this potentially life-threatening disease is based on intraoperative detection of pus and postoperative histopathological analysis. Clinically, pituitary abscesses usually present with neurological signs and symptoms (headache, visual disturbances), signs of neuroendocrine dysfunction (anterior hypopituitarism, AVP deficiency) and signs and symptoms related to infections (fever, leukocytosis) (5, 8, 14). The largest series of primary pituitary abscesses (84 patients) during a 20-year period reported asthenia as the most common clinical presentation (75%), followed with visual impairment (71%), and headache (50%) (6).

Compared to patients with a pituitary adenoma who rarely have neuroendocrine dysfunction, most patients with pituitary abscesses have hypopituitarism (8, 9, 13). The large case series of 66 pituitary abscesses reported anterior pituitary hypopituitarism in 81.8% of patients, while AVP deficiency was diagnosed in 47.9% of patients (8). Nine percent of patients (9.3%) had isolated hypogonadism, 3.7% had isolated ACTH deficiency, 1.8% had isolated hypothyroidism, and 1.8% had combined hypogonadism and ACTH deficiency (8). The possible source of the pituitary infection was found in 14 out of 66 patients (sepsis, sinusitis, pulmonary tuberculosis) (8). Recently published the largest series of 84 patients with primary pituitary abscesses confirmed the high incidence (73%) of preoperative neuroendocrine dysfunction in patients with pituitary abscess: panhypopituitarism in 46%, isolated corticotropic insufficiency in 13%, isolated thyrotropic insufficiency in 10%, isolated gonadotropic insufficiency in 8%, and combined two pituitary axes insufficiencies in 22% (6).

On MRI, pituitary abscesses present as a sella masses, hypointense or isointense on T1-weighted imaging, hyperintense or isointense on T2-weighed imaging, with typical rim enhancement after gadolinium injection, mimicking apoplexy of the pituitary adenoma or other cystic sella lesions (7-9, 13, 15-17; Fig. 1). Diffusion-weighted imaging (DWI) sequences of pituitary abscesses often demonstrate high signal intensity with a reduction in the apparent diffusion coefficient, different from necrotic brain tumors (18).

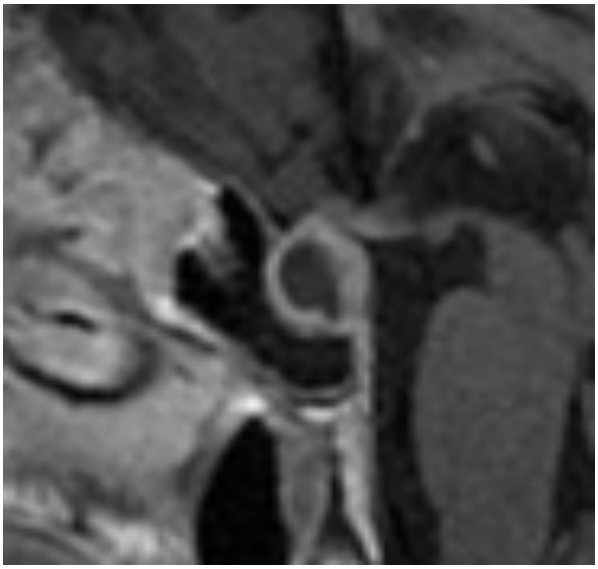

Figure. 1. Pituitary abscess: gadolinium-enhanced T1-weighted MRI scan (sagittal view) shows sellar and suprasellar mass with peripheral contrast enhancement.

Neuroimaging with nuclear medicine investigations (18-FDG PET scan, labelled leukocyte scintigraphy) could increase the preoperative diagnostic rate in challenging patients with pituitary abscess (6).

The majority of patients are treated with transsphenoidal surgery, rarely with a transcranial approach (8). Intraoperatively, pus is found in the sella (19, 20). In patients with secondary pituitary abscesses, the sphenoid sinus is the most common site of extrasellar invasion (5).
On histopathological analysis, there is evidence of acute or chronic inflammation, while Gram staining and bacterial cultures in some cases may identify the infecting pathogen. In most cases, the etiological agents cannot be isolated (6, 12). In the two largest studies on pituitary abscesses, positive results on gram staining or bacterial cultures were found in only 19.7% and 25% of patients, respectively (6, 8). The most prevalent organisms are Gram-positive cocci (*Staphylococcus Aureus* and *Streptococcus* species), but also Gram-negative bacteria (*Neisseria, Esherichia coli, Pseudomonas*, *Brucella*) (5, 6, 9, 21).

Patients with bacterial pituitary abscesses are treated with intravenous and oral antibiotics for three to six weeks to prevent the recurrence of the pituitary abscesses, but in some cases, reoperation was required. In rare cases, AVP deficiency and hypopituitarism are reversible, occasionally followed by secondary empty sella (22). In most cases, neuroendocrine dysfunction and AVP deficiency are irreversible findings (6, 13). The preoperative diagnosis of pituitary abscess represented a protective factor for pituitary function recovery (in 23% of patients) (6).

Although pituitary abscesses are more indolent than other intracranial abscesses, secondary pituitary abscesses in patients with pituitary adenomas (not in Rathke´s cleft cyst) is associated with high mortality rate (26%) due to the dissemination of the infection or meningitis (5). In patients with infected Rathke´s cleft cyst, clinical manifestations are commonly subacute, without septic symptoms (9, 11).

Recently published the largest systematic review of 488 cases of pituitary abscess examined presentation, radiological findings, endocrinological abnormalities, treatment, and mortality of these patients (23). The most common symptoms were headache (76%) and visual field loss. The median time from onset of

symptoms to presentation was 120 days. Symptoms and biochemical markers of infection were absent in 57% of cases. The appearance of hypointensity on T1 weighted images and hyperintensity on T2 weighted images, as well as peripheral contrast enhancement of the pituitary on MRI were the most common radiological findings. Fifty-five percent of patients had negative culture results. Endocrinological abnormalities were present in 84.5% of cases (panhypopituitarism in 41%, AVP deficiency in 25%) and persisted in over half of cases. The mortality rate was 5.1%, with delayed presentation increasing risk of mortality (23).

Hypopituitarism Caused by Treponema Pallidum Infection (Syphilis)

Syphilis is a sexually transmitted chronic bacterial infection caused by Treponema Pallidum which progresses over years through a series of clinical stages. Syphilis is a well-recognized cause of hypopituitarism, with granulomatous hypophysitis (noncaseating giant cell granuloma), syphilitic gumma in sella region, or congenital syphilis causing hypothalamic-pituitary dysfunction. The first cases of hypopituitarism caused by syphilis were described almost 70 years ago, mostly in postmortem cases (24). The use of penicillin caused a decline in syphilis presentations and late complications, including congenital syphilis. Nowadays, the incidence of syphilis has been rising again and this sexually transmitted disease should be considered again in the differential diagnosis of neurological, psychiatric, and endocrine cases in high-income countries in risk groups (HIV positive patients, men-men relationships, crack cocaine users, and among intravenous drug users) (25, 26). Spirochete *Treponema Pallidum* is also described as a cause of hypophysitis and pituitary gland enlargement with hypopituitarism, mostly in immunocompromised patients (HIV-infected patients) with syphilitic meningitis (27). Syphilis may cause a sella mass with suprasellar extension mimicking a pituitary tumor and causing severe headache and hypopituitarism (28). The diagnosis is confirmed by positive treponemal antibody or by detection of *Treponema Pallidum* by immunohistochemistry or PCR on the resected pituitary. This disorder is treated with antibiotics.

Hypopituitarism Caused by Leptospira Interrogans Infection (Sy Weil)

Leptospirosis is a common tropical febrile, zoonotic infectious disease caused by spirochete *Leptospira Interrogans*. The bacteria are spread through the urine of infected animals (cattle, pigs, horses, dogs, rodents, wild animals). Humans can become infected through contact with urine or other body fluids from infected animals or through contact with water, soil, or food contaminated with the urine of infected animals. This disease presents with hepatorenal syndrome and systemic hemorrhagic manifestations. The first case of pituitary apoplexy and panhypopituitarism caused by leptospirosis in a 56-year-old male with type 2 diabetes mellitus was recently published (29). The patient developed fever, nausea, vomiting and acute kidney injury. Leptospirosis was diagnosed by positive leptospira antibody test, and he started treatment with antibiotics. After five days of admission, he developed signs and symptoms of pituitary apoplexy. A brain MRI scan was consistent with apoplexy in a pituitary adenoma (the mass showed T2W hyper intensity and TIW isointensity with hypo intense areas which suggested hemorrhage). The patient developed hypopituitarism and was replaced with glucocorticoids and thyroid hormones. The follow-up MRI scan showed resolution of the hemorrhagic focus and regression of the pituitary adenoma. The proposed mechanism of pituitary apoplexy is platelet dysfunction (caused by uremia and directly by leptospira) and non-inflammatory vasculopathy (increased vascular permeability due to disruption of endothelial cell-cell junctions, cell retraction and opening of intercellular gaps) (29). Leptospirosis clinically presents very similar to another zoonosis, hantavirus infection, is more common worldwide and serology and PCR are

necessary to distinguish between these two diseases (30).

