occur virtually anywhere in the nervous system. Cavernoma in the hypothalamus is fairly rare, occurring in less than 1% of intracranial cavernomas, with most cases reported as individual case reports.

Vascular malformations are broken down based on the flow within the lesion into four categories. There are high-flow (arteriovenous) and low-flow (capillary, cavernous, venous) lesions. The low-flow state of cavernomas leads to much lower rates of hemorrhage compared with other vascular malformations, with symptomatic hemorrhage reported in 0.7–6.5% of cases, although it is hard to draw conclusions due to high rates of undiagnosed cavernomas discovered at autopsy or incidentally (6–65% of cavernomas diagnosed incidentally) [42–44]. Cavernous malformations consist of enlarged blood vessels with no intervening brain parenchyma that are surrounded by gliosis and hemosiderin from intermittent bleeding as well as occasional calcification [42].

Cavernomas are sporadic in up to 60% of cases, with sporadic cases associated with single lesions and familial cases with multiple lesions [44]. Autosomal dominant loss of function mutations in the CCM1, CCM2, and CCM3 genes are often involved in familial cases. These genes are associated with capillary endothelial tight junction and cytoskeletal protein encoding during angiogenesis [45].

Clinical course of a cavernoma is indolent, presenting symptoms that are most often headache, ataxia, and visual symptoms, such as homonymous hemianopsia, scotoma, temporal hemianopsia, oculomotor nerve deficits [46]. Due to small hemorrhage and recurrent hemorrhage, symptoms can range in severity, including a period of complete resolution. Lesions can also change in size as they can grow or shrink. The annual rate of hemorrhage has been reported to be 0.7–1.1% in patients with no prior history of hemorrhage with that number increasing to 4.5% in patients with prior hemorrhage [41]. At 2–3 years post-symptomatic hemorrhage, the rate begins to decline [47].

Cavernous malformations consist of enlarged and hyalinized capillaries with no intervening brain parenchyma that are surrounded by gliosis and hemosiderin from intermittent bleeding as well as occasional calcification. Abnormalities in endothelial gap junctions can be appreciated on electron microscopy and the lack of smooth muscle wall on light microscopy. Cavernomas are often described as "mulberry-like" on gross examination [48].

Radiographically, MR imaging is the modality of choice for cavernomas. Due to the low-flow state of these lesions, angiography is not sensitive for the detection of cavernomas. Cavernomas can be visualized on CT imaging, which can identify high-density demarcation of the lesions due to calcification, hemosiderin deposits, increased blood volume, and thrombosis. Contrast enhancement can be observed in some cases, but the degree is highly variable. Cavernomas are not associated with edema or mass effect except in the cases of acute hemorrhage [49]. Cavernomas can be categorized into four groups based on the MR imaging findings. Type I cavernomas are hyperintense on T1- and T2-weighted sequences due to subacute hemorrhage and hemosiderin core. Type II lesions have multiple loculated hemorrhages at various stages within a gliotic wall. These lesions can have a mixed appearance on T1- and T2-weighted sequences and are the classic "popcorn" lesions. Type III cavernomas have an isointense core due to chronic hemorrhage. Type IV lesions can appear as small capillary telangiectasias and can only be observed on gradient resonance echo sequences [50]. Type IV lesions are difficult to distinguish not only from capillary telangiectasias but also from other causes of micro hemorrhage, such as amyloid angiopathy, and thus require either histological or molecular (in the case of familial cavernomas) data for definite diagnosis [51].

Type	T1-weighted	T2-weighted	Additional findings
I	Hyperintense	Hypo/hyperintense	
II	Mixed signal at lesion core	Mixed signal at lesion core; low signal rim with blooming	Classic "popcorn" appearance
III	Hypo/iso- intense	Hypointense at lesion core; low signal rim with blooming	
IV	–	–	T2 gradient echo: Blooming "black dots"; difficult to distinguish from capillary telangiectasias

Cavernous malformation classification proposed by Zabramski et al. Note: prior to SWI sequences

Based on the 2017 Cerebral Cavernous Malformations Care Guidelines, surgical resection is not recommended in asymptomatic cases, especially those involving multiple lesions and lesions located in deep or eloquent tissue. Treatment is aimed at reducing the risk of recurrent hemorrhage; thus, gross total resection is recommended to remove all of the friable vessels in symptomatic patients as well as in patients where cavernoma is a suspect epileptogenic focus in medically refractory epilepsy (in these patients, as much of the associated gliosis and hemosiderin stained brain parenchyma should also be removed as safely feasible). Earlier intervention in patients where the cavernoma is considered the epileptogenic focus is important to not only reduce the current symptoms but also prevent the reduction of seizure threshold by decreasing the exposure of brain parenchyma to seizure activity ("kindling effect"), thus leading to higher likelihood for seizure freedom. Due to the technically difficult location, timing of surgical intervention is weighted against patient's symptoms. While no guidelines are available specific for hypothalamic cavernomas, the general approach for brainstem cavernomas is to pursue surgery after two symptomatic hemorrhages [52]. In patients with visual symptoms, earlier intervention may be warranted as improvement, and resolution of symptoms is possible with early intervention. In a study by Liu et al., in five patients with visual symptoms due to a hypothalamic cavernoma, gross total resection was achieved in four out of five of the patients with improvement of symptoms in two of the gross total resection patients and were stable in the other three patients; no worsening was noted [46]. While stereotactic radiosurgery has been explored for cavernomas and has shown to decrease hemorrhage rates, it is associated with an increased rate of adverse effects compared to the treatment of arteriovenous malformations [53].

Hypothalamic Hamartoma

Rare congenital nonneoplastic malformations that typically present in the pediatric population with a mean onset of 2.8 years. The incidence of hypothalamic hamartomas is hard to estimate with a wide range of as high as 1 in 50,000–100,000 to as rare as 1 in 1000,000 people. The lesion arises for tuber cinereum and inferior hypothalamus [54]. The classic triad of the clinical presentation includes gelastic epilepsy, central precocious puberty, and developmental delay [55]. Central precocious puberty is observed in larger lesions, where the tuber cinereum is involved.

The typical clinical course begins with gelastic seizures which often develop into more severe seizure disorder between the ages of 4 and 10 through propagation via the mammillothalamic pathway by direct attachment of the tumor and development of a mirror focus, which in some cases can progress into an autonomous epileptogenic focus [55]. Multiple seizure types are associated with progression and include complex partial (35.5%), atonic (33.3%), tonic (17.7%), and tonic-clonic seizures (15.1%) [56]. Severity of seizure semiology has been correlated with epileptic encephalopathy and behavioral disturbances. Common behavioral disturbances associated with hypothalamic hamartomas include oppositional defiant disorder and attention hyperactivity disorder [57].

In 25% of pediatric patients, seizures do not progress, and cognition remains intact. The pattern of gelastic seizures in these children tends to alter in duration, frequency, and intensity [58]. Hypothalamic hamartomas can also present as part of the Pallister-Hall syndrome, which is an autosomal dominant genetic disorder characterized by hypothalamic hamartomas, panhypopituitarism, polydactyly, bifid epiglottis, and an imperforate anus. In these patients, seizures can be absent or amendable to medical therapy. Cognitive and behavioral symptoms are rare, likely due to the mild and nonprogressive nature of the seizure type [55, 59]. In adult patients, the seizures associated with hypothalamic hamartomas are milder, non-gelastic seizures with less severe and frequent cognitive and behavioral sequalae [60].

Noninvasive electrophysiology is not effective at detecting intrinsic hamartoma activity due to the deep location of the hypothalamus and the complex connectivity of the hamartoma itself [54]. Evolution of gelastic seizures can lead to apparent activity in the frontal and temporal lobes, with symptomatic generalized epilepsy associated with interictal slow spike and wave and polyspike morphology [61].

Histopathologic analysis reveals small hypothalamic hamartoma neurons clustered in a neutrophil-like stroma with individual neurons and fibrillary astrocytes observed at the periphery. These neurons are NeuN-positive and GFAP-negative, which is the pattern characteristic to neurons. The positive GAD67 labeling suggests that these neurons are GABAnergic. Patch-clamp techniques have shown pacemaker-like activity in these neurons and increased network synchrony characteristic of fetal GABA neurotransmitters [62].

Morphologic classification includes sessile and pedunculated hypothalamic hamartomas. Sessile or intrahypothalamic hamartomas are attached to the mammillary region, can distort and displace the mammillary bodies, can displace the forniceal columns anterolaterally, have a variable degree of extension below the third ventricle, and present with seizures. Pedunculated or parahypothalamic hamartomas are attached to the tuber cinereum and project into the suprasellar cistern and present with precocious puberty without seizures [55, 63].

Radiographically, hypothalamic hamartomas are stable mass lesions in terms of size, shape, and signal intensity over time that appear similar to the normal cortex. They are composed of near-normal neurons and occasional glial cells. Hypothalamic hamartomas are best distinguished from normal grey matter on T2-weighted MR imaging, where these lesions are often hyperintense (93% of lesions as reported by Freeman et al.). T1-weighted images can appear iso- (26% of cases) to hypointense (74% of cases) [64, 65]. MR spectroscopy is a useful tool in differentiating normal grey versus hamartomas, where hamartomas are found to have reduced N-acetylaspartate and increased myoinositol content. MR spectroscopy and T2-weighted imaging suggest a reduced neuronal density and increased gliosis in hypothalamic hamartomas when compared to normal grey-matter landscape [65]. Most commonly, the mass appears as a non-enhancing nodule of tissue without calcification. Occasionally, calcification can be observed as well as erosion of dorsum sellae or an enlarged pituitary fossa.

The aim of treatment is seizure control in the majority of patients, since the lesion does not appear to grow dramatically [66]. In patients with Pallister-Hall syndrome as well as adult patients and pediatric patients with mild gelastic seizures, surgery can be held off in favor of medical therapy. In patients with worsening seizures or apparent cognitive and behavioral decline, disconnective surgery is often effective, and total resection is not required for good seizure control. Cognitive and behavioral improvement corresponds to the degree of surgical control postoperatively. There is an ongoing debate for early intervention to prevent autonomous focus development outside of the hamartoma and cognitive decline [55].

Infectious Lesions

Abscess

Abscesses in the hypothalamic-pituitary region are rare and are mostly described in case reports and small series. Sources of infection include hematogenous spread, seen in immunocompromised states; direct extension from adjacent structures, seen in meningitis; sinus infections; iatrogenic spread; and prior infections of the CNS [67]. The pathogens most often involved in hypothalamic abscesses include bacterial, viral, fungal, parasitic, and tuberculosis in nature. An infection in the hypothalamic-pituitary region can often be initially diagnosed as a pituitary adenoma among other more common entities. Abscess and infection in this region make up less than 1% of all lesions. These infections can either be primary or occur in conjunction with pre-existing lesions. Acute and subacute infections present with systemic symptoms, such as fever and neck stiffness, and can be associated with leukocytosis. Chronic infection and infection in immunocompromised patients can have a more indolent course. Abscess in the pituitary region often presents with symptoms of hypopituitarism, diabetes insipidus, as well as visual disturbances and headache [68, 69].

Radiographically, abscesses present as iso- to hypointense lesions on T1-weighted MR sequences and iso- to hyperintense on T2-weighted sequences and exhibit rim enhancement on post-gadolinium sequences. Depending on the exact location of the lesions, differential diagnosis includes pituitary apoplexy, adenoma, or cystic lesions [68, 70–73].

Histopathologic analysis includes evidence of acute or chronic inflammation such as lymphocytic infiltrate, neutrophils, macrophages, and necrotic components. Gram stain can be helpful in identifying the responsible pathogen in some cases [68].

Treatment is centered around removal of the majority of the abscess contents operatively followed by a prolonged course of intravenous or oral antibiotics directed at the infectious organism. Unfortunately, endocrine dysfunction, especially diabetes insipidus, is not usually reversible [70, 74].

Toxoplasmosis

Toxoplasmosis is the most common parasitic infection in humans and the most common CNS infection in immunocompromised patients. These lesions most commonly occur at the grey-white junction, thalamus, and basal ganglia. Toxoplasmosis involvement in the suprasellar and sellar region can cause focal neurologic deficits, endocrine disruption, as well as fever and headache [75, 76]. MRI findings are similar to those seen with metastatic lesions with multiple irregular ring-enhancing lesions on T2-weighted images and surrounding edema [67]. Toxoplasmosis infection can be diagnosed based on biopsy and confirmed presence of the organism by PCR. Yet, in many cases, it is treated empirically based on clinical suspicion and positive serology. A biopsy is reserved for those patients who do not respond to treatment. Treatment includes a combination of pyrimethamine, sulfadiazine, clindamycin, trimethoprim, sulfamethoxazole, atovaquone, and dapsone as well as hormone replacement as necessary [77].

Tuberculosis

CNS involvement in tuberculosis occurs in approximately 1% of patients with tuberculosis and can present as tuberculosis meningitis or more rarely as a tuberculoma or tuberculous hypophysitis. Majority of cases of CNS involvement occur in patients with known pulmonary or systemic tuberculosis, but initial presentation of CNS tuberculoma has also been reported. Tuberculomas can affect the hypothalamus, the pituitary, the infundibulum, or the sphenoid sinuses [78–80].

Clinical presentation of tuberculoma in the hypothalamic-pituitary region includes endocrine abnormalities, such as diabetes insipidus. Hypothalamic lesions can also include fibrosis,

gliosis, and calcification after recovery of tuberculosis meningitis. Cases of symptom improvement and resolution have been reported in those patients treated with antituberculous medications with length of treatment based on the radiographical response with at least 12 months of prescribed therapy [67, 81]. Corticosteroids can be used as an adjunct in cases with paradoxical lesion enlargement and to aid in control of the peripheral edema. Surgical intervention is reserved for cases where the lesion is not sensitive to medical management or shows enlargement or mass effect leading to possibly irreversible neurologic disability [82].

MR imaging presents a space occupying lesion with areas of central necrosis, irregular borders with ring-enhancement, and peripheral edema [82].

Histology is consistent with granulomas with central caseous necrosis and giant Langerhans cell infiltration. Lowenstein-Jensen media and Ziehl-Neelsen stain, as well as PCR, can serve as confirmatory tests [81].

Syphilis

Syphilis is a sexually transmitted disease caused by infection with *Treponema pallidum*, a bacterium of the spirochete family. Hypothalamic-pituitary involvement is characterized by granulomatous hypophysitis, syphilitic gumma in the sellar region with suprasellar extension, and congenital hypothalamic-pituitary dysfunction and presents mostly in immunocompromised patients [83]. Presentation of refers to patients with CNS symptoms has not been cited as the initial diagnosis of syphilis in the literature and occurs in patients with known systemic disease. Clinical presentation includes severe headaches and hypothalamic-pituitary dysfunction and can mimic pituitary adenomas on imaging [83]. Noncaseating or caseating granulomas with surrounding granulation tissue, lymphocytes, multinucleated cells, and epithelial cells can be observed on histopathologic analysis. Diagnosis is based on PCR detection of intraoperative samples and is treated with penicillin [83, 84].

Radiographically, syphilitic gummas appear as iso- to hypointense on T1-weighted MR sequences and variable intensity on T2-weighted sequences. These lesions are homogeneously enhancing with surrounding edema and mass effect or can show ring enhancement with central necrosis. The radiographic appearance usually leads to a differential diagnosis of high-grade diffuse glioma or metastatic brain lesion [85].

Isolated viral infections of the hypothalamus are exceedingly rare and have been reported in mostly immunocompromised patients. Direct invasions resulting in the reduction of AVP and oxytocin cells in the hypothalamus by cytomegalovirus have been reported with resultant diabetes insipidus [86].

Post-meningitis and post-encephalitis hypothalamic and pituitary dysfunction in the acute as well as late stages has been reported and can be attributed to the development of anti-hypothalamic and anti-pituitary antibodies during the initial disease process [87, 88]. In other cases, inflammatory and autoimmune process leading to axonal injury of the hypothalamus has also been suggested [89]. The spectrum of clinical presentation ranges from isolated hormone deficiency to panhypopituitarism with varying outcomes [67, 90].

Inflammatory Lesions

Wegner's Granulomatosis/ Granulomatosis with Polyangiitis

A type of vasculitis involving the small blood vessels, granulomatosis with polyangiitis, most commonly affects the vessels of the renal and respiratory systems.

Clinically, granulomatous lesions in the hypothalamus and surrounding structures present with headaches, hearing loss, visual disturbances, hypogonadism, and diabetes insipidus. Patients generally present in early to middle age, with female predominance. In 7.6% of patients with granulomatosis with polyangiitis, symptomatic sellar/suprasellar disease is diagnosed prior to the development of systemic symptoms, with 46% of

patients diagnosed concomitantly, and in 46% of patients, these intracranial lesions presented after initial diagnosis of vasculitis [91].

On histopathologic analysis, the lesions appear as small, necrotic foci, within a fibrotic capsule, containing neutrophils and neutrophil debris surrounded by lymphocytes, plasma cells, multinucleated giant cells, and epithelioid histiocytes [92]. Diagnosis is confirmed with antibodies positive for c-ANCA and proteinase-3 IgG.

On MR imaging, these lesions most commonly present as infundibular thickening, but they can also appear as a heterogeneous cystic mass that is peripherally enhancing, has a necrotic core, and is associated with hyperintense edema of the surrounding structures on T2-weighted sequences [93].

As with renal and respiratory involvement, treatment consists of immunosuppressive therapy with either high-dose glucocorticoids, cyclophosphamide, or rituximab. Although the lesions show response radiographically, no improvement of endocrinopathies has been reported [91].

Lymphocytic and Granulomatous Infundibuloneurohypophysitis

Lymphocytic infundibulohypophysitis is an autoimmune process whereby lymphocytes and plasma cells infiltrate the hypothalamus, infundibulum, and neurohypophysis. This disorder is more prevalent in women, especially in the peripartum period although lesions unrelated to pregnancy have been reported [94]. Granulomatous hypophysitis is a related inflammatory condition that has been hypothesized to be the same entity presenting at different points in time of the inflammatory process. It is characterized by granulomas with multinucleated giant cells, epithelioid cells, as well as lymphocyte infiltrate [95–97]. On macroscopic examination, the lesions are reported as firm and cartilaginous to fibrotic capsule with a creamy, fluid center.

Clinical presentation includes symptoms of pituitary dysfunction, such as fatigue, nausea, weight changes, and diabetes insipidus. Other common symptoms include recurrent fevers, headache, and neck stiffness, often concerning meningitis [94–97]. A case of visual dysfunction was also noted in a series by Honegger et al. [94]. Due to the common symptoms concerning for infectious etiology, CSF cytology and blood work are typically obtained. CSF cytology is significant for an elevated cell count, while blood work is significant for elevated erythrocyte sedimentation rate (ESR). Viral and bacterial analyses are usually negative [94].

Radiographically, these lesions are best accessed using MR imaging. The lymphocytic infiltrate appears as an enlargement of the hypothalamus and infundibulum and involves the pituitary gland. The pituitary fossa can be either normal or slightly enlarged with normal to thin sellar floor. T1- and T2-weighted sequences are nonspecific, but these lesions are contrast-enhancing with some cases showing central hypointensity. The lesions show either contact or infiltration of the basal hypothalamus [64, 94–98].

Treatment can include a trial of high-dose glucocorticoids followed by surgical excision in cases of medical failure, or surgical intervention can be the first-line therapy with glucocorticoids used in case of residual disease allowing for maximally safe resection. These lesions respond well to both forms of treatment and recur at a low rate [94, 98].

Encephalitis and Hypothalamitis

There are two types of hypothalamitis: relapsing autoimmune hypothalamitis and paraneoplastic limbic hypothalamitis.

Autoimmune hypothalamitis is a rare and controversial diagnosis which is associated with autoimmune disease of the pituitary gland as well as other systemic autoimmune processes [99]. Due to the findings of anti-hypothalamus antibodies in patients with lymphocytic neurohypophysitis, it can be concluded that autoimmune hypothalamitis can occur in conjunction with and is not an expansion of neurohypophysitis. Rare cases of isolated autoimmune hypothalamitis have been described [99–103]. Recently, anti-

hypothalamus Ab and anti-arginine vasopressin-secreting cell antibodies have been found in the CSF of many patients with otherwise idiopathic central diabetes insipidus concluding that autoimmune hypothalamitis may be more prevalent than once thought [100, 104, 105].

This disorder commonly presents as diabetes insipidus in conjunction with other pituitary hormone dysregulation, memory and personality changes, autonomic disturbances, and visual problems [99–103, 106].

Radiographically, hypothalamitis presents as a heterogeneous lesion that can extend into the optic apparatus and is contrast-enhancing on post-gadolinium MR sequences [99].

Histological examination is significant for perivascular lymphocytic (CD3+) and neutrophil infiltrate among healthy cerebral tissue with a proliferation index of less than 1% (Ki-67) excluding neoplastic process [100].

Treatment is aimed at initial tissue biopsy for appropriate diagnosis followed by decreasing the immune response; hence, corticosteroids and azathioprine have been cited as treatments effective at halting the progression of symptoms and in cases of short duration of symptoms, symptom alleviation [99, 101, 102].

Paraneoplastic limbic encephalitis is a subacute form of encephalitis that can be associated with solid tumors such as small cell lung carcinoma in half of the reported cases, testicular teratoma (20% of cases), and breast carcinoma (8%) as well as others. Due to the presence of various autoantibodies in the CSF of the patients, an autoimmune process is suggested. Currently, two specific antibodies have been described; the anti-Hu antibodies are associated with SCLC, while anti-Ta antibodies are associated with testicular teratoma [107, 108].

Clinical presentation includes diabetes insipidus, seizures, personality changes, depression, memory loss, and dementia. PLE has a high mortality rate; hence, early detection and intervention not only of PLE but also of the underlying malignancy are essential for good outcomes [109].

Radiographically, PLE presents as a hyperdensity in the hypothalamic region with bilateral hypodensities extending toward the temporal lobes. The lesions can go through spontaneous remission, but they can also relapse leading to the possibility of strikingly different MRI or CT scans performed days apart. CT perfusion studies show increased blood flow to the area which correlates with the hyperdense appearance on CT imaging [109].

CSF analysis is negative for infectious organisms but does show increased white blood count pointing to an inflammatory process [109]. While biopsy is not generally suggested in cases of good radiographic evidence, histological analysis shows lymphocytic inflammatory infiltrates [101, 110, 111].

Sarcoidosis

Sarcoidosis is a chronic granulomatous disease that can affect virtually any organ leading to scarring and permanent organ damage. The incidence of sarcoidosis in the United States is 2.8%–8.4%. It is diagnosed based on the identification of non-caseating granulomas within lesions. Any organ system can be involved, with pulmonary system being the most common [112]. CNS involvement in systemic sarcoidosis is observed in approximately 5% of patients with 0.5% of patients with hypothalamic-pituitary region infiltration. Most patients have known systemic sarcoid disease (80%—textbook: Pituitary), but rarely, neurosarcoid is the initial presentation. Leptomeningeal disease is most common, but parenchymal involvement is not infrequent. Neurosarcoid has a predilection for the base of the brain as well as midline structures, including the hypothalamus and the pituitary gland [113]. Sarcoid granulomas are commonly found in the basal hypothalamus and the floor of the third ventricle, and it can also be found in the posterior pituitary [114, 115].

Clinically, sarcoid lesions of the hypothalamus present as hypothalamically induced hypopituitarism in the majority of patients, visual disturbances (53%), diabetes insipidus (37.5%), cranial nerve I, V, VII, or VIII dysfunction (44%), and other CNS involvement is noted in up to 71% of patients [116, 117]. More rare manifestations

include thermal dysregulation, somnolence, personality changes, and obesity [118–120]. Patients with CNS involvement typically have higher disease burden and are more symptomatic than those with no CNS lesions [121].

Mainstay of therapy for sarcoid, including CNS involvement, is high-dose glucocorticoids. This therapy has been shown to improve visual symptoms but has not shown to improve long-standing symptoms or diabetes insipidus [122, 123].

Multiple Sclerosis

Hypothalamic lesions occur in the majority of advanced multiple sclerosis (MS), an autoimmune disease usually affecting the white matter of the CNS [124]. The high prevalence of hypothalamic lesions can be attributed to the lack of the blood brain barrier in the area leading to easier access to the CNS by the lymphocytic infiltrate. Hypothalamus is, additionally, well vascularized allowing an influx of lymphocytes into the tissue [125]. However, a study by Qiu et al. looked at the frequency of hypothalamic involvement in classical as well as longitudinal extensive myelopathy (LEM). The frequency of hypothalamic lesions was 13.3% in the MS group and zero in the LEM group. Eighteen percent of patients with active disease showed involvement of the hypothalamus, whereas only 8% involved the hypothalamus in stable disease, although the difference was not statistically significant [126].

While hypothalamic lesions are common in advanced MS, only rare reports of symptomatic hypothalamic disease have been published. Clinical symptoms include paroxysmal hypothermia, autonomic dysfunction, hyperprolactinemia, and decrease in appetite. Disease course is not usually affected by the presence of this specific lesion [125, 127–129].

Histology of MS lesions hyperintense of T2-weighted MR images represent active lesions and show a variable level of edema, small clusters of microglia with enhanced major histocompatibility complex class II antigen, CD45 and CD68 antigen expression, and a variable number of perivascular lymphocytes [130, 131].

Radiographically these lesions are best identified using T2-weighted and FLAIR MR sequences. The lesions are bilateral in the majority of studied cases (85.8%) and lacked well-defined borders [126]. The lesions have also been described as triangular and abutting the floor of the third ventricle. Lesions that were larger and extended beyond the hypothalamus are described as lobulated. The lesions are iso- to hypointense on T1-weighted sequences and varying degrees of hyperintensity on T2-weighted sequences. These lesions do not enhance on post-gadolinium sequences but do show hyperintensity on FLAIR sequences [125, 126, 130, 131].

Treatment of hypothalamic lesions specifically has not been widely described nor does it appear necessary, as many of the lesions are asymptomatic or present with nonspecific symptoms such as fatigue. Focus on overall disease burden control is the mainstay of treatment.

MS lesions in the hypothalamus can, thus, explain the often present autonomic and endocrine dysfunction seen in multiple sclerosis [125]. Hypothalamic lesions are rarely the presenting symptoms in newly diagnosed patients but have been reported with symptoms of hypersomnia in some cases [132].

Neuromyelitis optica (NMO) is a related disorder that is characterized by the presence of acute optic neuritis and myelitis with an additional two out of three criteria: spinal cord lesion extending over three vertebral segments, brain MRI lesions not meeting criteria for multiple sclerosis, and NMO-IgG seropositive status. This disorder has a more relapsing remitting type course with resolution of symptoms followed by severe relapses [132]. Hypothalamic involvement is considered a rare event in this disorder, and a few cases have been reported in the literature [133]. Presentations include insomnia, somnolence, hypothermia, endocrine dysregulation, and personality changes [135–137].

Radiographically, the lesions are similar to those of multiple sclerosis and include hyperintensity on T2-weighted and FLAIR MR sequences [134].

Treatment consists of intravenous glucocorticoids at symptom onset, and occasionally, plasmapheresis has been used in unremitting cases [138].

Ectopic Posterior Pituitary

Patients with an ectopic posterior pituitary are at a higher risk of endocrine abnormalities due to pituitary dysfunction which is associated with an abnormal infundibulum and relatively small anterior pituitary gland. Patient who present with endocrine abnormalities due to ectopic posterior pituitary present during childhood with progressively worsening endocrine function associated with significant morbidity and mortality. It is therefore important to identify the abnormality as well as the source for improved outcomes. Ectopic pituitary has a relatively high rate of hypothalamic location compared to the infundibulum (56 versus 11 patients). Patients with EPP in the hypothalamus also had a higher rate of multiple endocrine deficiencies compared to other locations with a 31- and 25-patient distribution of multiple versus isolated pituitary hormone deficiency. Approximately half of the patients with known pregnancy history had major incidents during pregnancy, maternal drug use, consanguinity, traumatic delivery, and neonatal intensive care unit stay [139].