Hypothalamic-Pituitary Dysfunction Following Bacterial CNS Infections

Hypothalamic-pituitary dysfunction is a well-recognized complication of acute infectious diseases of the central nervous system (meningitis and encephalitis) and may occur in the acute phase or in the late stage of these diseases (1, 4, 31, 32). The clinical spectrum of neuroendocrine dysfunction may range from an isolated pituitary hormone deficiency to panhypopituitarism. Endocrine dysfunction in the acute phase of meningitis may return to normal after the acute period or be irreversible (32). The most common deficit is isolated GH deficiency diagnosed 6-48 months after the infection, reported at a rate of 28.6% (31).

Hypopituitarism following acute viral or bacterial meningitis in children is not as common as in adulthood (33, 34). The GH neurosecretory dysfunction (low IGF1 with normal GH response in clonidine test) was found in 3 out of 37 children tested at least 6 months following the diagnosis of bacterial meningitis (34). There are rare case reports on hypopituitarism during acute meningitis caused by *Streptococcus Group B* or sepsis caused by *Salmonella enteritidis* in a neonatal period (35, 36).

The pathophysiological mechanism responsible for hypothalamic-pituitary dysfunction following acute meningitis is not fully understood. In some patients, anti-pituitary and anti-hypothalamus antibodies are detected (37). It is proposed that acute infection provokes an autoimmune process and may cause axonal injury with consequent neuroendocrine dysfunction (38).

Idiopathic Granulomatous Inflammation of the Cavernous Sinus - the Tolosa-Hunt Syndrome

Tolosa-Hunt syndrome is defined as an idiopathic granulomatous inflammation of the cavernous sinus, therefore not infectious in origin, with variable extension into the superior orbital fissure/orbital apex, usually unilateral. The diagnosis is made by exclusion of other more common causes of cavernous sinus lesions (thrombosis, tumors, fungal infections, systemic granulomatous diseases-sarcoidosis, tuberculosis, Wegener´s granulomatosis) (39). In less than 5% of cases it can be bilateral, mimicking a pituitary adenoma in imaging studies (40). The etiology of Tolosa-Hunt syndrome is not fully understood. The disease is characterized by nonspecific granulomatous inflammation with infiltration of lymphocytes and plasmocytes. The patient presents with severe unilateral orbital pain and ipsilateral ocular motor neuropathy. The paralysis of one or more cranial nerves passing through the cavernous sinus (III, IV, VI) develops with orbital pain after less than 2 weeks. The signs of infection (fever, leukocytosis) are usually present. Granulomatous inflammation develops within the cavernous sinus causing acute throbbing orbital pain and disordered eye movement. Brain MRI scan demonstrate the inflammation in the cavernous sinus, orbital apex, and rarely in the sella. MR venography of the brain is important to exclude cavernous sinus thrombosis. Treatment consists of high dose corticosteroids and antibiotics. Refractory and steroid-intolerant cases may be treated with immunosuppressants (Methotrexate or Azathioprine) and gamma knife radiotherapy (41). Periorbital pain intensity is rapidly decreasing and resolving within 72h, while the resolution of ophthalmoplegia improves gradually and takes a longer time to resolve (several weeks) (42). If the patient is not responding to standard therapy, biopsy of the lesion is necessary to exclude other diseases, such as lymphoma.

Hypothalamic-Pituitary Tuberculosis

The incidence of tuberculosis is rising not only in developing countries, but also in developed countries, especially given the increasing population migration. Mortality has begun to increase after years of decline and since 2018 more than 7 million people have died of tuberculosis (43). Extrapulmonary tuberculosis may affect the brain causing tuberculous meningitis and tuberculoma of the central nervous cases. Tuberculous meningitis has a tendency to affect basal parts of the brain from where it can spread to the sella region. In rare cases, CNS tuberculosis may present as tuberculous hypophysitis or sella/suprasellar tuberculoma mimicking a pituitary adenoma or pituitary apoplexy (44-48). It may occur in the absence of systemic tuberculosis, but the majority of patients have a past history of pulmonary tuberculosis or tuberculosis of other organs (spine). Tuberculosis may affect the hypothalamus, pituitary, paranasal sinuses (sphenoid sinus), or tuberculoma may be located only in the pituitary stalk. Hypothalamic-pituitary dysfunction and AVP deficiency during the acute phase or years after recovery from acute tuberculous meningitis suggests a more destructive and more extensive hypothalamic and pituitary damage compared to other causes of acute viral and bacterial meningitis.

A significant proportion of patients with sella tuberculoma or tuberculous meningitis develop hypothalamic-pituitary dysfunction. In 18 cases of histologically proved sella tuberculoma (5 of them with past history of tuberculosis), 5 patients had hypopituitarism and 3 had hyperprolactinemia due to pituitary stalk compression (44).

In patients with tuberculous meningitis half of them developed neuroendocrine dysfunction: hyperprolactinemia (23-50% of patients), hypocortisolism (13-43%), hypothyroidism (17-31%), hypogonadism (34%), SIADH (10%) (4, 49, 50) during the acute phase. Multiple hormonal axes were affected in 23.5% of patients (49, 50). In young adult patients who survived tuberculous meningitis in childhood and were tested several years after recovery, hypopituitarism was diagnosed in 20% of patients (51). This is a consequence of fibrosis, gliosis, and calcification in the hypothalamus and pituitary after recovery of active tuberculous brain infection. In rare cases, pituitary function recovered after successful treatment with anti-tuberculous drugs (52).

The diagnosis of sella tuberculoma is a challenge, especially in cases without systemic tuberculosis. The signs and symptoms are nonspecific: fever, neurological abnormalities (headache, visual disturbances), and neuroendocrine dysfunction (44, 53). Sellar tuberculoma on MRI scans presents as thickening of the pituitary stalk or abnormal enhancement pattern of the sella lesion (54) (Fig. 2).

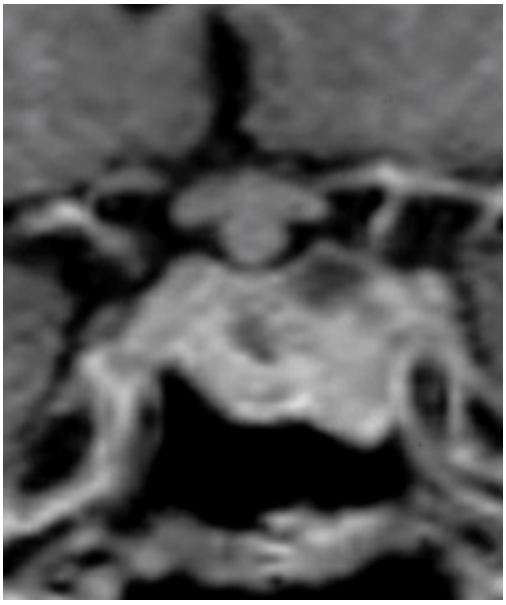

Figure 2. Tubercular hypophysitis: sellar MRI scan (coronal view) shows stalk thickening.

If the correct diagnosis is established, anti-tuberculosis drugs are effective and surgery is not indicated for tuberculous hypophysitis. With surgery the histological examination shows granulomas with central caseous necrosis surrounded by giant Langhans cells. In cases in whom Ziehl-Nielsen staining for acid fast bacilli and the culture on Lowenstein-Jensen media are negative, PCR for detection of mycobacterial DNA in tissue or CSF may help.

HYPOTHALAMIC-PITUITARY FUNGAL INFECTIONS

Hypothalamic-pituitary fungal infections are extremely rare and occur usually in immunocompromised patients (diabetes mellitus, granulocytopenia, solid organ transplantation). There are only few case reports of Candida and Aspergillus sella abscesses and reviews of fungal sellar abscesses (55-61). Aspergillus is a ubiquitous saprophitic fungus found in the nasal mucosa of healthy people and patients with chronic sinusitis. This fungus may cause CNS infection, such as meningitis, encephalitis, brain abscess, subdural abscess, pituitary abscess, and mycotic arteritis with thrombosis and aneurysm (61-63). Fungal sella abscesses have a nonspecific presentation, with neurological signs and symptoms (headache, visual disturbances) and hypothalamic-pituitary dysfunction. Sella MRI images are nonspecific, with a T1W hypointense or isointense mass with rim enhancement and may be misdiagnosed as a pituitary adenoma (Fig. 3). It is proposed that a low signal on T2W images due to iron deposition may be a more specific sign of fungal abscess (58, 64; Fig. 4). Diagnosis of fungal pituitary abscess is made by histopathological finding (Grocott–Gömöri's methenamine silver stain demonstrates septate fungal hyphae), cultivation, or PCR identification of fungus DNA. A combination of transsphenoidal drainage and antifungal therapy (liposomal Amphotericin B, itraconazole, voriconazole, caspofungin, micafungin) can result in a good prognosis (55, 59, 60, 65). Endocrinopathies caused by fungal abscess have a low rate of recovery (59).

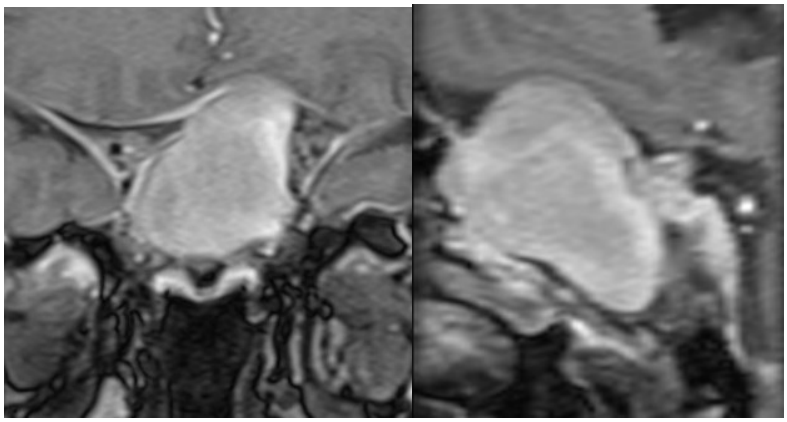

Figure 3. Fungal pituitary abscess spreading from fungal sinusitis: sellar MRI scan (coronal and sagittal views) shows a large sellar mass pushing the pituitary upwards.

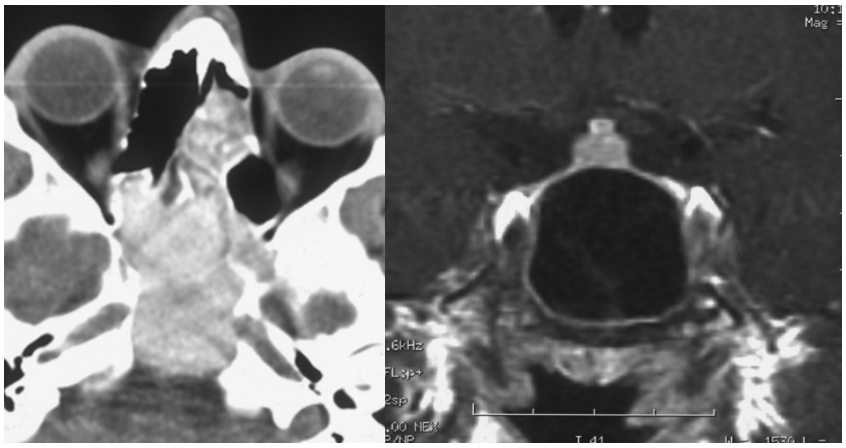

Figure 4. Fungal infections in the sella: a) CT scan of the sinuses (axial view) shows a large sellar mass, erosion in sellar floor, propagation of the pathological process and opacification of the sinuses, and B) sellar MRI scan (coronal view) shows a giant hypointense lesion in the sellar region.

An unusual form of allergic fungal sinusitis which expands from the sphenoid sinus through a bone erosion to the sella in immunocompetent patient has been described (64) (Fig. 4). This patient had hyperprolactinemia (in the setting with no pituitary stalk compression), which resolved after successful transsphenoidal operation followed by anti-mycotics and corticosteroids (64). It is speculated that fungal glucans may directly stimulate glucan-specific receptors on somatomammotroph cells to stimulate prolactin secretion (66).

HYPOTHALAMIC-PITUITARY VIRAL INFECTIONS

Hypothalamic-pituitary dysfunction (hypopituitarism and cranial diabetes insipidus) may develop in the acute phase of viral infections of the CNS (meningitis and encephalitis) or in the late stage of these diseases (1, 31, 32). Infectious agents which cause CNS viral infections are listed in Table 5.

Table 5 – Infectious Agents Which Cause CNS Viral Infections	
MENINGITIS	**ENCEPHALITIS**
Herpes virus	Tick-borne
Varicella	Herpes simplex
Enterovirus	Cytomegalovirus
	Neuroborreliosis
SARS-CoV-2 virus	SARS-CoV-2 virus

The investigation of hypothalamic-pituitary function at least 6 months after recovery from mild-to-moderate meningitis/encephalitis showed that 21% patients developed isolated corticotroph deficiency, while other neuroendocrine abnormalities or AVP deficiency were not found (1).

Hantavirus

Hemorrhagic fever with renal syndrome (HFRS), caused by Hantaviruses in the Bunyaviridae family, is an endemic zoonotic disease transmitted by rodents. There are several serotypes of these RNA viruses causing systemic infection, milder form called nephropathia endemica (Puumala) or severe form (Dobrava, Belgrade). The disease is endemic in Europe (Balkans, Finland, Germany) and Asia (Korea), where several outbreaks have been recorded. Farmers and solders are exposed to the virus by inhalation of infected rodent urine, feces, or saliva. Hantavirus infiltrates the vascular system causing increased capillary permeability, renal failure, thrombocytopenia, hemorrhage, fever, hypotension, and shock. The mortality rate is 6.6%. Autopsy findings reported a slightly enlarged pituitary with ischemia/infarction, hemorrhage, and necrosis (67-69). Direct viral invasion was confirmed in the pituitary causing viral hypophysitis (69). Hypothalamic-pituitary dysfunction has been reported during the acute phase of the disease or after long-term follow-up (70-79). A milder form of HFRS infection caused by Puumala virus (nephropathia epidemica) is associated with a lower incidence of hypopituitarism (80). It is speculated that in some patients with no signs of hemorrhage in the sella, hantavirus may cause autoimmune hypophysitis and hypopituitarism (81). Sellar MRI imaging in hypopituitary patients reveals an edematous pituitary gland or increased signal intensity in the pituitary due to hemorrhage during the acute phase, while pituitary atrophy and secondary empty sella develops months and years after acute infection (76, 79-81) (Fig 5). A retrospective study of 60 adults who had recovered from HFRS reported that 18% of patients developed hypopituitarism (82). Ten percent of patients had a single pituitary deficit (three GH, two gonadal, and one adrenal), and 8.3% had multiple pituitary hormone deficiencies (82). In rare cases, HFRS may cause injury of the pituitary stalk or acute/subacute hemorrhage in the pituitary gland and AVP deficiency with panhypopituitarism (30, 77).

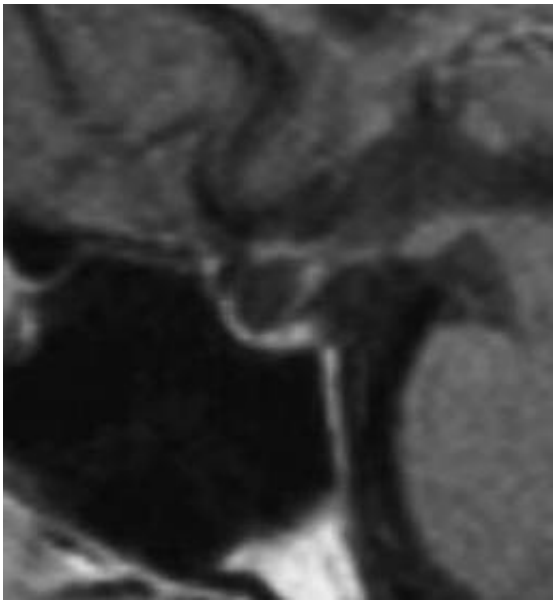

Figure. 5. Hemorrhagic fever with renal syndrome: sellar MRI scan (sagittal view) shows pituitary atrophy and secondary empty sella.

SARS-CoV-2

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a cause of coronavirus disease 2019 (COVID-19). This virus is responsible for a variety of clinical manifestations, ranging from an asymptomatic stage to severe pulmonary disease (respiratory distress syndrome) and various extrapulmonary manifestations, including endocrine axes (83-85).

SARS-CoV-2 is a neuroinvasive virus which enters the brain through the nasopharyngeal epithelium via the olfactory nerve, passes through the blood-brain barrier, or enters the brain through the median eminence where this barrier is absent (86). Neurons, glial cells, and cerebrovascular endothelia cells, as well as hypothalamus and pituitary cells express an angiotensin-converting enzyme 2 (ACE2) receptor responsible for the entry of the virus into these cells which induce neuroinflammation (86-88). SARS-CoV-2 virus is also detected in cerebrospinal fluid of patients with encephalitis caused by COVID-19 and in pituitary tissues from patients who died from SARS (89, 90). SARS-CoV-2 is responsible for a variety of neurological complications, including headache, anosmia, confusion, ataxia, neuropathic pain, seizures, and delirium (89).