References/Bibliography

1. Nagasawa D, Yew A, Safaee M, Fong B, Gopen Q, Parsa AT, Yang I. Clinical characteristics and diagnostic imaging of epidermoid tumors. J Clin Neurosci. 2011;18(9):1158–62. https://doi.org/10.1016/j.jocn.2011.02.008.
2. Zada G, Lopes MBS, Mukundan S, Laws E. Sellar Region Epidermoid and Dermoid Cysts. In: Zada G, Lopes M, Mukundan Jr S, Laws Jr E, editors. Atlas of Sellar and Parasellar Lesions. Springer: Cham; 2016. p. 245–50.
3. Caldarelli M, Massimi L, Kondageski C, Di Rocco C. Intracranial midline dermoid and epidermoid cysts in children. J Neurosurg. 2004;100(Suppl 5):473–80.
4. Kucera JN, Roy P, Murtagh R. Ruptured intracranial dermoid cyst manifesting as new onset seizure: a case report. J Radiol Case Rep. 2011;5(4):10–8. https://doi.org/10.3941/jrcr.v5i4.592.
5. Guidetti B, Gagliardi FM. Epidermoid and dermoid cysts. Clinical evaluation and late surgical results. J Neurosurg. 1977;47:12–8.
6. Murphy MJ, Risk WS, VanGilder JC. Intracranial dermoid cyst in Goldenhar's syndrome. J Neurosurg. 1980;53(3):408–10.
7. Kumerasan R, Srinivasan B, Narayanan M, Cugati N, Karthikeyan P. Craniofacial abnormalities in Goldenhar syndrome: a case report with review of the literature. Plast Aesthet Res. 2014;1:108–13. https://doi.org/10.4103/2347-9264.143557.
8. Hamlat A, Hua ZF, Saikali S, et al. Malignant transformation of intra-cranial epithelial cysts: systematic article review. J Neurooncol. 2005;74:187–94. https://doi.org/10.1007/s11060-004-5175-4.
9. Khan AB, Goethe EA, Hadley CC, Rouah E, North R, Srinivasan VM, Gallagher KK, Fuentes A, Vaz-Guimaraes F. Infundibular epidermoid cyst: case report and systematic review. World Neurosurg. 2019;130:110–4. https://doi.org/10.1016/j.wneu.2019.06.205.
10. Aprile I, Iaiza F, Lavaroni A, et al. Analysis of cystic intracranial lesions performed with fluid-attenuated inversion recovery MR imaging. AJNR Am J Neuroradiol. 1999;20:1259–67.
11. Ikushima I, Korogi Y, Hirai T, et al. MR of epidermoids with a variety of pulse sequences. AJNR Am J Neuroradiol. 1997;18(7):1359–63.
12. Kato K, Ujiie H, Higa T, et al. Clinical presentation of intracranial epidermoids: a surgical series of 20 initial and 4 recurred cases. Asian J Neurosurg. 2010;5:32–40.
13. Lynch JC, Aversa A, Pereira C, Nogueira J, Gonçalves M, Lopes H. Surgical strategy for intracranial dermoid and epidermoid tumors: an experience with 33 patients. Surg Neurol Int. 2014;5:163.
14. André A, Zérah M, Roujeau T, Brunelle F, Blauwblomme T, Puget S, Bourgeois M, Sainte-Rose C, Ville Y, Di Rocco F. Suprasellar Arachnoid Cysts: Toward a New Simple Classification Based on Prognosis and Treatment Modality. Neurosurgery. 2016;78(3):370–80. https://doi.org/10.1227/NEU.0000000000001049.
15. Choi JU, Kim DS. Pathogenesis of arachnoid cyst: congenital or traumatic? Pediatr Neurosurg. 1998;29:260–6. https://doi.org/10.1159/000028733.
16. Al-Holou WN, Terman S, Kilburg C, Garton HJ, Muraszko KM, Maher CO. Prevalence and natural history of arachnoid cysts in adults. J Neurosurg. 2013;118(2):222–31. https://doi.org/10.3171/2012.10.JNS12548.
17. Kornienko VN, Pronin IN. Sellar and parasellar tumours. In: Kornienko VN, Pronin IN, editors. Diagnostic neuroradiology. Berlin–Heidelberg: Springer; 2009. p. 598–605. https://doi.org/10.1007/978-3-540-75,653-8.
18. Mattox A, Choi JD, Leith-gray L. et-al. Guidelines for the management of obstructive hydrocepha-

lus from suprasellar-prepontine arachnoid cysts using endoscopic third ventriculocystocisternostomy. Surg Innov. 2010;17(3):206–16. https://doi.org/10.1177/1553350610377212.
19. Lee JY, Lee YA, Jung HW, Chong S, Phi H, Kim SK, Shin CH, Wang KC. Long-term endocrine outcome of suprasellar arachnoid cysts. J Neurosurg Pediatr. 2017;19(6):696–702. https://doi.org/10.3171/2017.1.PEDS16404.
20. Sansregret A, Ledoux R, Duplantis F. et-al. Suprasellar subarachnoid cysts. Radioclinical features. Am J Roentgenol Radium Ther Nucl Med. 1969;105(2):291–7.
21. Harsh GRT, Edwards MS, Wilson CB. Intracranial arachnoid cysts in children. J Neurosurg. 1986;64:835–42. https://doi.org/10.3171/jns.1986.64.6.0835.
22. Wenger M, Simko M, Markwalder R, Taub E. An entirely suprasellar Rathke's cleft cyst: case report and review of the literature. J Clin Neurosci. 2001;8(6):564–7. https://doi.org/10.1054/jocn.2000.0925.
23. Mukherjee JJ, Islam N, Kaltsas G, Lowe DG, Charlesworth M, Afshar F, Trainer PJ, Monson JP, Besser GM, Grossman AB. Clinical, radiological and pathological features of patients with Rathke's cleft cysts: tumors that may recur. J Clin Endocrinol Metab. 1997;82(7):2357–62. https://doi.org/10.1210/jcem.82.7.4043.
24. Raghunath A, Sampath S, Devi BI, Chandramouli BA, Lal GJ, Chickabasaviah YT, et al. Is there a need to diagnose Rathke's cleft cyst preoperatively? Neurol India. 2010;58:69–73.
25. Esiri M. Russell and Rubinstein's pathology of tumors of the nervous system. 6th edition. J Neurol Neurosurg Psychiatry. 2000;68(4):538D.
26. Teramoto A, Hirakawa K, Sanno N, Osamura Y. Incidental pituitary lesions in 1000 unselected autopsy specimens. Radiology. 1994;193:161–4. https://doi.org/10.1148/radiology.193.1.8090885.
27. Raper DMS, Besser M. Clinical features, management and recurrence of symptomatic Rathke's cleft cyst. J Clin Neurosci. 2009;16(3):385–9. https://doi.org/10.1016/j.jocn.2008.04.023.
28. Takanashi J, Tada H, Barkovich AJ, Saeki N, Kohno Y. Pituitary cysts in childhood evaluated by MR imaging. AJNR Am J Neuroradiol. 2005;26:2144–7.
29. Oh YJ, Park HK, Yang S, Song JH, Hwang IT. Clinical and radiological findings of incidental Rathke's cleft cysts in children and adolescents. Ann Pediatr Endocrinol Metab. 2014;19:20–6. https://doi.org/10.6065/apem.2014.19.1.20.
30. Nomikos P, Buchfelder M, Fahlbusch R. Intra- and suprasellar colloid cysts. Pituitary. 1999;2:123–6. https://doi.org/10.1023/A:1009983414014.
31. Peeters SM, Daou B, Jabbour P, Ladoux A, Abi Lahoud G. Spontaneous regression of a third ventricle colloid cyst. World Neurosurg. 2016;90:704.e19–22. https://doi.org/10.1016/j.wneu.2016.02.116.
32. Hernesniemi J, Leivo S. Management outcome in third ventricular colloid cysts in a defined population: a series of 40 patients treated mainly by transcallosal microsurgery. Surg Neurol. 1996;45:2–14. https://doi.org/10.1016/0090-3019(95)00379-7.
33. Boogaarts HD, Decq P, Grotenhuis JA, Le Guérinel C, Nseir R, Jarraya B, Djindjian M, Beems T. Long-term results of the neuroendoscopic management of colloid cysts of the third ventricle: A series of 90 cases. Neurosurgery. 2011;68:179–87. https://doi.org/10.1227/NEU.0b013e3181ffae71.
34. Hohenstein C, Herdtle S. Unexpected death from a colloid cyst. Int J Emerg Med. 2010;27:65–6. https://doi.org/10.1007/s12245-009-0153-4.
35. Turillazzi E, Bello S, Neri M, Riezzo I, Fineschi V. Colloid cyst of the third ventricle, hypothalamus, and heart: a dangerous link for sudden death. Diagn Pathol. 2012;7:144. https://doi.org/10.1186/1746-1596-7-144.
36. de Witt Hamer PC, Verstegen MJ, De Haan RJ, Vandertop WP, Thomeer RT, Mooij JJ, et al. High risk of acute deterioration in patients harboring symptomatic colloid cysts of the third ventricle. J Neurosurg. 2002;96:1041–5. https://doi.org/10.3171/jns.2002.96.6.1041.
37. Margetis K, Christos PJ, Souweidane M. Endoscopic resection of incidental colloid cysts. J Neurosurg. 2014;120:1259–67. https://doi.org/10.3171/2014.3.JNS131289.
38. Mackenzie IRA, Gilbert JJ. Cysts of the neuraxis of endodermal origin. J Neurol Neurosurg Psychiatry. 1991;54(7):572–5. https://doi.org/10.1136/jnnp.54.7.572.
39. Bender B, Honegger JB, Beschorner R, Ernemann U, Horger M. MR imaging findings in colloid cysts of the sellar region: comparison with colloid cysts of the third ventricle and Rathke's cleft cysts. Acad Radiol. 2013;20(11):1457–65. https://doi.org/10.1016/j.acra.2013.08.014.
40. Guduk M, Sun HI, Sav MA, Berkman Z. Pituitary colloid cyst. J Craniofac Surg. 2017;28(2):e166–8. https://doi.org/10.1097/SCS.0000000000003142.
41. Mouchtouris N, Chalouhi N, Chitale A, Starke RM, Tjoumakaris SI, Rosenwasser RH, Jabbour PM. Management of cerebral cavernous malformations: from diagnosis to treatment. Scientific World J. 2015;2015:808314. https://doi.org/10.1155/2015/808314.
42. Batra S, Lin D, Recinos P, et al. Cavernous malformations: natural history, diagnosis and treatment. Nat Rev Neurol. 2009;5:659–70. https://doi.org/10.1038/nrneurol.2009.177.
43. Ene C, Kaul A, Kim L. Natural history of cerebral cavernous malformations. Handb Clin Neurol. 2017;143:227–32. https://doi.org/10.1016/B978-0-444-63,640-9.00021-7.
44. Dalyai RT, Ghobrial G, Awad I, Tjoumakaris S, et al. Management of incidental cavernous malformations: a review. Neurosurg Focus. 2011;31(6):E5. https://doi.org/10.3171/2011.9.FOCUS11211.

45. Kim J. Introduction to cerebral cavernous malformation: a brief review. BMB Rep. 2016;49(5):255–62. https://doi.org/10.5483/BMBRep.2016.49.5.036.
46. Liu JK, Lu Y, Raslan AM, et al. Cavernous malformations of the optic pathway and hypothalamus, analysis of 65 cases in the literature. Neurosurg Focus. 2010;29(3):E17. https://doi.org/10.3171/2010.5.FOCUS10129.
47. Wurm G, Schnizer M, Fellner FA. Cerebral cavernous malformations associated with venous anomalies: surgical considerations. Neurosurgery. 2005;57(1 Suppl):42–58. https://doi.org/10.1227/01.neu.0000163482.15158.5a.
48. Wong JH, Awad IA, Kim JH. Ultrastructural pathological features of cerebrovascular malformations: a preliminary report. Neurosurgery. 2000;46(6):1454–9. https://doi.org/10.1097/00006123-200,006,000-00027.
49. Zyck S, Gould GC. Cavernous venous malformation. [Updated 2019 Jun 18]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526009/.
50. Zabramski JM, Wascher TM, Spetzler RF, et al. The natural history of familial cavernous malformations: results of an ongoing study. J Neurosurg. 1994;80(3):422–32. https://doi.org/10.3171/jns.1994.80.3.0422.
51. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165–74. https://doi.org/10.1016/S1474-4422(09)70013-4.
52. Akers A, Al-Shahi SR, Awad IA, Dahlem K, Flemming K, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the angioma alliance scientific advisory board clinical experts panel. Neurosurgery. 2017;80(5):665–80. https://doi.org/10.1093/neuros/nyx091.
53. Pollock BE, Garces YI, Stafford SL, Foote RL, Schomberg PJ, Link MJ. Stereotactic radiosurgery for cavernous malformations. J Neurosurg. 2000;93:987–91. https://doi.org/10.3171/jns.2000.93.6.0987.
54. Weissenberger AA, Dell ML, Liow K, Theodore W, Frattali CM, Hernandez D, Zametkin AJ. Aggression and psychiatric comorbidity in children with hypothalamic hamartomas and their unaffected siblings. J Am Acad Child Adolesc Psychiatry. 2001;40:696–703. https://doi.org/10.1097/00004583-200,106,000-00015.
55. Maixner W. Hypothalamic hamartomas—clinical, neuropathological and surgical aspects. Childs Nerv Syst. 2006;22:867–73. https://doi.org/10.1007/s00381-006-0129-0.
56. Tassinari C, Riguzzi P, Rizzi R. Gelastic seizures. In: Tuxhorn I, Holthausen H, Boenigk K, editors. Paediatric epilepsy syndromes and their surgical management. London: John Libbey; 1997. p. 429–46.
57. Palmini A, Chandler C, Andermann F, Costa Da Costa J, et al. Resection of the lesion in patients with hypothalamic hamartomas and catastrophic epilepsy. Neurology. 2002;58:1338–47. https://doi.org/10.1212/wnl.58.9.1338.
58. Arzimanoglou AA, Hirsch E, Aicardi J. Hypothalamic hamartoma and epilepsy in children: illustrative cases of possible evolutions. Epileptic Disord. 2003;5:187–99.
59. Boudreau EA, Liow K, Frattali CM, Wiggs E, Turner JT, Feuillan P, Sato S, et al. Hypothalamic hamartomas and seizures: distinct natural history of isolated and Pallister-Hall syndrome cases. Epilepsia. 2005;46:42–7. https://doi.org/10.1111/j.0013-9580.2005.68303.x.
60. Mullatti N. Hypothalamic hamartoma in adults. Epileptic Disord. 2003;5:201–4.
61. Freeman JL, Harvey AS, Rosenfeld JV, Wrennall JA, Bailey CA, Berkovic SF. Generalized epilepsy in hypothalamic hamartoma: evolution and postoperative resolution. Neurology. 2003;60:762–7. https://doi.org/10.1212/01.wnl.0000049457.05670.7d.
62. Wu J, Xu L, Kimdo Y, Rho JM, St John PA, Lue LF, Coons S, Ellsworth K, et al. Electrophysiological properties of human hypothalamic hamartomas. Ann Neurol. 2005;58:371–82. https://doi.org/10.1002/ana.20580.
63. Harrison VS, Oatman O, Kerrigan JF. Hypothalamic hamartoma with epilepsy: Review of endocrine comorbidity. Epilepsia. 2017;58(Suppl 2):50–9. https://doi.org/10.1111/epi.13756.
64. Saleem SN, Said AM, Lee DH. Lesions of the hypothalamus: MR imaging diagnostic features. Radiographics. 2007;27(4):1087–108. https://doi.org/10.1148/rg.274065123.
65. FreemanJL CLT, Wellard RM, et al. MR imaging and spectroscopic study of epileptogenic hypothalamic hamartomas: analysis of 72 cases. AJNR Am J Neuroradiol. 2004;25(3):450–62.
66. Veldueza J, Cristante L, Dammann O, et al. Hypothalamic hamartomas: with special reference to gelastic epilepsy and surgery. Neurosurgery. 1994;34:949–58. https://doi.org/10.1227/00006123-199,406,000-00001.
67. Pekic S, Miljic D, Popovic V. Infections of the Hypothalamic-Pituitary Region. In: Feingold KR, Anawalt B, Boyce A, et al., Endotext. South Dartmouth (MA): MDText.com, Inc.; 2018.
68. Gao L, Guo X, Tian R, Wang Q, Feng M, Bao X, et al. Pituitary abscess: clinical manifestations, diagnosis and treatment of 66 cases from a large pituitary center over 23 years. Pituitary. 2017;20:189–94. https://doi.org/10.1007/s11102-016-0757-7.
69. 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;117:469–76. https://doi.org/10.1007/s11060-013-1285-1.

70. 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 (Oxf). 2011;74:79–88. https://doi.org/10.1111/j.1365-2265.2010.03890.x.
71. Vates GE, Berger MS, Wilson CB. Diagnosis and management of pituitary abscess: a review of twenty-four cases. J Neurosurg. 2001;95:233–41. https://doi.org/10.3171/jns.2001.95.2.0233.
72. Ciappetta P, Calace A, D'Urso PI, De Candia N. Endoscopic treatment of pituitary abscess: two case reports and literature review. Neurosurg Rev. 2008;31:237–46. https://doi.org/10.1007/s10143-007-0096-2.
73. Dalan R, Leow MK. Pituitary abscess: our experience with a case and a review of the literature. Pituitary. 2008;11:299–306. https://doi.org/10.1007/s11102-007-0057-3.
74. Pepene CE, Ilie I, Mihu D, Stan H, Albu S, Duncea I. Primary pituitary abscess followed by empty sella syndrome. Pituitary. 2010;13(4):385–9. https://doi.org/10.1007/s11102-008-0150-2.
75. Hamdeh S, Abbas A, Fraker J, Lambrecht JE. Intracranial toxoplasmosis presenting as panhypopituitarism in an immunocompromised patient. Am J Emerg Med. 1848;2015(33):e1–2. https://doi.org/10.1016/j.ajem.2015.04.071.
76. 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;77:760–4. https://doi.org/10.1016/0002-9343(84)90381-4.
77. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep. 2009;58(RR-4):1–207.
78. 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;102:72–7. https://doi.org/10.1016/s0303-8467(00)00063-9.
79. Arunkumar MJ, Rajshekhar V. Intrasellar tuberculoma presenting as pituitary apoplexy. Neurol India. 2001;49:407–10.
80. Husain N, Husain M, Rao P. Pituitary tuberculosis mimicking idiopathic granulomatous hypophysitis. Pituitary. 2008;11:313–5. https://doi.org/10.1007/s11102-007-0068-0.
81. Poonnoose SI, Rajshekhar V. Rate of resolution of histologically verified intracranial tuberculomas. Neurosurgery. 2003;53:873–9. https://doi.org/10.1227/01.neu.0000083553.25421.6 f.
82. Monteiro R, Carneiro JC, Costa C, Duarte R. Cerebral tuberculomas – A clinical challenge. Respir Med Case Rep. 2013;9:34–7. https://doi.org/10.1016/j.rmcr.2013.04.003.
83. 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;100:2837–40. https://doi.org/10.1210/jc.2015-2049.
84. Shao X, Qiang D, Liu Y, Yuan Q, Tao J, Ji B. Diagnosis and treatment of cerebral syphilitic gumma: a report of three cases. Front Neurosci. 2018;12:100. https://doi.org/10.3389/fnins.2018.00100.
85. Shen S, Yang R, Wang L, Tang L, Liu B. Intracranial and spinal cord syphilitic gumma in a human immunodeficiency virus-negative man with untreated syphilis. Medicine. 2019;98(36):e16887. https://doi.org/10.1097/MD.0000000000016887.
86. 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;88:51–4. https://doi.org/10.1210/jc.2002-020879.
87. 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. https://doi.org/10.1530/EJE-07-0484.
88. 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;5:579–88. https://doi.org/10.1007/s11102-011-0371-7.
89. 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;28:33–9. https://doi.org/10.5414/npp28033.
90. Tsiakalos A, Xynos ID, Sipsas NV, Kaltsas G. Pituitary insufficiency after infectious meningitis: a prospective study. J Clin Endocrinol Metab. 2010;957:3277–81. https://doi.org/10.1210/jc.2010-0144.
91. De Parisot A, Puechal X, Langrand C, et al. Pituitary involvement in granulomatosis with polyangiitis: Report of 9 patients and review of the literature. Medicine (Baltimore). 2015;94:e748. https://doi.org/10.1097/MD.0000000000000748.
92. Abushamat LA, Kerr JM, Lopes BS, Kleinschmidt-DeMasters BK. Very Unusual Sellar/Suprasellar Region Masses: A Review. J Neuropathol Exp Neurol. 2019;78(8):673–84. https://doi.org/10.1093/jnen/nlz044.
93. Yong TY, Li JYZ, Amato L, et al. Pituitary involvement in Wegener's granulomatosis. Pituitary. 2008;11:77–84. https://doi.org/10.1007/s11102-007-0021-2.

94. Honegger, et al. Lymphocytic and granulomatous hypophysitis: experience with nine cases. Neurosurgery. 1997;40(4):713–22. https://doi.org/10.1097/00006123-199,704,000-00010.
95. Doniach I, Wright EA. Two cases of giant-cell granuloma of the pituitary gland. J Pathol Bacteriol. 1951;63:69–79. https://doi.org/10.1002/path.1700630109.
96. Scanarini M, D'Avella D, Rotilio A, Kitromilis N, Mingrino S. Giant-cell granulomatous hypophysitis: A distinct clinicopathological entity. J Neurosurg. 1989;71:681–6. https://doi.org/10.3171/jns.1989.71.5.0681.
97. Yoshioka MK, Yamakawa N, Saito H, Yoneda M, Nakayama T, Kuroki M, Tsuchida T. Sekiya M Granulomatous hypophysitis with meningitis and hypopituitarism. Intern Med. 1992;31:1147–50. https://doi.org/10.2169/internalmedicine.31.1147.
98. Naik RG, Ammini A, Shah P, Sarkar C, Mehta VS, Berry M. Lymphocytic hypophysitis: Case report. J Neurosurg. 1994;80:925–7. https://doi.org/10.3171/jns.1994.80.5.0925.
99. Bianchi A, Mormando M, Doglietto F, Tartaglione L, Piacentini S, Lauriola L, et al. Hypothalamitis: a diagnostic and therapeutic challenge. Pituitary. 2014;17:197–202. https://doi.org/10.1007/s11102-013-0487-z.
100. Bertulli L, Bertani GA, Gianelli U, Mantovani G, Rampini PM, Locatelli M. Long-standing isolated autoimmune hypothalamitis diagnosed with endoscopic transventricular biopsy. World Neurosurg. 2017;105:1036.e5–9. https://doi.org/10.1016/j.wneu.2017.06.055.
101. Zhang S, Ye H, Zhang Z, Lu B, Yang Y, He M, et al. Successful diagnosis of hypothalamitis using stereotactic biopsy and treatment: a case report. Medicine. 2015;94:e447. https://doi.org/10.1097/MD.0000000000000447.
102. Wang XL, Lu JM, Yang LJ, Lü ZH, Dou JT, Mu YM, et al. A case of relapsed autoimmune hypothalamitis successfully treated with methylprednisolone and azathioprine. Neuro Endocrinol Lett. 2008;29:874–6.
103. Garg MK, Gundgurthi A, Dutta MK, Kharb S, Pathak HC, Bharadwaj R, et al. Hypopituitarism due to isolated lymphocytic hypothalamitis in a young girl. World J Endocr Surg. 2011;3:33–7.
104. De Bellis A, Sinisi AA, Pane E, Dello Iacovo A, Bellastella G, Di Scala G, et al. Involvement of hypothalamus autoimmunity in patients with autoimmune hypopituitarism: role of antibodies to hypothalamic cells. J Clin Endocrinol Metab. 2012;97:3684–90. https://doi.org/10.1210/jc.2012-2269.
105. Pivonello R, De Bellis A, Faggiano A, Di Salle F, Petretta M, Di Somma C, et al. Central diabetes insipidus and autoimmunity: relationship between the occurrence of antibodies to arginine vasopressin-secreting cells and clinical, immunological, and radiological features in a large cohort of patients with central diabetes insipidus of known and unknown etiology. J Clin Endocrinol Metab. 2003;88:1629–36. https://doi.org/10.1210/jc.2002-020791.
106. Scherbaum WA. Autoimmune hypothalamic diabetes insipidus ("autoimmune hypothalamitis"). In: Swaab DF, Hofman MA, Mirmiran M, Ravid R, Van Leeuwen FW, editors. The human hypothalamus in health and disease, vol. 93; 1992. p. 283–92. [discussion: 292–293].
107. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain. 2000;123:1481–94. https://doi.org/10.1093/brain/123.7.1481.
108. Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain. 1968;91:481–96. https://doi.org/10.1093/brain/91.3.481.
109. Bataduwaarachchi VR, Tissera N. Paraneoplastic limbic encephalitis with associated hypothalamitis mimicking a hyperdense hypothalamic tumor: a case report. BMC Med Imaging. 2016;16(8):PMC4716643. https://doi.org/10.1186/s12880-016-0113-4.
110. Lecube A, Francisco G, Rodríguez D, Ortega A, Codina A, Hernández C, et al. Lymphocytic hypophysitis successfully treated with azathioprine: first case report. J Neurol Neurosurg Psychiatry. 2003;74(11):1581–3. https://doi.org/10.1136/jnnp.74.11.1581.
111. Yang GQ, Lu ZH, Gu WJ, Du J, Guo QH, Wang XL, et al. Recurrent autoimmune hypophysitis successfully treated with glucocorticoids plus azathioprine: a report of three cases. Endocr J. 2011;58(8):675–83. https://doi.org/10.1507/endocrj.k10e-334.
112. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of sarcoidosis 1946–2013: a population-based study. Mayo Clin Proc. 2016;91(2):183–8. https://doi.org/10.1016/j.mayocp.2015.10.024.
113. Mana J. Magnetic resonance imaging and nuclear imaging in sarcoidosis. Curr Opin Pulm Med. 2002;8:457–63. https://doi.org/10.1097/00063198-200,209,000-00020.
114. Bihan H, Christozova V, Dumas JL, et al. Sarcoidosis. Clinical, hormonal, and magnetic resonance imaging (MRI) manifestations of hypothalamic-pituitary disease in 9 patients and review of the literature. Medicine. 2007;86:259–68. https://doi.org/10.1097/MD.0b013e31815585aa.
115. Vesely DL, Maldonado A, Levey GS. Partial hypopituitarism and possible hypothalamic involvement in sarcoidosis. Am J Med. 1977;62(3):425–31. https://doi.org/10.1016/0002-9343(77)90842-7.
116. Delaney P. Neurologic manifestations in sarcoidosis. Review of the literature, with a report of 23 cases. Ann Intern Med. 1977;87(3):336–45. https://doi.org/10.7326/0003-4819-87-3-336.
117. Stuart CA, Neelon FA, Lebovitz HF. Hypothalamic insufficiency: The cause of hypopituitarism in sar-

coidosis. Ann Intern Med. 1978;88(5):589–94. https://doi.org/10.7326/0003-4819-88-5-589.
118. Bell NH. Endocrine complications of sarcoidosis. Endocrinol Metab Clin North Am. 1991;20(3):645–54.
119. Vesely DL. Hypothalamic sarcoidosis: A new cause of morbid obesity. South Med J. 1989;82(6):758–61.
120. Nakao K, Noma K, Sato B, Yano S, Yamamura Y, Tachibana T. Serum prolactin levels in eighty patients with sarcoidosis. Eur J Clin Invest. 1978;8(1):37–40. https://doi.org/10.1111/j.1365-2362.1978.tb00806.x.
121. Ferriby D, de Seze J, Stojkovic T, Hachulla E, Wallaert B, Destee A, et al. Long-term follow-up of neurosarcoidosis. Neurology. 2001;57(5):927–9. https://doi.org/10.1212/wnl.57.5.927.
122. Wijsenbeek MS, Culver DA. Treatment of sarcoidosis. Clin Chest Med. 2015;36(4):751–67. https://doi.org/10.1016/j.ccm.2015.08.015.
123. Christoforidis GA, Spickler EM, Recio, Bharat MV, Mehta M. MR of CNS sarcoidosis: correlation of imaging features to clinical symptoms and response to treatment. Am J Neuroradiol. 1999;20(4):655–69.
124. Huitinga I, De Groot CJ, Van der Valk P, et al. Hypothalamic lesions in multiple sclerosis. J Neuropathol Exp Neurol. 2001;60:1208–18. https://doi.org/10.1093/jnen/60.12.1208.
125. Huitinga I, De Groot CJA, Van der Valk P, Kamphorst W, Tilders FJH, Swaab DF. Hypothalamic lesions in multiple sclerosis. J Neuropathol Exp Neurol. 2001;60(12):1208–18. https://doi.org/10.1093/jnen/60.12.1208.
126. Qiu W, Raven S. Wu J, et al Hypothalamic lesions in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2011;82(7):819–22. https://doi.org/10.1136/jnnp.2009.198192.
127. Kamalian N, Keesey RE, ZuRhein GM. Lateral hypothalamic demyelination and cachexia in a case of 'malignant' multiple sclerosis. Neurology. 1975;25(1):25–30. https://doi.org/10.1212/wnl.25.1.25.
128. Kira J, Harada M, Yamaguchi Y, et al. Hyperprolactinemia in multiple sclerosis. J Neurol Sci. 1991;102:61–6. https://doi.org/10.1016/0022-510x(91)90094-n.
129. Weiss N, Hasboun D, Demeret S, et al. Paroxysmal hypothermia as a clinical feature of multiple sclerosis. Neurology. 2009;72(2):193–5. 1212/01.wnl.0000339102.12168.ee
130. CJA DG, Bergers L, Kamphorst W, et al. Postmortem MRI-guided sampling of multiple sclerosis brain lesions: Increased yield of active demyelinating and (p)reactive lesions. Brain. 2001;124:1635–45. https://doi.org/10.1093/brain/124.8.1635.
131. Waesberghe JHTM, Kamphorst W, De Groot CJA, et al. Axonal loss in multiple sclerosis lesions: Magnetic resonance imaging insights into substrates of disability. Ann Neurol. 1999;46(5):747–54. https://doi.org/10.1002/1531-8249(199911)46:5<747::aid-ana10 >3.3.co;2-w.
132. Sharma CM, Jain A, Kumawat BL, Khanderlwal D, Jain D. Is hypothalamic involvement truly a red flag for multiple sclerosis? Neurology Asia. 2013;18(3):323–5.
133. Jacob A, Matiello M, Wingerchuk DM, Lucchinetti CF, Pittock SJ, Weinshenker BG. Neuromyelitis optica: changing concepts. J Neuroimmunol. 2007;187:126–38. https://doi.org/10.1016/j.jneuroim.2007.04.009.
134. Samart K, Phanthumchinda K. Neuromyelitis optica with hypothalamic involvement: a case report. J Med Assoc Thai. 2010;93(4):505–9.
135. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol. 2006;63:964–8. https://doi.org/10.1001/archneur.63.7.964.
136. Poppe AY, Lapierre Y, Melancon D, Lowden D, Wardell L, Fullerton LM, et al. Neuromyelitis optica with hypothalamic involvement. Mult Scler. 2005;11:617–21. https://doi.org/10.1191/1352458505ms1200cr.
137. Vernant JC, Cabre P, Smadja D, Merle H, Caubarrere I, Mikol J, et al. Recurrent optic neuromyelitis with endocrinopathies: a new syndrome. Neurology. 1997;48:58–64. https://doi.org/10.1212/wnl.48.1.58.
138. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology. 2002;58:143–6. https://doi.org/10.1212/wnl.58.1.143.
139. Murray PG, Hague C, Fafoula O, Patel L, Raabe AL, et al. Associations with multiple pituitary hormone deficiency in patients with an ectopic posterior pituitary gland. Clin Endocrinol (Oxf). 2008;69:597–602. https://doi.org/10.1111/j.1365-2265.2008.03236.x.