There are also indirect systemic effects of COVID-19 virus: an altered immune response (cytokine storm), infection-induced thrombocytopenia, platelet dysfunction, coagulopathy (hypercoagulable state), endothelitis, and endothelial dysfunction (91). All these direct and indirect systemic effects of COVID-19 virus may be responsible for ischemic and hemorrhagic vascular syndromes, affecting also the hypothalamo-pituitary region. Another possible indirect effect of COVID-19 may be mediated by cytokines that can trigger hypothalamo-pituitary inflammation with consequent neuroendocrine dysfunction (92). Also, it has been shown that SARS-CoV-2 express an amino-acid sequence that mimics human ACTH and induces the production of autoantibodies against ACTH causing cortisol insufficiency and inadequate adrenal response to the stress (83).

SARS-CoV-2 infection may involve the hypothalamo-pituitary axis causing pituitary apoplexy, hypophysitis, and hyponatremia (83, 85, 91, 93-97).

There are nine case reports of pituitary adenoma (6 males/3 females, between 27 and 56 years of age, eight with pituitary macroadenoma) and two series of three patients with pituitary adenomas, complicated by apoplexy during COVID-19 infection (93-102). In one patient this occurred during the third trimester of pregnancy. Four patients had transsphenoidal surgery and recovered, one patient had transcranial resection, three patients were conservatively managed, and one patient died 12 hours after admission. There is also a report of a 65-year-old woman with no underlying pituitary disease who developed acute pituitary apoplexy one month after the initial diagnosis of COVID-19 (103). She developed anterior hypopituitarism with no evidence of AVP deficiency. An MRI pituitary scan showed the resolution of intrapituitary hemorrhage, with normal size of the pituitary gland after six months of follow-up. A small case series reported three patients with previously unknown pituitary adenoma complicated by apoplexy during COVID-19 infection: a 54-year-old female with null cell adenoma, a 52-year-old and a 56-year-old men, both obese with hypertension, both with a lactotroph pituitary adenoma (94). In another series of three patients with pituitary macroadenoma complicated with apoplexy following a symptomatic COVID-19 infection, two of these patients' developed symptoms of pituitary apoplexy days following the viral infection, whereas the third patient developed pituitary apoplexy after a 2-month period (96).

In some patients COVID-19 caused an acute lymphocytic hypophysitis with temporal evolution of symptoms, suggesting an immune-mediated parainfectious pattern of disease (104, 105). An 18-year-old previously healthy girl with a history of symptomatic COVID-19 three weeks prior to the acute onset of headache and dizziness, presented with diffuse thickening and enlargement of the infundibulum with homogenous contrast enhancement of the pituitary (104). She was treated with glucocorticoids with a significant clinical improvement on day 3 and complete resolution of MRI finding on day 5. A similar case is a 16-year-old girl who presented with headaches, polyuria/polydipsic syndrome, and impaired visual acuity three weeks after COVID-19 infection (105). She had pituitary enlargement on MRI, was treated with methylprednisolone and improved on day 5. Such a rapid headache resolution after steroid treatment suggests a transitory acute hypophysitis, an immune-mediated process, triggered by viral infection. It has been hypothesized that SARS-CoV-2 may induce hypothalamo-pituitary autoimmunity, with positive anti-hypothalamus (AHA) and anti-pituitary (APA) antibodies (106). The current results in the literature about antigens which are targets of AHA and APA are still contradictory (83). It is possible that patients at high-risk for such a complication are carriers of specific HLA alleles. The human leukocyte antigen (HLA) complex has a central role in the recognition and presentation of viral antigens to immune system. HLA class I molecules mediates innate defense strategies against viral infection. HLA-c 04:01, DRB1 08, DQB1 06 carriers have an increased risk of a severe clinical course of COVID-19 and generate a robust response and susceptibility to autoimmune diseases (107-110).

Even these two acute pituitary disorders (pituitary apoplexy with transition to acute hypophysitis) can occur in patients with COVID-19 and preexisting unknown pituitary adenoma (97).

Several cases of AVP deficiency as a late complication of COVID-19 infection were published (111-114). All patients (2 males/2 females, 28-60 years of age) suddenly developed polyuria, nocturia, and polydipsia four to eight weeks after the diagnosis of COVID-19 infection. In one of the published cases, a sellar MRI scan showed an enlarged pituitary with an absent posterior pituitary bright spot on T1W

images associated with thickening of the pituitary stalk of 3.5 mm suggesting infundibulo-neurohypophysitis (113). Other pituitary hormone evaluations were normal. They were treated with oral desmopressin.

A case of a young woman with hypothalamic amenorrhea following COVID-19, with normal appearance of the sella turcica and regular dimensions of the pituitary was reported (95). This case suggests clinicians need to follow patients for possible delayed neuroendocrine dysfunctions after COVID-19 infection.

Hyponatremia was reported in 30-60% of patients with SARS-CoV-1 infection and was associated with worse outcomes and increased mortality (115). The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) was the most common reason for hyponatremia, followed by adrenal insufficiency (116).

There are also data on the association between COVID-19 vaccination and the subsequent development of pituitary diseases (85, 117-120). A recently published systematic review analyzed 23 case reports of post COVID-19 vaccination pituitary diseases: hypophysitis in 9 patients, pituitary apoplexy in 6 patients, SIADH in 5 patients, and isolated ACTH deficiency in two patients (119). Symptoms of pituitary disease typically occurred shortly (several days) after vaccine administration and the pathogenetic mechanisms potentially include molecular mimicry, vaccine adjuvants, and vaccine-induced thrombotic thrombocytopenia (83, 119). The presence of ACE2 receptors in the hypothalamo-pituitary system contributes to these post vaccinal pituitary diseases. Isolated infundibulo-neurohypophysitis and AVP deficiency or isolated ACTH deficiency may also develop several days after immunization with BNT 162b2 mRNA COVID-19 vaccine (117, 121). In some cases of panhypopituitarism and AVP deficiency due to hypophysitis after COVID-19 vaccination, hormonal secretion partially improved during follow-up (120).

Other Viruses

Cytomegalovirus, herpes simplex, varicella zoster, and enterovirus have also been described in very rare cases of central diabetes insipidus, mainly in immunocompromised patients with encephalitis (such as HIV infection, Cushing´s syndrome, lymphoma or immunosuppressive therapy) (122-126). Direct cytomegalovirus invasion and reduction in the number of AVP and oxytocin cells was confirmed in the hypothalamus (123).

HYPOTHALAMIC-PITUITARY PARASITIC INFECTIONS

Parasitic infections of the pituitary are rare and infections in the sellar region caused by *Toxoplasma gondii*, Echinococcus species, and *Taenia solium* have been reported anecdotally (4).

Toxoplasmosis is a worldwide zoonosis, caused by the protozoan parasite *Toxoplasma gondii*. This is one of the most common parasitic infections of warm-blooded animals and humans. Approximately one-third of humans have been exposed to *T. gondii*, mostly with no serious diseases, except in immunocompromised patients (HIV) and congenital toxoplasmosis. Two cases of prolactinomas with *T. gondii* cysts among tumor cells were reported (127). Toxoplasmosis is the most common CNS infection in immunocompromised patients (patients with HIV infection) and may cause hypopituitarism, accompanied by focal neurological deficits, headache, and fever (128, 129). The brain MRI shows lesions with significant enhancement of T2W images and peri-lesional edema, which may be misdiagnosed as intracranial metastasis. The diagnosis is based on brain biopsy with confirmed presence of *T. gondii* by PCR. Infection with *T. gondii* is treated with antimicrobial therapy and with hormone replacement therapy as needed.

The most common parasitic infestation of the brain is neurocysticercosis, caused by *Taenia solium*. A systematic review of 23 patients with intrasellar cysticercosis reported endocrine abnormalities (panhypopituitarism, hyperprolactinemia, AVP deficiency, and isolated hypothyroidism) in 56% of the affected population (130). These infections present with a cystic mass in the sella with hypopituitarism caused by compression, subarachnoid cysts, obstructive hydrocephalus, or neuroinflammation (ventriculitis, focal arachnoiditis) (4, 131). Neurocysticercosis may involve the pituitary stalk too (132). Transsphenoidal or transcranial operation is required for the definitive histopathological diagnosis and cure, because medical therapy with praziquantel is usually ineffective (130).