18 Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation/Neuroendocrine Tumor (ROHHAD/NET) syndrome

Victoria Habet and Dania Felipe

Introduction

ROHHAD is a very rare and complex pediatric disorder involving the endocrine, nervous, and respiratory systems. In 1965, Fishman et al. described the first case of primary alveolar hypoventilation associated with hypothalamic dysfunction in a 3-year old child with obesity, cyanotic episodes, and diabetes insipidus. Since this first publication, ROHHAD has been associated and confused with CCHS, also referred to as "Ondine's curse". The classic cases of CCHS present in the newborn period with alveolar hypoventilation but some cases have been reported in late childhood and adulthood (late-onset CCHS) [2, 3]. Patients with CCHS and LO-CCHS have a mutation in the paired-like homeobox 2B (PHOX2B) gene, whereas ROHHAD patients do not.

In 2000, Katz et al. summarized a group of 11 patients who presented with hyperphagia/obesity, hypercapnic respiratory failure and hypothalamic/autonomic dysfunction. This group coined the term late-onset central hypoventilation syndrome with hypothalamic dysfunction (LO-CHS/HD) to describe these subjects [4].

Ize-Ludlow et al. determined rapid-onset obesity is the main criterion and presenting sign in all patients with LOCHS/HD. They proposed that the condition be renamed ROHHAD to expedite identification of affected patients [5]. Bougnères et al. proposed consideration of adding "NET" to the ROHHAD acronym to include those patients that also presented with neural crest tumors [6].

Epidemiology

To date, less than 200 cases have been reported since the syndrome was first described in 1965. This can be attributed to advancing knowledge of the clinical presentation and clinical course and creation of the acronym ROHHAD to aid in diagnosis. Despite the increased recognition, the variable onset and timing of clinical features in ROHHAD often result in delayed or missed diagnosis, potentially leading to fatal central hypoventilation, cardiorespiratory arrest, and impaired neurocognitive development [7].

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Pathogenesis

The pathogenesis of ROHHAD is still unknown, although genetic and paraneoplastic or immune alterations have been suggested. Due to similarities with other central hypoventilation syndromes, ROHHAD was presumed to be a monogenic syndrome, but various studies have failed to identify any disease-associated gene variants functionally linked to cellular and altered physiopathlogic processes. Candidate gene investigations have not identified a genetic association with any of the following genes: *PHOX2B*, *TRKB*, *BDNF*, *ASCL1*, *NECDIN*, HTR_{1A}, *OTP*, *PACAP, neurotrophic tyrosine kinase receptor type 2, or brain-derived neutrophic factor* [9]. This is in contrast to CCHS, for which *PHOX2B* was identified as the disease-causing gene. Furthermore, Patwari et al. reported monozygotic twins, one of whom was diagnosed to have ROHHAD while the other twin was unaffected, suggesting that epigenetic factors play a role in the pathogenesis [10]. CSF studies in ROHHAD cases have been reported that include low 5-hydroxyindoleacetic acid, hypocretin-1 deficiency in a child with narcoleptic and cataplectic features, and elevated CSF cytometry for B-cell levels [11]. In another study, abnormalities were confined to the brainstem and consisted of complete loss of neurons with severe fibrillary gliosis [12].

An autoimmune determinant has been postulated based on the presence of CSF oligoclonal bands [13]; postmortem examination of the brain which showed a diffuse, lymphocytic infiltration within the hypothalamus [14]; and partial response to intravenous immunoglobulins and high doses of cyclophosphamide [15]. In addition, Giacomozzi et al. identified anti-pituitary antibodies (APA) and anti-hypothalamus antibodies (AHA) in monkey tissue incubated with a patient's postmortem serum/CSF. Sirvent et al. have suggested the hypothalamic dysfunction of this syndrome resembles a paraneoplastic disorder although they were not able to identify any typical paraneoplastic neurologic antibodies [17].

Clinical Manifestations

Diagnosing ROHHAD is challenging due to lack of any specific markers and nonsynchronous clinical findings. Classically, ROHHAD presents in a previously non-obese and seemingly normal child with rapid and extreme weight gain in preschool years with evidence of hypothalamic dysfunction, alveolar hypoventilation, and features of autonomic dysregulation. The initial manifestation is always rapid weight gain followed closely by hypothalamic dysfunction (Table 18.1).

Hypothalamic Dysfunction. One of the first symptoms of ROHHAD is a 20- to 30-pound weight gain in a child between the ages of 2 and 7 years of age (Figs. 18.1, 18.2) [15, 16]. Often, the plotted weight on the growth curve crosses multiple percentiles by age and/or leaps beyond the standard curves above the 97th percentile within a few months (Fig. 18.3). The diagnosis could be delayed or missed due to the assumption that obesity is exogenous. The most common hypothalamic-pituitary disorder reported

Table 18.1 Phenotypes of 15 children with ROHHAD [5]

n	15
HD	
Rapid-onset obesity	15
Failed growth hormone stimulation test	9
Hyperphagia	8
Polydipsia	8
Hypernatremia	7
Hyperprolactinemia	7
Diabetes insipidus	5
Hypothyroidism	5
Adrenal insufficiency	4
Hypodipsia	4
Polyuria	4
Short stature	3
Delayed puberty	2
Hyponatremia	2

Table 18.1 (continued)

Low IGF-1 and IGFBP-3 levels	2
Precocious puberty	2
Premature adrenarche	2
Transient SIADH	2
Amenorrhea	1
Hypogonadotropic hypogonadism	1
Irregular menses	1
Transient diabetes insipidus	1
Respiratory manifestations	
Alveolar hypoventilation	15
Cardiorespiratory arrest	9
Reduced carbon dioxide ventilatory response	9
Obstructive sleep apnea	8
Cyanotic episodes	4
Developmental disorder	
Developmental delay	3
Developmental regression	3
Autonomic dysregulation	
Ophthalmologic manifestations	13
Thermal dysregulation	11
Gastrointestinal dysmotility	10
Altered perception of pain	8
Altered sweating	8
Cold hands and feet	6
Bradycardia	5
Tumor of neural crest origin	5
Syncopal episodes	1
Other findings	
Abnormal brain MRI scans	7
Seizure	5
Enuresis	4
Hypotonia	4
Asthma	3
Hypercholesterolemia	3
Scoliosis	3
Hypersomnolence	2
Recurrent pneumonia before diagnosis	2
Deceased	1
Impaired glucose tolerance	1
Type 2 diabetes mellitus	1
Behavioral disorders	
Depression	2
Flat affect	2
Psychosis	2
Behavioral outbursts	1
Bipolar disorder	1
Emotional lability	1
Obsessive-compulsive disorder	1
Oppositional-defiant disorder	1
Tourette's syndrome	1
Hallucinations	1

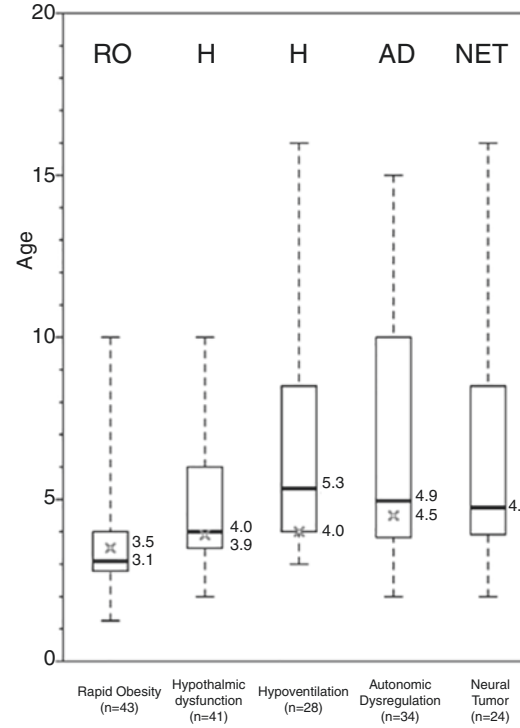

Fig. 18.1 ROHHAD general timeline. Box plots show the median values and the first and third quartiles for each group

in the literature is hyperprolactinemia. Water balance alterations such as hypernatremia, hyponatremia, SIADH, and diabetes insipidus are the second most common, followed by growth hormone deficiency, adrenal insufficiency, and central hypothyroidism. Short stature, delayed and early puberty have also been recognized (Fig. 18.4).

Hypoventilation. Breathing abnormalities develop with variable timing either with or after onset of obesity and can consist of both obstructive sleep apnea and central hypoventilation. Hypoventilation occurred at a median of 5.3 years of age, 2.2 years after the onset of obesity. Some patients have been documented to have nocturnal or both nocturnal/diurnal hypoventilation. All ROHHAD patients eventually require, at a minimum, noninvasive positive pressure ventilation (PPV) during sleep, with as many as

Fig. 18.2 Patient with ROHHAD at (**a**) 2 years 11 months, (**b**) 3 years 6 months, (**c**) 4 years of age, and (**d**, **e**) 9 years 10 months

half requiring ventilation 24 hours per day. Close to 30% of reported patients have required tracheostomy. If adequate ventilatory support is not provided, some patients suffer from cardiorespiratory arrest. Hence, if a child has unexplained rapid weight gain and presents with an endocrinology disorder or dysautonomia, a polysomnography should be recommended. It has also been well-described that some patients may experience neurobehavioral disturbances, including anxiety, depression, aggressiveness, hyperactivity, irritability, and episodes of psychosis. It has been hypothesized, however, that these issues occur due to inadequate oxygenation as a result of undiagnosed or improperly managed hypoventilation [24].

Autonomic Dysregulation. Dysautonomia is an important clinical criterion. Thermal dysregulation (hypothermia/hyperthermia) is the most common manifestation, but pupillary dysfunction (altered responses to light), altered pain perception/sweating, and gastrointestinal dysmotility have been reported as well.

Neural Crest Tumor. Approximately 40–50% of patients with ROHHAD were noted to have neural crest tumors (ganglioneuroblastomas, ganglioneuromas, and rarely neuroblastomas). The median age of occurrence was 4.75 years (4–8.45 years). The neural tumor locations reported included adrenal, thoracic, paravertebral, cervical, paravertebral abdominal, and retropancreatic.

Other Clinical Manifestations. In the majority of patients, brain MRI was normal except for absence of the posterior bright spot in one patient and general cerebral atrophy in another. Other described phenomena included developmental disorder, developmental regression, pneumonia, seizures, narcolepsy, hypercholesterolemia, rectal prolapse, celiac disease, and scoliosis [24].

Table 18.1 details the presenting clinical phenotypes of 15 children with ROHHAD reported in one cohort in the medical literature.

Figure 18.2 shows a child with ROHHAD pre- and post-onset with his accompanying growth charts.

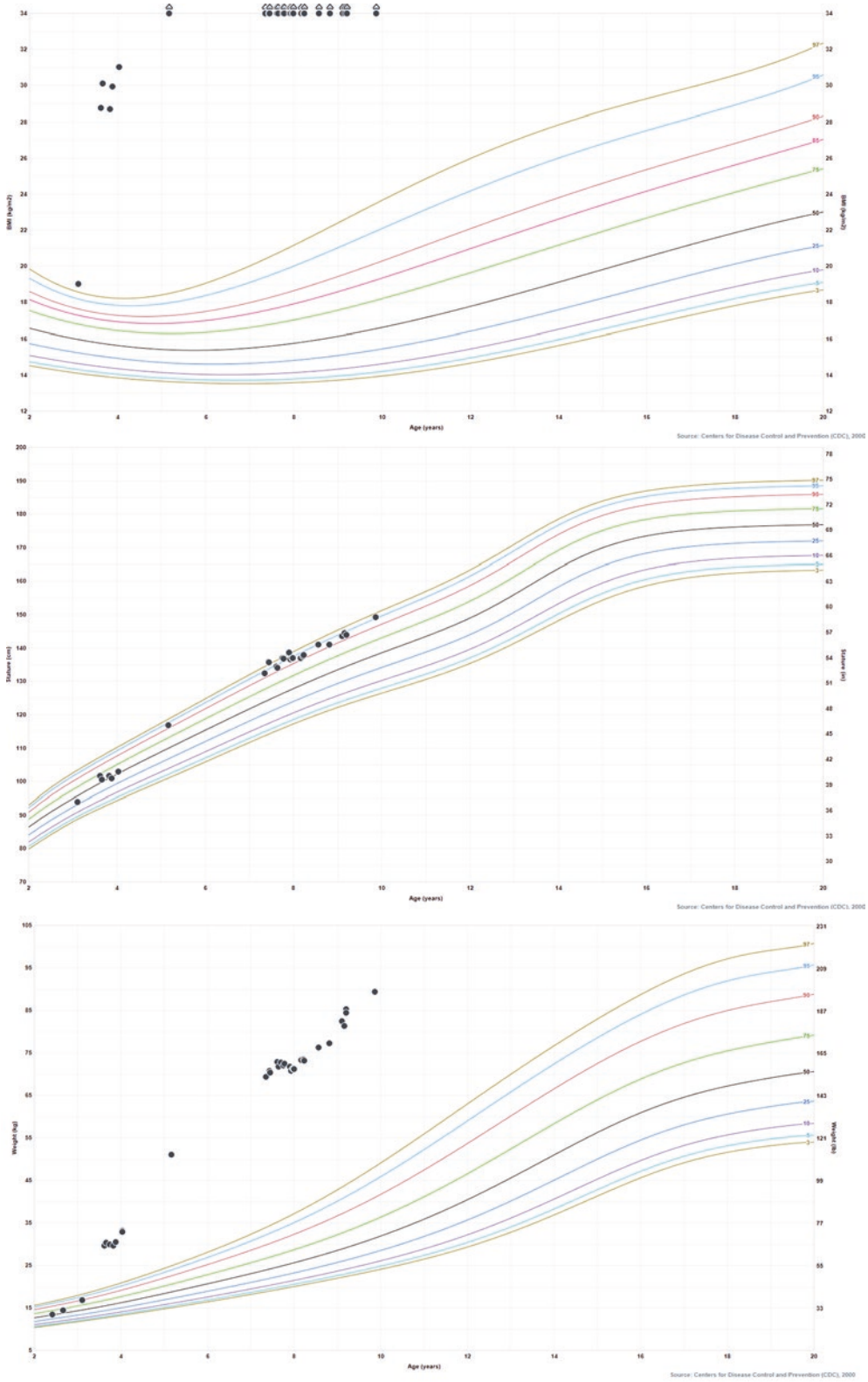

Fig. 18.3 Growth chart of a patient with ROHHAD (same patient as in Fig. 18.2)

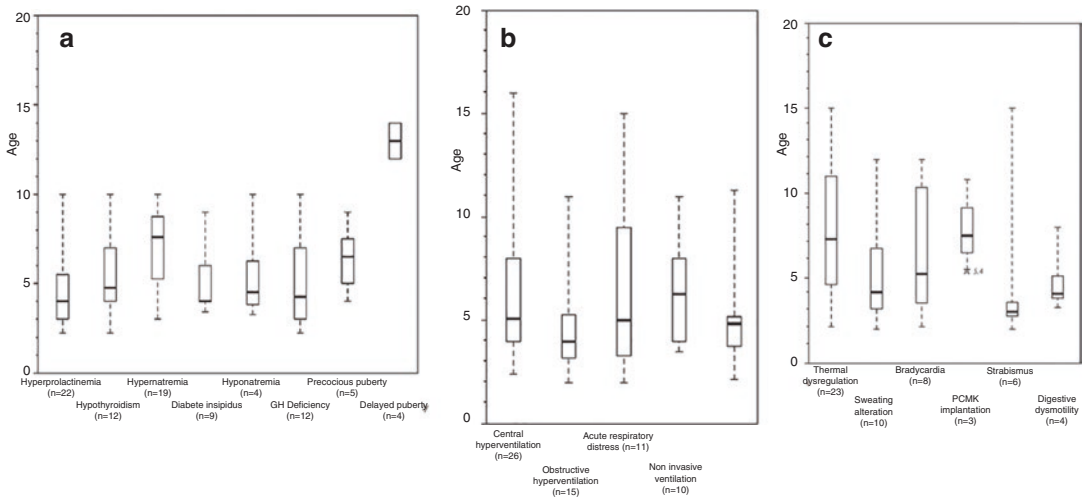

Fig. 18.4 Phenotypic features of ROHHAD. (**a**), onset of hypothalamic clinical findings; (**b**), onset of respiratory events (hypoventilation); (**c**), onset of autonomic symptoms [24]

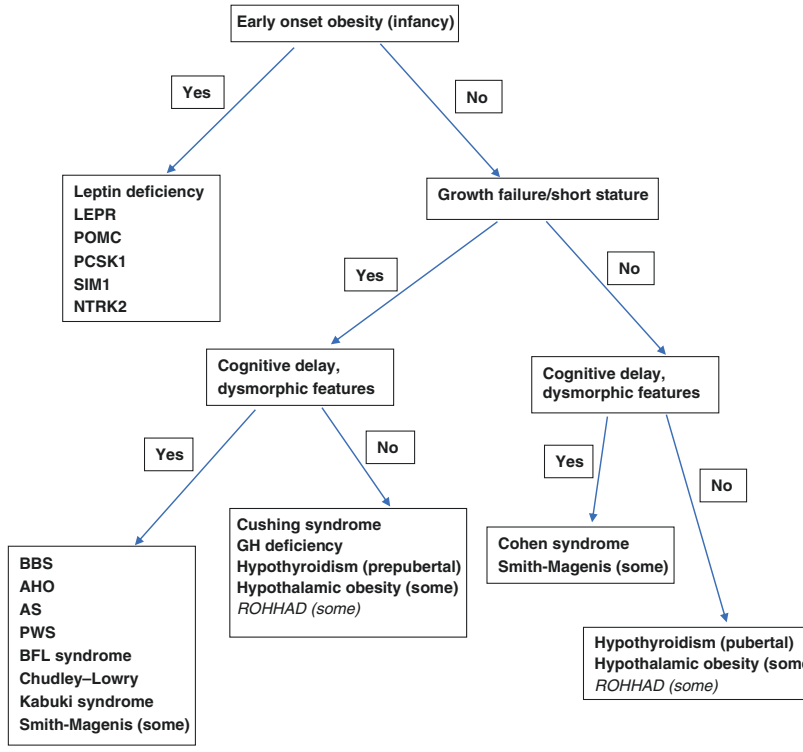

Fig. 18.5 Flowchart of hormonal, monogenic, and syndromic causes of childhood obesity. AHO = Albright's hereditary osteodystrophy; AS = Alström syndrome; BBS = Bardet-Biedl syndrome; GH = growth hormone; LEPR = leptin receptor mutation; MC4R = melanocortin 4 receptor mutation; POMC = proopiomelanocortin deficiency; PWS = Prader-Willi syndrome; ROHHAD = rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation

Diagnosis

There is no gold standard for diagnosing ROHHAD to date. Instead, diagnosis is based on fulfilling certain clinical criteria. Children with ROHHAD appear to have normal growth, development, and general health prior to the onset of symptoms. The first signs of ROHHAD typically present between 2 to 7 years of age and then progress over months to years [11]. The first sign is rapid weight gain with typically normal linear growth. Breathing abnormalities develop with variable timing, either with or after the onset of obesity. To be diagnosed with ROHHAD, patients must have:

1. Rapid weight gain occurring after 2 years of age
2. Evidence of hypothalamic dysfunction, defined as at least one of the following: hyperphagia hyperprolactinemia, central hypothyroidism, disordered water balance, GH deficiency, corticotrophin deficiency, or altered onset of puberty
3. Genetic evaluation to rule out CCHS (absence of PHOX2B mutation) and Prader-Willi syndrome (PWS) should be performed. For patients with growth failure, 24-hour collection of urine for free cortisol should be completed.

The detailed clinical management of these patients requires comprehensive evaluation of the hypothalamic-pituitary axis with hormonal replacement when needed; respiratory physiologic assessment during wakefulness and sleep; and MRI or computed tomographic screening of the chest and abdomen for neural crest tumors. During the evaluation of a patient with suspected ROHHAD, formal water deprivation tests, with measurements of arginine-vasopressin levels should be performed. Other serum measurements to evaluate include prolactin, TSH, free T4, morning cortisol, electrolytes, and gonadotropin levels. Brain imaging should be performed to exclude the possibility of hypothalamic- pituitary abnormalities attributable to intracranial lesions [24]. All patients should be screened with a polysomnogram (PSG). Those who meet criteria but fail to show nocturnal hypoventilation on initial PSG need close follow up with serial PSGs as hypoventilation may develop over time [7]. Once nocturnal hypoventilation becomes evident, daytime monitoring of cardiopulmonary variables is recommended. To assess for neural crest tumors, an abdominal and chest CT or MRI is recommended yearly for the first few years after diagnosis.

Management

A multidisciplinary team should be involved in the evaluation and care of these patients, including general pediatricians, endocrinologists, pulmonologists, oncologists and neurologists, and regular communication with centers with known expertise in ROHHAD. Immunosuppressive treatment is only partially and temporarily efficacious as it has not been shown to stop progression of disease or prevent cardiorespiratory arrest long term. Immunomodulating therapies used have included intravenous immunoglobulin, corticosteroids, rituximab, mycophenolate, and cyclophosphamide. Acnedotal reports have shown favorable response to high-dose cyclophosphamide [22]. For example, Sanklecha et al. report a patient who showed reduction in the need for nighttime BIPAP in response to cyclophosphamide therapy [23]. Jacobson et al. showed improved behavior and neuropsychological functioning after high-dose cyclophosphamide [15]. High-dose cyclophosphamide is thought to modulate the immune response by ablating the mature immune elements. It has been efficacious in patients who have failed conventional immunosuppression. There have also been patients who have responded to therapy with rituximab, though effects appear to be short-lived with symptom recurrence. None of these therapies have led to complete resolution of this condition. While these immunomodulating therapies seem promising, the most important therapeutic approach is the aggressive management of hypoventilation, independently from other treatments, to prevent cardiorespiratory arrest in these high-risk patients.

Conclusion

ROHHAD is a complex and devastating pediatric disorder. Even though there continues to be increased awareness of this syndrome, it remains a challenging diagnosis due to its variable presentation and overlapping features with other obesity syndromes. Thus, ROHHAD should be considered in all cases of rapid and early-onset obesity associated with hypothalamic-pituitary axis dysfunction. Moreover, there is no clear or unifying etiology though several theories have been proposed based on clinical findings and variable but unsustained therapeutic response to immunomodulating agents. Currently, no definitive treatment exists to halt the progression of this disease. Due to the high morbidity and mortality associated with ROHHAD, early diagnosis is key, with aggressive management of hypoventilation being the priority. Further studies are needed to better understand the pathophysiology of ROHHAD and to achieve improved outcomes.

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References

1. Fishman LS, Samson JH, Sperling DR. Primary alveolar hypoventilation syndrome (Ondine's curse). Am J Dis Child. 1965;110:155–61.
2. Weese-Mayer DE, et al. An official ATS clinical policy statement: congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med. 2010;181:626–44.
3. Weese-Mayer DE, Berry-Kravis EM, Zhou L. Adult identified with congenital central hypoventilation syndrome – mutation in PHOX2b gene and late-onset CHS. Am J Respir Crit Care Med. 2005;171(1):88.
4. Katz ES, McGrath S, Marcus CL. Late-onset central hypoventilation with hypothalamic dysfunction: a distinct clinical syndrome. Pediatr Pulmonol. 2000;29(1):62–8.
5. Ize-Ludlow D, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. Pediatrics. 2007;120(1):e179–88.
6. Bougneres P, et al. Endocrine manifestations of the rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, and neural tumor syndrome in childhood. J Clin Endocrinol Metab. 2008;93(10):3971–80.
7. Rand CM, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: analysis of hypothalamic and autonomic candidate genes. Pediatr Res. 2011;70(4):375–8.
8. Reppucci D, et al. ROHHAD syndrome and evolution of sleep disordered breathing. Orphanet J Rare Dis. 2016;11(1):106.
9. De Pontual L, et al. Delineation of late onset hypoventilation associated with hypothalamic dysfunction syndrome. Pediatr Res. 2008;64(6):689–94.
10. Patwari PP, et al. Monozygotic twins discordant for ROHHAD phenotype. Pediatrics. 2011;128(3):e711–5.
11. Patwari PP, Wolfe LF. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: review and update. Curr Opin Pediatr. 2014;26(4):487–92.
12. Frank Y, et al. Sleep apnea and hypoventilation syndrome associated with acquired nonprogressive dysautonomia: clinical and pathological studies in a child. Ann Neurol. 1981;10(1):18–27.
13. Sartori S, et al. Intrathecal synthesis of oligoclonal bands in rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome: new evidence supporting immunological pathogenesis. J Child Neurol. 2014;29(3):421–5.
14. Nunn K, et al. Idiopathic hypothalamic dysfunction: a paraneoplastic syndrome? J Child Neurol. 1997;12(4):276–81.
15. Jacobson LA, et al. Improved behavior and neuropsychological function in children with ROHHAD after high-dose cyclophosphamide. Pediatrics. 2016;138(1):e20151080.
16. Giacomozzi C, et al. Anti-hypothalamus and anti-pituitary auto-antibodies in ROHHAD syndrome: additional evidence supporting an autoimmune etiopathogenesis. Horm Res Paediatr. 2019:1–9.
17. Sirvent N, et al. Hypothalamic dysfunction associated with neuroblastoma: evidence for a new Paraneoplastic syndrome? Med Pediatr Oncol. 2003;40(5):326–8.
18. Barclay SF, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD): exome sequencing of trios, monozygotic twins and tumours. Orphanet J Rare Dis. 2015;10:103.
19. Barclay SF, et al. ROHHAD and Prader-Willi syndrome (PWS): clinical and genetic comparison. Orphanet J Rare Dis. 2018;13(1):124.
20. Aljabban L, et al. Rapid-onset obesity, hypoventilation, hypothalamic dysfunction, autonomic dysregulation and neuroendocrine tumor syndrome with a homogenous enlargement of the pituitary gland: a case report. J Med Case Reports. 2016;10(1):328.

21. Kocaay P, et al. ROHHAD syndrome: reasons for diagnostic difficulties in obesity. J Clin Res Pediatr Endocrinol. 2014;6(4):254–7.
22. Paz-Priel I, Cooke DW, Chen AR. Cyclophosphamide for rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome. J Pediatr. 2011;158(2):337–9.
23. Sanklecha M, Sundaresan S, Udani V. ROHHAD syndrome: the girl who forgets to breathe. Indian Pediatr. 2016;53(4):343–4.
24. Harvengt J, et al. ROHHAD(NET) syndrome: systematic review of the clinical timeline and recommendations for diagnosis. J Clin Endocrinol Metabol. 2020;105(7):2119–31.