ACKNOWLEDGMENT

This study was supported by The Science Fund of the Republic of Serbia, Grant No: 7754282 — Prediction, prevention and patient's participation in diagnosis of selected fungal infections (FI): an implementation of a novel method for obtaining tissue specimens, "FungalCaseFinder".

REFERENCES

1. Schaefer S, Boegershausen N, Meyer S, Ivan D, Schepelmann K, Kann PH. Hypothalamic-pituitary insufficiency following infectious diseases of the central nervous system. Eur J Endocrinol 2008; 158: 3-9.
2. Pekic S, Popovic V. Alternative causes of hypopituitarism: traumatic brain injury, cranial irradiation, and infections. Handb Clin Neurol 2014; 124: 271-290
3. Pekic S, Popovic V. Diagnosis of endocrine disease: Expanding the cause of hypopituitarism. Eur J Endocrinol 2017; 176: R269-R282
4. Das L, Dutta P. Approach to the patient: a case with an unusual cause of hypopituitarism. J Clin Endocrinol Metab 2023; 108: 1488-1504.
5. Awad AJ, Rowland NC, Mian M, Hiniker A, Tate M, Aghi MK. Etiology, prognosis, and management of secondary pituitary abscesses forming in underlying pituitary adenomas. J Neurooncol 2014; 117: 469–476
6. Mallereau CH, Todeschi J, Ganau M, Cebula H, Bozzi MT, Romano A, Le Van T, Ollivier I, Zaed I, Spatola G, Nannavecchia B, Mahoudeau P, Djennaoui I, Debry C, Signorelli F, Ligarotti GKI, Pop R, Baloglu S, Fasciglione E, Goichot B, Bund C, Gaudias J, Proust F, Chibbaro S. Pituitary abscess: a challenging preoperative diagnosis-a multicenter study. Medicina (Kaunas) 2023; 59: 565.
7. Naser PV, Papadopoulou P, Teuber J, Kopf S, Jesser J, Unterberg AW, Beynon C. Characteristics of inflammatory and infectious diseases of the pituitary gland in patients undergoing transsphenoidal surgery. Pituitary 2023; 26: 451-460.
8. Gao L, Guo X, Tian R, Wang Q, Feng M, Bao X, Deng K, Yao Y, Lian W, Wang R, Xing B. Pituitary abscess: clinical manifestations, diagnosis and treatment of 66 cases from a large pituitary center over 23 years. Pituitary 2017; 20: 189-194
9. Aranda F, Garcia R, Guarda FJ, Nilo F, Cruz JP, Callejas C, Balcells ME, Gonzales G, Rojas R, Villanueva P. Rathke´s cleft cyst infections and pituitary absesses: case series and review of the literature. Pituitary 2021; 24: 374-383
10. Warmbier J, Lüdecke DK, Flitsch J, Buchfelder M, Fahlbusch R, Knappe UJ, Kreutzer J, Buslei R, Bergmann M, Heppner F, Glatzel M, Saeger W. Typing of inflammatory lesions of the pituitary. Pituitary 2022; 25: 131-142.
11. Rabiei MM, Ebrahimzadeh K, Davoudi Z, Bidari Zerehpoosh F, Javandoust Gharehbagh F, Sedaghati R, Lotfollahi L, Kalhor F, Alavi Darazam I. A case of pituitary gland abscess associated with granulomatous hypophysitis. BMC Neurol 2023; 23:11.
12. Inoue E, Kesumayadi I, Fujio S, Makino R, Hanada T, Masuda K, Higa N, Kawade S, Niihara Y, Takagi H, Kitazono I, Takahashi Y, Hanaya R. Secondary hypophysitis associated with Rathke's cleft cyst resembling a pituitary abscess. Surg Neurol Int 2024; 15: 69.
13. Liu F, Li G, Yao Y, Yang Y, Ma W, Li Y, Chen G, Wang R. Diagnosis and management of pituitary abscess: experiences from 33 cases. Clin Endocrinol 2011; 74: 79-88
14. Xue Q, Shi X, Fu X, Yin Y, Zhou H, Liu S, Sun Q, Meng J, Bian L, Tan H, He H. Pituitary abscess: a descriptive analysis of a series of 19 patients-a multi-center experience. Eur J Med Res 2024; 29: 262.

15. Vates GE, Berger MS, Wilson CB. Diagnosis and management of pituitary abscess: a review of twenty-four cases. J Neurosurg 2001; 95: 233-241
16. Ciappetta P, Calace A, D'Urso PI, De Candia N. Endoscopic treatment of pituitary abscess: two case reports and literature review. Neurosurg Rev 2008; 31: 237-246
17. Dalan R, Leow MK. Pituitary abscess: our experience with a case and a review of the literature. Pituitary 2008; 11: 299-306
18. Takao H, Doi I, Watanabe T. Diffusion-weighted magnetic resonance imaging in pituitary abscess. J Comp Assist Tomogr 2006; 30: 514–516
19. Zhang X, Sun J, Shen M, Shou X, Qiu H, Qiao N, Zhang N, Li S, Wang Y, Zhao Y. Diagnosis and minimally invasive surgery for the pituitary abscess: A review of twenty nine cases. Clin Neurol Neurosurg 2012; 114: 957-961
20. Al Salman JM, Al Agha RAMB, Helmy M. Pituitary abscess. BMJ Case Rep 2017; 2017
21. De la Peña-Sosa G, Cabello-Hernández AI, Gómez-Ruíz RP, Gómez-Sámano MA, Gómez-Pérez FJ. Pituitary abscess causing panhypopituitarism in a patient with neurobrucellosis: case report. AACE Clin Case Rep 2023; 10: 10-13.
22. Pepene CE, Ilie I, Mihu D, Stan H, Albu S, Duncea I. Primary pituitary abscess followed by empty sella syndrome in an adolescent girl. Pituitary 2010; 13: 385-389
23. Stringer F, Foong YC, Tan A, Hayman S, Zajac JD, Grossmann M, Zane JNY, Zhu J, Ayyappan S. Pituitary abscess: a case report and systematic review of 488 cases. Orphanet J Rare Dis 2023; 18: 165.
24. Oelbaum M. Hypopituitarism in male subjects due to syphilis with a discussion of androgen treatment. Q J Med 1952; 83: 249–264
25. Noblett J, Roberts E. The importance of not jumping to conclusions: syphilis as an organic cause of neurological, psychiatric and endocrine presentations. BMJ Case Rep 2015; 2015.
26. Hook EW 3rd. Syphilis. Lancet 2017; 389: 1550-1557.
27. Spinner CD, Noe S, Schwerdtfeger C, Todorova A, Gaa J, Schmid RM, Busch DH, Neuenhahn M. Acute hypophysitis and hypopituitarism in early syphilitic meningitis in a HIV-infected patient: a case report. BMC Infect Dis 2013; 13: 481-484
28. Bricaire L, Van Haecke C, Laurent-Roussel S, Jrad G, Bertherat J, Bernier M, Gaillard S, Groussin L, Dupin N. The great imitator in endocrinology: a painful hypophysitis mimicking a pituitary tumor. J Clin Endocrinol Metab 2015; 100: 2837-2840
29. Gohil J, Gowda A, George T, Easwer HV, George A, Nair P. Pituitary apoplexy and panhypopituitarism following acute leptospirosis. Pituitary 2021 May 21; 1-5.
30. Schwab S, Lissmann S, Schafer N, Isaak A, Klingmuller D, Attenberger U, Eis-Hubinger AM, Hofmann J, Strassburg C, Lutz P. When polyuria does not stop: a case report on an unusual complication of hantairus infection. BMC Infectious Diseases 2020; 20: 713
31. Tanriverdi F, Alp E, Demiraslan H, Dokmetas HS, Unluhizarci K, Doganay M, Casanueva FF, Kelestimur F. Investigation of pituitary functions in patients with acute meningitis: a pilot study. J Endocrinol Invest 2008; 31: 489-491
32. Tsiakalos A, Xynos ID, Sipsas NV, Kaltsas G. Pituitary insufficiency after infectious meningitis: a prospective study. J Clin Endocrinol Metab 2010; 957: 3277-3281
33. Giavoli C, Tagliabue C, Profka E, Senatore L, Bergamaschi S, Rodari G, Spada A, Beck-Peccoz P, Esposito S. Evaluation of pituitary function after infectious meningitis in childhood. BMC Endocr Disord 2014; 14: 80-84
34. Karadag-Oncel E, Cakir M, Kara A, Gonc N, Cengiz AB, Ozon A, Ciftci E, Alikasifoglu A, Ceyhan M, Kandemir N. Evaluation of hypothalamic-pituitary function in children following acute bacterial meningitis. Pituitary 2015; 18: 1-7
35. Saranac L, Bjelakovic B, Djordjevic D, Novak M, Stankovic T. Hypopituitarism occurring in neonatal sepsis. J Pediatr Endocrinol Metab 2012; 25: 847-848
36. Ferreira AS, Fernandes AL, Guaragna-Filho G. Hypopituitarism as consequence of late neonatal infection by Group B streptococcus: a case report. Pan Afr Med J 2015; 20: 308
37. Tanriverdi F, De Bellis A, Teksahin H, Alp E, Bizzarro A, Sinisi AA, Bellastella G, Paglionico VA, Bellastella A, Unluhizarci K, Doganay M, Kelestimur F. Prospective investigation of pituitary functions in patients with acute infectious meningitis: is acute meningitis induced pituitary dysfunction associated with autoimmunity? Pituitary 2012; 5: 579–588
38. Gerber J, Seitz RC, Bunkowski S, Bruck W, Nau R. Evidence for frequent focal and diffuse acute axonal injury in human bacterial meningitis. Clin Neuropathol 2009; 28: 33–39
39. Bhatkar S, Goyal MK, Takkar A, Mukherjee KK, Singh P, Singh R, Lal V. Cavernous sinus syndrome: A prospective study of 73 cases at a tertiary care centre in Northern India. Clin Neurol Neurosurg 2017; 155: 63-69
40. Swiątkowska-Stodulska R, Stodulski D, Babinska A, Piskunowicz M, Sworczak K. Bilateral Tolosa-Hunt syndrome mimicking pituitary adenoma. Endocrine 2017; 58: 582-586
41. Lee JM, Park JS, Koh EJ. Gamma Knife radiosurgery in steroid-intolerant Tolosa-Hunt syndrome: case report. Acta Neurochir (Wien) 2016; 158: 143-145
42. Arshad A, Nabi S, Panhwar MS, Rahil A.Tolosa-Hunt syndrome: an arcane pathology of cavernous venous sinus. BMJ Case Rep 2015; 2015.
43. Reid M, Agbassi YJP, Arinaminpathy N, Bercasio A, Bhargava A, Bhargava M, Bloom A, Cattamanchi A, Chaisson R, Chin D, Churchyard G, Cox H, Denkinger CM,