19 Infectious Diseases of the Hypothalamic-Pituitary Axis

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Introduction

The information we have regarding hypothalamic infections comes from case reports and small case series [98]. *Mycobacterium tuberculosis* is the most common infectious agent affecting the hypothalamic-pituitary axis [31]. The most common complaints of patients with hypothalamic infections are visual disturbances and headaches. Physical and endocrine dysfunction findings range from CN (III, IV, VI) deficits, hypopituitarism, hypogonadotropic hypogonadism, hyperprolactinemia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hyponatremia, and central diabetes insipidus [5, 98]. Infections can frequently be misdiagnosed as a tumor when forming a sellar or suprasellar mass [98]. The centers controlling fever and leukocytosis in the hypothalamus can be affected. Thus, patients with hypothalamic infections may be afebrile, have normal white blood cell counts, and lack other symptoms of infection. This lack of signs or symptoms of infection can make the diagnosis very difficult.

Infectious of the hypothalamic-pituitary region include bacterial infections, fungal, viral, and parasitic infections. Risk factors for hypothalamic infectious disease are meningitis, paranasal sinusitis, and head surgery. Immunocompromise due to conditions like diabetes mellitus, non-Hodgkin lymphoma, HIV or tuberculosis, malignancies, chemotherapy, immunosuppression treatment, Cushing's syndrome, and organ transplantation is also a risk factor for hypothalamic infection [98].

Hematogenous dissemination probably is the most frequent route for microorganisms accessing the hypothalamus. Pathogens can also reach the hypothalamus after surgical procedures or through shared venous drainage from the nasal cavity and paranasal region.

Case reports or small case series that we found in the literature mention several biological agents as causes of hypothalamic-pituitary infectious. Bacteria report etiology included *Staphylococcus*, *Streptococcus*, *Neisseria*, *E. coli*, *Borrelia*, *Pseudomonas*, *Treponema pallidum*, and *M. tuberculosis*. Reported viruses are HSV, VZV, cytomegalovirus, Tick-borne, Hantaan virus, enterovirus, and *Borrelia*. Fungal pathogens reported were Candida and Aspergillus. Toxoplasma gondii was the only parasitic organism.

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Primary infections of the hypothalamic-pituitary region are the most common; in these infections, the source is unknown or not identifiable. Secondary pituitary infections occur in patients with pituitary adenomas, Rathke's cleft cyst, or craniopharyngioma [98].

Hypothalamic Involvement in Tuberculosis

Epidemiology

*Mycobacterium tuberculosis is an acid-fast g*ram-positive bacillus. Mycolic acid is the principal constituent of the cell membrane and confers the ability to resist destaining by acid alcohol after being stained by certain aniline dyes. Inhalation of *Mycobacterium* and accumulation in the lungs lead to immediate clearance of the organism, primary disease, latent infection (with or without subsequent reactivation disease), or reactivation disease after many years following a latent infection.

The incidence of tuberculosis is still rising in both developing and developed countries. Worldwide, tuberculosis is one of the top ten causes of death and the leading cause due to a single infectious agent even above HIV. The WHO best estimate is that 10.0 million people developed TB disease in 2017 [138].

TB cases occurred in all countries and age groups. Ninety percent of people with tuberculosis are adults, 9% are infected with HIV, and two-thirds live in just eight high-prevalence countries (India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa) [138]. The public health crisis of drug-resistant TB is becoming a civilization existential problem. In 2017, 558,000 people developed TB resistant to rifampicin, the most effective first-line drug. Of these, 82% had multidrug-resistant TB. WHO estimates that 1.7 billion people, 23% of the world's population, have latent TB infection [138].

Central Nervous System Tuberculosis

Central nervous system tuberculosis includes three clinical categories: meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis. The majority of the patients with CNS tuberculosis have a past medical history of pulmonary tuberculosis, but CNS tuberculosis may occur in the absence of systemic disease. Tuberculosis may affect the hypothalamus, pituitary, paranasal sinuses (sphenoid sinus), or a tuberculoma may be located only in the pituitary stalk [98].

Tuberculous meningitis usually spreads to basal parts of the brain from where it can extend to the sellar region. Initially, in the prodromal phase, patients present with an insidious onset of malaise, lassitude, headache, low-grade fever, and personality change for two or three weeks. Patients then develop the two other phases of the disease. The meningitic phase consists of meningismus, prolonged headache, vomiting, lethargy, confusion, cranial nerve involvement, and long-tract signs. The paralytic phase follows and consists of altered mental status progressing to stupor and coma, seizures, and hemiparesis [41, 47, 54, 113]. Early recognition of the CNS TB is critical because prompt treatment is the main predictor of clinical outcome [104].

Hypothalamic-Pituitary Involvement after CNS Tuberculosis

Tuberculous meningitis frequently affected the hypothalamic nuclei of patients that underwent autopsy [134].

The best data we have on the incidence of endocrine abnormalities in adults with tuberculous meningitis comes from prospective studies done in India [32, 82, 83]. Table 19.1 summarizes the findings of these three studies. Hyperprolactinemia was the most frequent finding, followed by cortisol, gonadotrophic, and thyroid hormone.

Basal exudates on MRI predicted the occurrence of endocrine dysfunction [83]. More et al. found small hypothalamic infarcts in three out of 115 patients. Hyperprolactinemia was associated with the presence of basal exudates, hydrocephalus, or tuberculomas. Tuberculomas were also a strong predictor of hypogonadism. Cortisol deficiency was associated with hydrocephalus [82].

Patients with endocrine dysfunction were more likely to die or have a Barthel index

Table 19.1 Endocrine abnormalities in adults with tuberculous meningitis

Baseline									
Number	Multiple Axis	Cortisol	PRL	TSH	FSH/LH	GH	DI	SIADH	
75	29%	43%	49%	31%			0%		[32]
115	23%	13%	23%	17%	34%	8%	0%	10%	[83]
63	44%	43%	49%	10%	38%				[82]
253	30%	29%	37%	19%	35%	8%	0%	10%	Weighted average
Six months follow-up									
38		11%	13%	11%	16%				[82]

score ≤ 12[83]. The most common abnormalities on MRI were basal exudates (25%). Tuberculomas occurred in 3/115 patients and hypothalamic infarcts in 2/115 patients [83].

More et al. treated all their patients with corticosteroids as part of the standard regime and added mineralocorticoids to patients with persistent hypotension. More et al. found SIADH in 10% of their patients and treated them with water restriction, vasopressin receptor antagonists, and 3% sodium chloride solution [83]. Hyperprolactinemia was asymptomatic and did not require treatment [83]. Hypopituitarism persisted in 20% of 49 young adult patients (23 ± 6 years old) who survived tuberculosis in their childhood (6 ± 5 years of age) [64].

Figure PMID: 28716240 more other pending clearance

Tuberculomas

Tuberculous bacilli in the blood lodge in the capillaries forming tubercles that can coalesce into larger caseous masses forming tuberculomas [68]. More et al. found that three of their 115 has suprasellar tuberculomas [83]. Hypothalamic-pituitary tuberculomas are very rare. The review of the literature by More et al. indicates only 86 published cases of suprasellar tuberculomas [83]. Mohammed et al. found that tuberculomas in the hypothalamus-pituitary region were very strong (p = 0.006) predictor of secondary hypogonadism [82]. Tuberculomas can mimic hypothalamic gliomas, and in areas like India of high tuberculous incidence, biopsy should be pursued [13].

Behari et al. classified tuberculomas into three groups [10].

Group A (Fig. 19.1) had sellar and suprasellar masses causing obstructive hydrocephalus due to occlusion of the third ventricle. These lesions required subtotal decompression and placement of a ventriculoperitoneal shunt.

Group B (Fig. 19.2) lesions have multiple ring-enhancing granulomas. They involve the hypothalamus due to the extension of the edema from the pituitary tuberculoma resulting in diabetes insipidus and gonadotrophic hormone deficiency that persisted after resection. [10].

Group C is intrasellar abscesses. The case reported had 2 years of headache, lethargy, and weight gain. The patient had hypogonadism and hypothyroidism. The pituitary stalk was thick and enhancing on MRI, but there was no other hypothalamic involvement. The lesion was full of yellowish pus that showed no acid-fast bacilli or granulomas. However, mycobacterial cultures were positive after 6 weeks. This patient had no deficits after surgery but required ongoing hormone replacement.

Group D lesions consist of pachymeningitis that extends into the suprasellar region. This patient presented with meningism, vomiting, anorexia, and weight loss.

In rare cases, CNS TB may present as tuberculous hypophysitis. Uncommon presentations also include sellar/suprasellar tuberculoma (as illustrated in Fig. 19.3 above) simulating a pituitary adenoma or pituitary apoplexy [4, 49, 112]. Fever, neurological abnormalities like headache and visual disturbances, and neuroendocrine dysfunction are some symptoms and signs found in sellar tuberculoma.

A sellar and suprasellar tuberculoma with thickening of the pituitary stalk requiring biopsy caused reversible hypopituitarism improved after multidrug antituberculosis therapy [122].

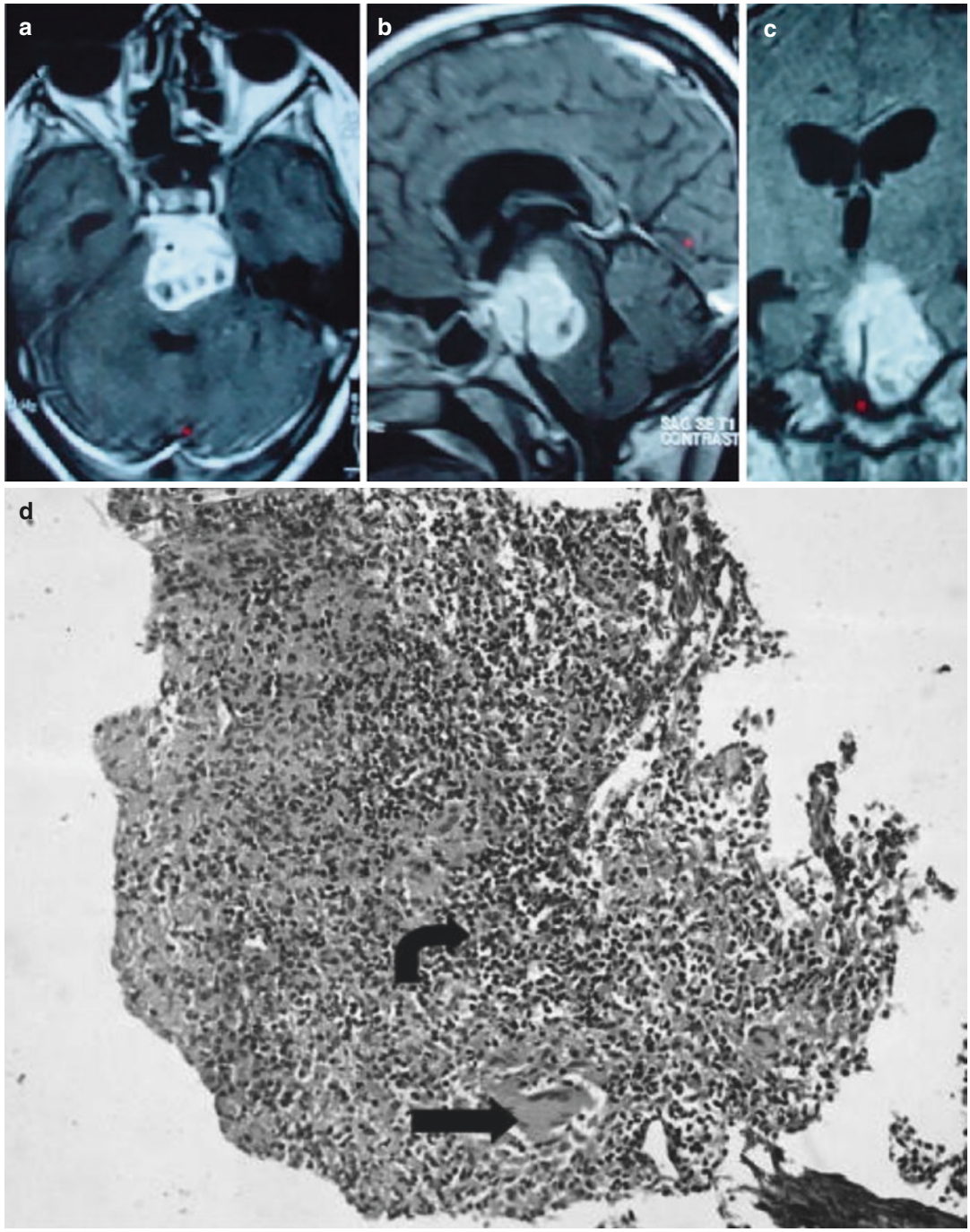

Fig. 19.1 Group A tuberculomas are infiltrating the hypothalamus and causing hydrocephalus. (**a**–**c**) Contrast-enhanced MRIs. (**d**) Histopathology shows epithelioid cell granuloma (curved arrow) and the Langerhans type of histiocytic giant cells (straight arrow). Haematoxylin and eosin stain, original magnification ×200. (Reproduced with permission from [10])