Ditiu L, Dowdy D, Dybul M, Fauci A, Fedaku E, Gidado M, Harrington M, Hauser J, Heitkamp P, Herbert N, Herna Sari A, Hopewell P, Kendall E, Khan A, Kim A, Koek I, Kondratyuk S, Krishnan N, Ku CC, Lessem E, McConnell EV, Nahid P, Oliver M, Pai M, Raviglione M, Ryckman T, Schäferhoff M, Silva S, Small P, Stallworthy G, Temesgen Z, van Weezenbeek K, Vassall A, Velásquez GE, Venkatesan N, Yamey G, Zimmerman A, Jamison D, Swaminathan S, Goosby E. Scientific advances and the end of tuberculosis: a report from the Lancet Commission on Tuberculosis. Lancet 2023; 402: 1473-1498.

44. Sharma MC, Arora R, Mahapatra AK, Sarat-Chandra P, Gaikwad SB, Sarkar C. Intrasellar tuberculoma--an enigmatic pituitary infection: a series of 18 cases. Clin Neurol Neurosurg 2000; 102: 72-77

45. Arunkumar MJ, Rajshekhar V. Intrasellar tuberculoma presenting as pituitary apoplexy. Neurol India 2001, 49: 407-410

46. Husain N, Husain M, Rao P. Pituitary tuberculosis mimicking idiopathic granulomatous hypophysitis. Pituitary 2008; 11: 313-315

47. Aziz Khan A, Ahuja S, Malik S, Naaz S, Zaheer S. Pituitary tuberculoma with panhypopituitarism masquerading as a pituitary adenoma. Neuropathology 2023; 43: 496-499.

48. Elfarissi MA, Dahamou M, Dehneh Y, Lhamlili M, Khoulali M, Oulali N, Moufid F. Pediatric sellar-suprasellar tuberculosis: A case report and review of the literature. Surg Neurol Int 2023; 14: 379.

49. Dhanwal DK, Vyas A, Sharma A, Saxena A. Hypothalamic pituitary abnormalities in tubercular meningitis at the time of diagnosis. Pituitary 2010; 13: 304-310

50. More A, Verma R, Garg RK, Malhotra HS, Sharma PK, Uniyal R, Pandey S, Mittal M. A study of neuroendocrine dysfunction in patients of tuberculous meningitis. J Neurol Sci 2017; 379: 198-206

51. Lam KS, Sham MM, Tam SC, Ng MM, Ma HT. Hypopituitarism after tuberculous meningitis in childhood. Ann Intern Med 1993; 118: 701-706

52. Tanimoto K, Imbe A, Shishikura K, Imbe H, Hiraiwa T, Miyata T, Ikeda N, Kuroiwa T, Terasaki J, Hanafusa T. Reversible hypopituitarism with pituitary tuberculoma. Intern Med 2015; 54: 1247-1251

53. Jain A, Dhanwal DK, Kumar J. A rare case of pituitary tuberculoma-diagnosed and managed conservatively. Pituitary 2015; 18: 579-580

54. Bonifacio-Delgadillo D, Aburto-Murrieta Y, Salinas-Lara C, Sotelo J, Montes-Mojarro I, Garcia-Marquez A. Clinical presentation and magnetic resonance findings in sellar tuberculomas. Case Rep Med 2014; 2014: 961913.

55. Liu W, Chen H, Cai B, Li G, You C, Li H. Successful treatment of sellar aspergillus abscess. J Clin Neurosci 2010; 17: 1587-1589

56. Vijayvargiya P, Javed I, Moreno J, Mynt MA, Kotapka M, Zaki R, Ortiz J. Pituitary aspergillosis in a kidney transplant recipient and review of the literature. Transpl Infect Dis 2013; 15(5): E196-200

57. Hong W, Liu Y, Chen M, Lin K, Liao Z, Huang S. Secondary headache due to aspergillus sellar abscesssimulating a pituitary neoplasm: case report and review of literature. Springerplus 2015; 4: 550

58. Lim JC, Rogers TW, King J, Gaillard F. Successful treatment of pituitary sella Aspergillus abscess in a renal transplant recipient. J Clin Neurosci 2017; 45: 138-140

59. Strickland BA, Pham M, Bakhsheshian J, Carmichael J, Weiss M, Zada G. Endoscopic endonasal transsphenoidal drainage of a spontaneous candida glabrata pituitary abscess. World Neurosurg 2018; 109: 467-470

60. Saffarian A, Derakhshan N, Taghipour M, Eghbal K, Roshanfarzad M, Dehghanian A. Sphenoid Aspergilloma with headache and acute vision loss. World Neurosurg 2018; 115: 159-161

61. Funakoshi S, Nishiyama M, Komori M, Hyodo M, Kawanishi Y, Ueba T, Fujimoto S, Terada Y. Hypopituitarism due to CNS Aspergillus infection. Intern Med 2024 Mar 11. doi: 10.2169/internalmedicine.3390-23.

62. Iplikcioglu AC, Bek S, Bikmaz K, Ceylan D, Gökduman CA. Aspergillus pituitary abscess. Acta Neurochir 2004; 146: 521-524

63. Hao L, Jing C, Bowen C, Min H, Chao Y. Aspergillus sellar abscess: case report and review of the literature. Neurol India 2008; 56: 186-188

64. Pekic S, Arsenijevic VA, Gazibara MS, Milojevic T, Pendjer I, Stojanovic M, Popovic V. What lurks in the sellar? Lancet 2010; 375: 432

65. Ouyang T, Zhang N, Wang L, Jiao J, Zhao Y, Li Z, Chen J. Primary Aspergillus sellar abscess simulating pituitary tumor in immunocompetent patient. J Craniofac Surg 2015; 26: e86-88

66. Breuel KF, Kougias P, Rice PJ, Wei D, De Ponti K, Wang J, Laffan JJ, Li C, Kalbfleisch J, Williams DL. Anterior pituitary cells express pattern recognition receptors for fungal glucans: implications for neuroendocrine immune involvement in response to fungal infections. Neuroimmunomodulation 2004; 11: 1–9

67. Klebanov IuA. Analysis of fatal outcome in hemorrhagic fever with renal syndrome. Klin Med 1990; 68: 64-67

68. Valtonen M, Kauppila M, Kotilainen P, Lähdevirta J, Svartbäck CM, Kosunen O, Nurminen J, Sarkkinen H, Brummer-Korvenkontio M. Four fatal cases of nephropathia epidemica. Scand J Infect Dis 1995; 27: 515-517

69. Hautala T, Sironen T, Vapalahti O, Pääkkö E, Särkioja T, Salmela PI, Vaheri A, Plyusnin A, Kauma H. Hypophyseal hemorrhage and panhypopituitarism during

Puumala Virus Infection: Magnetic Resonance Imaging and detection of viral antigen in the hypophysis. Clin Infect Dis 2002; 35: 96-101

70. Lim TH, Chang KH, Han MC, Chang YB, Lim SM, Yu YS, Chun YH, Lee JS. Pituitary atrophy in Korean (epidemic) hemorrhagic fever: CT correlation with pituitary function and visual field. Am J Neuroradiol 1986; 7: 633-637
71. Forslund T, Saltevo J, Anttinen J, Auvinen S, Brummer-Korvenkontio M, Korhonen A, Poutiainen M. Complications of nephropathia epidemica: three cases. J Intern Med 1992; 232: 87-90
72. Settergren B, Boman J, Linderholm M, Wiström J, Hägg E, Arvidsson PA. A case of nephropathia epidemica associated with panhypopituitarism and nephrotic syndrome. Nephron 1992; 61: 234-235
73. Suh DC, Park JS, Park SK, Lee HK, Chang KH. Pituitary hemorrhage as a complication of hantaviral disease. Am J Neuroradiol 1995; 16: 175-178
74. Park JE, Pyo HJ. Delayed onset of diuresis in a patient with acute renal failure due to hemorrhagic fever with renal syndrome who also developed anterior hypopituitarism. Clin Nephrol 1996; 46: 141-145
75. Kim NH, Cho JG, Ahn YK, Lee SU, Kim KH, Cho JH, Kim HG, Kim W, Jeong MH, Park JC, Kang JC. A case of torsade de pointes associated with hypopituitarism due to hemorrhagic fever with renal syndrome. J Korean Med Sci 2001; 16: 355-359
76. Pekic S, Cvijovic G, Stojanovic M, Kendereski A, Micic D, Popovic V. Hypopituitarism as a late complication of hemorrhagic fever. Endocrine 2005; 26: 79-82
77. Ahn HJ, Chung JH, Kim DM, Yoon NR, Kim CM. Hemorrhagic fever with renal syndrome accompanied by panhypopituitarism and central diabetes insipidus: a case report. J Neurovirol 2018; 24: 382-387
78. Bhoelan S, Langerak T, Noack D, van Schinkel L, van Nood E, van Gorp ECM, Rockx B, Goeijenbier M. Hypopituitarism after Orthohantavirus infection: what is currently known? Viruses 2019; 11: 340
79. Shi S, Zhang A, Zhang J, Xu S. Partial hypopituitarism with ACTH deficiency as the main manifestation as a complication of hemorrhagic fever with renal syndrome. BMC Endocr Disord 2024; 24: 61.
80. Partanen T, Koivikko M, Leisti P, Salmela P, Pääkkö E, Karttunen A, Sintonen H, Risteli L, Hautala N, Vapalahti O, Vaheri A, Kauma H, Hautala T. Long-term hormonal follow-up after human Puumala hantavirus infection. Clin Endocrinol 2016; 84: 85-91
81. Tarvainen M, Mäkelä S, Mustonen J, Jaatinen P. Autoimmune polyendocrinopathy and hypophysitis after Puumala hantavirus infection. Endocrinol Diabetes Metab Case Rep 2016; 2016
82. Stojanovic M, Pekic S, Cvijovic G, Miljic D, Doknic M, Nikolic-Djurovic M, Micic D, Hrvacevic R, Nesic V, Popovic V. High risk of hypopituitarism in patients who recovered from hemorrhagic fever with renal syndrome. J Clin Endocrinol Metab 2008; 93: 2722-2728
83. Bellastella G, Cirillo P, Carbone C, Scappaticcio L, Maio A, Botta G, Tomasuolo M, Longo M, Pontillo A, Bellastella A, Esposito K, De Bellis A. Neuroimmunoendocrinology of SARS-CoV 2 Infection. Biomedicines 2022; 10: 2855.
84. Clarke SA, Abbara A, Dhillo WS. Impact of COVID-19 on the endocrine system: a mini-review. Endocrinology 2022; 163: bqab203.
85. Capatina C, Poiana C, Fleseriu M. Pituitary and SARS CoV-2: An unremitting conundrum. Best Pract Res Clin Endocrinol Metab 2023; 37: 101752
86. Chigr F, Merzouki M, Najimi M Autonomic brain centers and pathophysiology of COVID-19. ACS Chem Neurosci 2020; 11: 1520–1522
87. Conde Cardona G, Quintana Pajaro LD, Quintero Marzola ID, Ramos Villegas Y, Moscote Salazar LR. Neurotropism of SARS-CoV 2: mechanisms and manifestations. J Neurol Sci 2020; 412: 116824
88. Han T, Kang J, Li G, Ge J, Gu J. Analysis of 2019-nCoV receptor ACE2 expression in different tissues and its significance study. Ann Transl Med 2020; 8: 1077
89. Abdel-Mannan O, Eyre M, Lobel U, Bamford A, Eltze C, Hameed B, Hemingway C, Hacohen Y. Neurologic and radiographic findings associated with COVID-19 infection in children. JAMA Neurol 2020; 77: 1440-1445
90. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z, Geng J, Cai J, Han H, Li X, Kang W, Weng D, Liang P, Jiang S. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004; 203: 622–630
91. Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A. COVID-19 and the pituitary. Pituitary, 2021; 24: 465-481
92. Puig-Domingo M, Marazuela M, Yildiz BO, Giustina A. COVID-19 and endocrine and metabolic diseases. An updated statement from the European Society of Endocrinology. Endocrine 2021; 72: 301-316.
93. Ghosh R, Roy D, Roy D, Mandal A, Dutta A, Naga D, Benito-Leon J. A rare case of SARS-CoV-2 infection associated with pituitary apoplexy without comorbidities. J Endocr Soc 2021; 5: bvaa203.
94. Martinez-Perez R, Kortz MW, Carroll BW, Duran D, Neill JS, Luzardo GD, Zachariah MA. Coronavirus disease 2019 and pituitary apoplexy: a single-center case series and review of the literature. World Neurosurg 2021; 152: e678-e687.
95. Facondo P, Maltese V, Delbarba A, Pirola I, Rotondi M, Ferlin A, Cappelli C. Case report: hypothalamic amenorrhea following COVID-19 infection and review of literatures. Front Endocrinol (Lausanne) 2022; 13: 840749.
96. Hazzi C, Villemure-Poliquin N, Nadeau S, Champagne PO. SARS-CoV-2 infection, a risk factor for pituitary apoplexy?

A case series and literature review. Ear Nose Throat J 2024; 103: 153S-161S.

97. Racca G, D'Agnano S, Fasano N, Gianotti L. Pituitary apoplexy with transition to acute hypophysitis in a patient with Sars-CoV-2 pneumonia. JCEM Case Rep 2022; 1: luac010.

98. Bray DP, Solares CA, Oyesiku NM. Rare case of a disappearing pituitary adenoma during the COVID-19 pandemic. World Neurosurg 2020; 146: 148-149

99. Chan JL, Gregory KD, Smithson SS, Naqvi M, Mamelak AN. Pituitary apoplexy associated with acute COVID-19 infection and pregnancy. Pituitary 2020; 23: 716-720

100. Santos CDSE, Filho LMDCL, Santos CAT, Neill JS, Vale HF, Kurnutala LN. Pituitary tumor resection in a patient with SARSCoV-2 (COVID-19) infection. A case report and suggested airway management guidelines. Braz J Anesthesiol 2020; 70: 165-170

101. Solorio-Pineda S, Almendarez-Sanchez CA, Tafur-Grandett AA, Ramos-Martinez GA, Huato-Reyes R, Ruiz-Flores MI, Sosa-Najera A. Pituitary macroadenoma apoplexy in a severe acute respiratory syndrome-coronavirus-2-positive testing: causal or casual? Surg Neurol Int 2020; 11: 304

102. LaRoy M & McGuire M. Pituitary apoplexy in the setting of COVID-19 infection: a case report. Am J Emerg Med 2021; S0735-6757(21)00153-4

103. Bordes SJ, Phang-Lyn S, Najera E, Borghei-Razavi H, Adada B. Pituitary apoplexy attributed to COVID-19 infection in the absence of an underlying macroadenoma or other identifiable cause. Cureus 2021; 13: e13315

104. Joshi M, Gunawardena S, Goenka A, Ey E, Kumar G. Post COVID-19 Lymphocytic hypophysitis: a rare presentation. Child Neurol Open 2022; 9: 2329048X221103051

105. Zerrouki D, Assarrar I, Rami I, Rouf S, Latrech H. Coronavirus as a trigger of lymphocytic hypophysitis in an adolescent girl: An exceptional case report. Int J Surg Case Rep 2024; 115: 109218.

106. Gonen MS, De Bellis A, Durcan E, Bellastella G, Cirillo P, Scappaticcio L, Longo M, Bircan BE, Sahin S, Sulu C, Ozkaya HM, Konukoglu D, Kartufan FF, Kelestimur F. Assessment of neuroendocrine changes and hypothalamo-pituitary autoimmunity in patients with COVID-19. Horm Metab Res 2022; 54: 153-161.

107. Littera R, Campagna M, Deidda S, Angioni G, Cipri S, Melis M, Firinu D, Santus S, Lai A, Porcella R, Lai S, Rassu S, Scioscia R, Meloni F, Schirru D, Cordeddu W, Kowalik MA, Serra M, Ragatzu P, Carta MG, Del Giacco S, Restivo A, Deidda S, Orrù S, Palimodde A, Perra R, Orrù G, Conti M, Balestrieri C, Serra G, Onali S, Marongiu F, Perra A, Chessa L. Human leukocyte antigen complex and other immunogenetic and clinical factors influence susceptibility or protection to SARS-CoV-2 infection and severity of the disease course. The Sardinian experience. Front Immunol 2020; 11: 605688.

108. Weiner J, Suwalski P, Holtgrewe M, Rakitko A, Thibeault C, Müller M, Patriki D, Quedenau C, Krüger U, Ilinsky V, Popov I, Balnis J, Jaitovich A, Helbig ET, Lippert LJ, Stubbemann P, Real LM, Macías J, Pineda JA, Fernandez-Fuertes M, Wang X, Karadeniz Z, Saccomanno J, Doehn JM, Hübner RH, Hinzmann B, Salvo M, Blueher A, Siemann S, Jurisic S, Beer JH, Rutishauser J, Wiggli B, Schmid H, Danninger K, Binder R, Corman VM, Mühlemann B, Arjun Arkal R, Fragiadakis GK, Mick E, Comet C, Calfee CS, Erle DJ, Hendrickson CM, Kangelaris KN, Krummel MF, Woodruff PG, Langelier CR, Venkataramani U, García F, Zyla J, Drosten C, Alice B, Jones TC, Suttorp N, Witzenrath M, Hippenstiel S, Zemojtel T, Skurk C, Poller W, Borodina T, Pa-Covid SG, Ripke S, Sander LE, Beule D, Landmesser U, Guettouche T, Kurth F, Heidecker B. Increased risk of severe clinical course of COVID-19 in carriers of HLA-C*04:01. EClinicalMedicine 2021; 40: 101099.

109. Hovhannisyan A, Madelian V, Avagyan S, Nazaretyan M, Hyussyan A, Sirunyan A, Arakelyan R, Manukyan Z, Yepiskoposyan L, Mayilyan KR, Jordan F. HLA-C*04:01 affects HLA class I heterozygosity and predicted affinity to SARS-CoV-2 peptides, and in combination with age and sex of armenian patients contributes to COVID-19 severity. Front Immunol 2022; 13: 769900.

110. Yasuda S, Suzuki S, Yanagisawa S, Morita H, Haisa A, Satomura A, Nakajima R, Oikawa Y, Inoue I, Shimada A. HLA typing of patients who developed subacute thyroiditis and Graves' disease after SARS-CoV-2 vaccination: a case report. BMC Endocr Disord 2023; 23: 54.

111. Rajevac H, Bachan M, Khan Z. Diabetes insipidus as a symptom of covid-19 infection: case report. Chest 2020, 158: A2576

112. Sheikh AB, Javed N, Sheikh AA, Upadhyay S, Shekhar R. Diabetes insipidus and concomitant myocarditis: a late sequelae of COVID-19 infection. J Investig Med High Impact Case Rep 2021, 9: 1–4

113. Misgar RA, Rasool A, Wani AI, Bashir MI. Central diabetes insipidus (infudibuloneuro hypophysitis): a late complication of COVID-19 infection. J Endocrinol Invest 2021 Jul 3; 1-2

114. Yavari A, Sharifan Z, Larijani B, Mosadegh Khah A. Central diabetes insipidus secondary to COVID-19 infection: a case report. BMC Endocr Disord 2022; 22: 134.

115. Berni A, Malandrino D, Corona G, Maggi M, Parenti G, Fibbi B, Poggesi L, Bartoloni A, Lavorini F, Fanelli A, Scocchera G, Nozzoli C, Peris A, Pieralli F, Pini R, Ungar A, Peri A. Serum sodium alterations in SARS CoV-2 (COVID-19) infection: impact on patient outcome. Eur J Endocrinol 2021; 185: 137-144.

116. Khidir RJY, Ibrahim BAY, Adam MHM, Hassan RME, Fedail ASS, Abdulhamid RO, Mohamed SOO. Prevalence and outcomes of hyponatremia among COVID-19 patients: A

systematic review and meta-analysis. Int J Health Sci (Qassim) 2022; 16: 69-84.
117. Morita S, Tsuji T, Kishimoto S, Uraki S, Takeshima K, Iwakura H, Furuta H, Nishi M, Inaba H, Matsuoka TA. Isolated ACTH deficiency following immunization with the BNT162b2 SARS-CoV-2 vaccine: a case report. BMC Endocr Disord 2022; 22:185.
118. Panos LD, Bargiotas P, Hadjigeorgiou G, Panos GD. Neurovascular adverse effects of Sars-Cov-2 vaccination. Drug Des Devel Ther 2024; 18: 1891-1905.
119. Verrienti M, Marino Picciola V, Ambrosio MR, Zatelli MC. Pituitary and COVID-19 vaccination: a systematic review. Pituitary 2024 May 18. doi: 10.1007/s11102-024-01402-2.
120. Watanabe S, Tamura Y, Oba K, Kitayama S, Sato M, Kodera R, Toyoshima K, Chiba Y, Araki A. Hypopituitarism with secondary adrenocortical insufficiency and arginine vasopressin deficiency due to hypophysitis after COVID-19 vaccination: a case report. BMC Endocr Disord 2024; 24(1): 71.
121. Bouça B, Roldão M, Bogalho P, Cerqueira L, Silva-Nunes J. Central diabetes insipidus following immunization with BNT162b2 mRNA COVID-19 vaccine: a case report. Front Endocrinol (Lausanne) 2022; 13: 889074.
122. Torres AM, Kazee AM, Simon H, Knudson PE, Weinstock RS. Central diabetes insipidus due to herpes simplex in a patient immunosuppressed by Cushing's syndrome. Endocr Pract 2000; 6: 26-28
123. Moses AM, Thomas DG, Canfield MC, Collins GH. Central diabetes insipidus due to cytomegalovirus infection of the hypothalamus in a patient with acquired immunodeficiency syndrome: a clinical, pathological, and immunohistochemical case study. J Clin Endocrinol Metab 2003; 88: 51-54.
124. Scheinpflug K, Schalk E, Reschke K, Franke A, Mogren M. Diabetes insipidus due to herpes encephalitis in a patient with diffuse large cell lymphoma. A case report. Exp Clin Endocrinol Diabetes 2006; 114: 31-34
125. Jones G, Muriello M, Patel A, Logan L. Enteroviral meningoencephalitis complicated by central diabetes insipidus in a neonate: a case report and review of the literature. J Pediatric Infect Dis Soc 2015; 4: 155-158.
126. Tsuji H, Yoshifuji H, Fujii T, Matsuo T, Nakashima R, Imura Y, Yukawa N, Ohmura K, Sumiyoshi S, Mimori T. Visceral disseminated varicella zoster virus infection after rituximab treatment for granulomatosis with polyangiitis. Mod Rheumatol 2017; 27: 155-161
127. Zhang X, Li Q, Hu P, Cheng H, Huang G. Two case reports of pituitary adenoma associated with Toxoplasma gondii infection. J Clin Pathol 2002; 55: 965-966
128. Milligan SA, Katz MS, Craven PC, Strandberg DA, Russell IJ, Becker RA. Toxoplasmosis presenting as panhypopituitarism in a patient with the acquired immune deficiency syndrome. Am J Med 1984; 77: 760-764
129. Hamdeh S, Abbas A, Fraker J, Lambrecht JE. Intracranial toxoplasmosis presenting as panhypopituitarism in an immunocompromised patient. Am J Emerg Med 2015; 33: 1848.e1-2
130. Del Brutto OH, Del Brutto VJ. Intrasellar cysticercosis: a systematic review. Acta Neurol Belg 2013; 113: 225-227.
131. Dutta D, Kumar M, Ghosh S, Mukhopadhyay S, Chowdhury S. Pituitary hormone deficiency due to racemose neurocysticercosis. Lancet Diabetes Endocrinol 2013; 1: e13.
132. Cheong JH, Kim JM, Kim CH. Neurocysticercosis involving the pituitary stalk: case report and literature review. J Korean Neurosurg Soc 2010; 48: 91-93