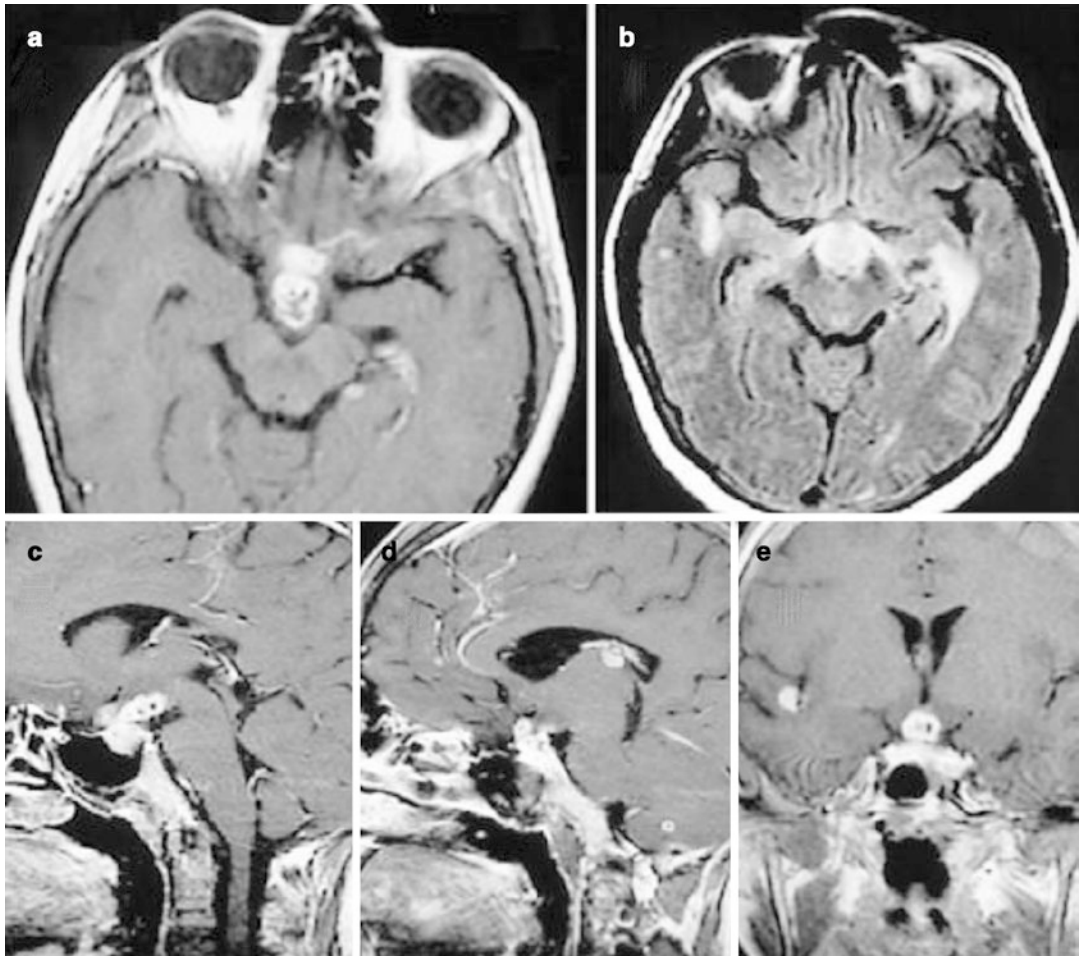

Fig. 19.2 Contrast-enhanced axial T1-weighted MRI showing multiple, coalescing ring-enhancing tuberculomas in the sellar and suprasellar region. The medial temporal lobe shows (**a**) small enhancing tuberculoma. (**b**) Fluid attenuated inversion recovery axial MRI was showing the extensive edema around the suprasellar lesions and the perisylvian lesion. (**c**, **d**). Contrast-enhanced sagittal T1-weighted MRI is showing the multiple ring-enhancing coalescing lesions in the sellar–suprasellar region with thickening and enhancement of the chiasma. There is mild perifocal edema around the granuloma in the hypothalamic area. There are also ring-enhancing granulomas present in the cerebellum and near the velum interpositum and thalamic regions. (**e**) Contrast-enhanced coronal T1-weighted MRI shows coalescing granulomas in the sellar-suprasellar area extending to the left cavernous sinus region. There is also a small right-sided perisylvian tuberculoma. [10]

A diagnosis could be a challenge, especially in cases when there is no systemic tuberculosis and the MRI shows thickening of the pituitary stalk or abnormal enhancement pattern of the sellar lesion mimicking adenomas [14, 50, 112].

Grade 1B (strong recommendation) recommendation is the initiation of antituberculous therapy if there is a strong clinical suspicion of CNS tuberculosis. For HIV-unifected patients and HIV-infected patients with established or suspected TB meningitis, adjunctive glucocorticoid therapy is recommended. For HIV-infected patients with CNS TB and not already on antiretroviral treatment, the best course is to defer initiating antiretrovirals for 8 weeks after starting TB treatment [69]. There is no indication for surgery in patients with tuberculous hypophysitis if antituberculous drugs are working [97].

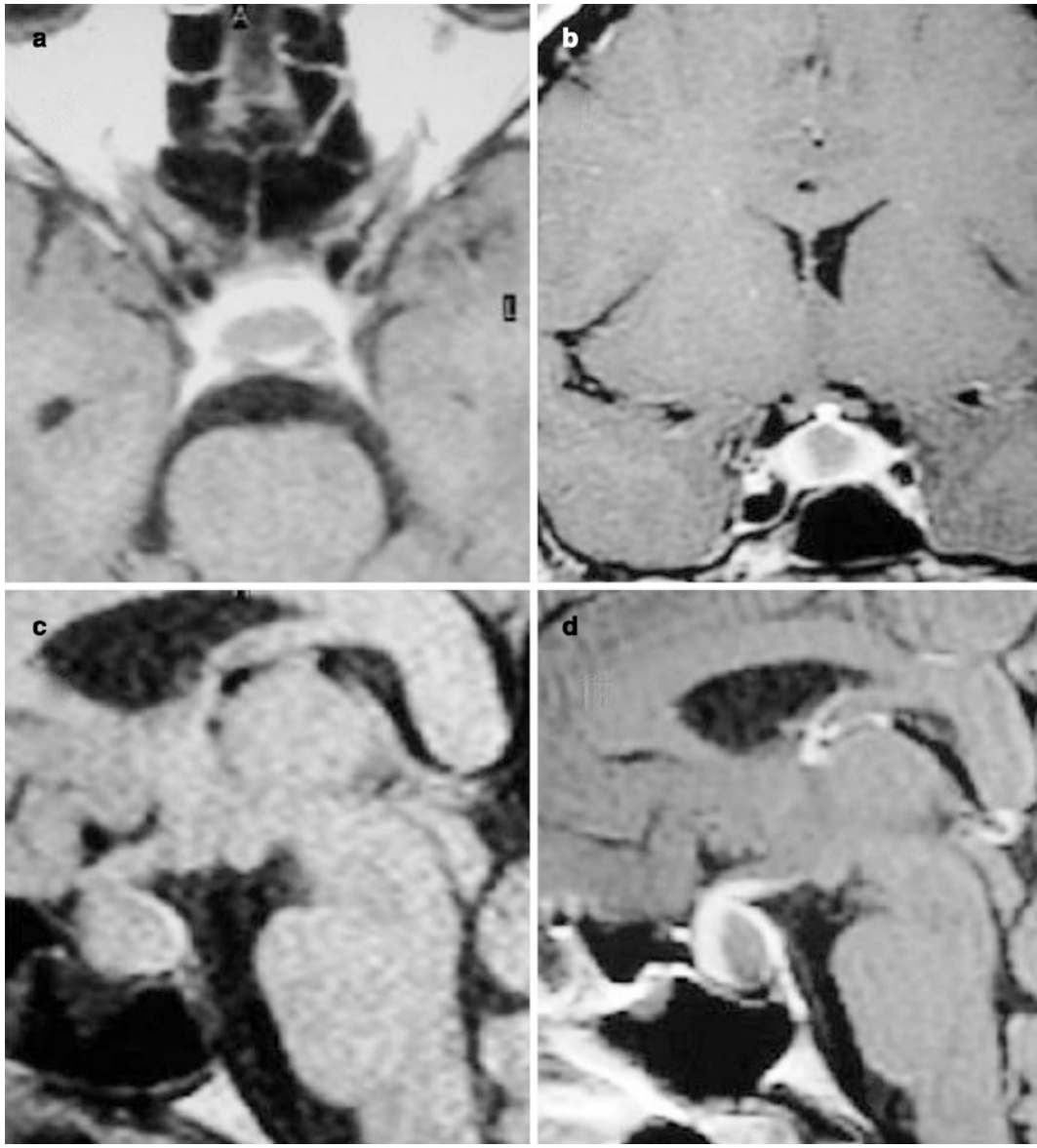

Fig. 19.3 (**a**) Contrast-enhanced T1-weighted axial MRI is showing the rim-enhancing sellar tuberculoma with a central hypointense area representing central caseation. (**b**) Contrast-enhanced T1-weighted coronal MRI showing the central caseation with the enhanced and thickened pituitary stalk. There is no extension to the cavernous sinus. (**c**) Plain T1-weighted sagittal MRI shows the isointense sellar lesion. The posterior pituitary appears hyperintense. (**d**) Enhanced T1-weighted sagittal MRI is showing the rim enhancement and the central hypointensity of the intrasellar tuberculoma with caseation. The pituitary stalk is thick and enhancing. (Reproduced with permission from [10])

Hypothalamic Pituitary Involvement After Non-mycobacterial Meningitis

When assessed systematically, it becomes clear that pituitary insufficiency occurs frequently after acute or late stages of non-tuberculosis CNS infections [31, 108, 123, 131]. Schaefer et al. studied 19 patients with a previous history of infectious CNS disease of different etiologies with a mild or moderate course and found isolated corticotrophic insufficiency in 21%; gonadotropic insufficiency in 11%; and no somatotropic, thyrotropic, or posterior pituitary insufficiency[108]. Four out of seven patients reporting fatigue in the study by Schaefer et al. had corticotropic insufficiency, and one of the four had a massive improvement in fatigue after replacement therapy. Tanriverdi et al. found a 29% growth hormone deficiency in their 14 patients with bacterial or viral meningitis [123].

The available prospective studies have also studied meningitis cases due to a mixture of viral, bacterial, fungal, or unknown agents. These studies show that pituitary dysfunction is frequent and resolves in some but not all cases. Tsiakalos et al. found pituitary dysfunction in 31% of their 16 sequential patients evaluated during the acute phase of meningitis and persistent dysfunction in 31% of the 12 patients who had a one-year follow-up. During the acute phase, deficiencies in IGF-1 production occurred in 3 out of 16 (19%) patients, 1 out of 16 (6%) patients had elevated prolactin, and 7 out of 16 (44%) patients had low T3 syndrome. Twelve months after the acute stage, 5 out of 12 (42%) patients in the study by Tsiakalos et al. had persistent somatotropic, corticotropic, or combined axis deficiencies [131]. Similarly, Dhanwal et al. found adrenal insufficiency in 23% and hyperprolactinemia in 30% of their 30 prospective cases with non-mycobacterial acute meningitis [31]. Tanriverdi et al. found anti-pituitary and anti-hypothalamic antibodies in 35–50% of their prospectively evaluated patients throughout a 12-month follow-up, but the presence of these antibodies did not predict hypopituitarism [124].

Hypopituitarism after nontuberculous meningitis in children is not as common as in adulthood [40, 53]. Giavoli et al. studied 19 children after meningitis of viral and bacterial etiologies and found no abnormalities in the levels of thyroid hormone, IGF-1, prolactin, sex steroids, and gonadotropin as well as no evidence of diabetes insipidus [40]. Karadag-Oncel et al. found no deficits in the ACTH stimulation test in 37 children evaluated 8 to 135 months after bacterial meningitis and GH neurosecretory dysfunction (low IGF1 with normal GH response in clonidine test) in 3 out of 37 (8%) [53].

Case reports show that neonates can develop with severe cases of hypopituitarism are reported in a neonate after acute meningitis caused by Streptococcus Group B [36] and a neonate after sepsis caused by Salmonella enteritidis [107]. The pituitary dysfunction in this last case may have been due to the prolonged use of dopamine to sustain blood pressure.

In summary, nontuberculous meningitis in adults frequently results in dysfunction of the hypothalamic-hypophysis axis. The studies so far have aggregated viral, bacterial, and unknown etiology cases. It remains to be seen whether these different etiologies have the same incidence of HPA dysfunction. Replacement of cortisol in some of the patients resulted in improvement in fatigue. Children seem to be more resilient, but some will have a deficiency in growth hormone secretion. Neonates may have very severe loss of pituitary function. Anti-hypothalamic antibodies are frequently detectable after meningitis, but they do not appear to predict dysfunction of the HPA axis. There is limited information regarding other hypothalamic functions after meningitis beyond the hormonal axis, such as sleep, circadian rhythm, and appetite.

Treponema pallidum Infection (Syphilis)

Treponemas are extremely thin spirochetes (0.1–0.2 × 6–20 μm). Due to their minimal cross-section, they are not visible under direct

microscopy. Treponema cannot be cultured because they are obligate intracellular microorganisms as they depend on the host cell for all purines, pyrimidines, and most amino acids [86].

Seventeen million people worldwide are affected by syphilis, according to the World Health Organization (WHO) estimates, and 5.6 million new syphilis cases occur each year [88], with 748,000 cases per year of infections during pregnancy [62]. Syphilis should remain in the differential diagnosis of endocrinological, psychiatric, and neurological conditions [89]. Developing countries are leading the list due to a lack of availability of prenatal testing and antibiotics. In 2001, the United States' rate of primary and secondary cases of syphilis was the lowest reported since reporting started in 1941. Since 2001, the incidence of primary and secondary syphilis has increased every year up to 10.8 cases per 100,000 in 2018, with the incidence rising among women and men that have sex with men [20].

Treponemas cause diverse clinical manifestations: acquired venereal syphilis with initial genital tract lesion (primary stage) followed by disseminated lesions (secondary stage) and, in approximately one-third of untreated individuals, cardiovascular and neurologic manifestations (tertiary stage) [86].

Syphilis is a well-recognized cause of hypopituitarism, with granulomatous hypophysitis (noncaseating giant cell granuloma), syphilitic gumma in the sellar region, or congenital syphilis causing hypothalamic-pituitary dysfunction [90].

Hypophysitis due to syphilis appears to be rare in the last decades. Spinner et al. report a case of pituitary gland enlargement with hypopituitarism caused by *Treponema pallidum* in a patient with HIV and syphilitic meningitis [115]. Benzick et al. reported a case of congenital gumma in the pituitary in an infant that died on the third day of life [11]. Syphilis may also cause sellar mass with suprasellar extension mimicking a pituitary tumor and causing hypopituitarism [16].

To review more florid reports, one has to go to textbooks and journals from the first half of the century. Cushing reports a case of a merchant that died from misdiagnosis of a pituitary syphilitic gumma. This patient had diabetes insipidus, lethargy, and hypothermia [26]. Syphilitic polyuria was a classic presentation of syphilis [102]. Hywel describes nine cases of diabetes insipidus, four of which were due to syphilis, usually due to basilar meningitis [28]. Oelbaum describes hypopituitarism in two cases due to syphilitic origin [90].

Pituitary Abscess

Pituitary abscesses can occur in a healthy normal gland (two-third of patients) or a gland affected by conditions such as pituitary adenoma, Rathke's cleft cyst, or craniopharyngioma [5]. They are infrequent pituitary lesions accounting for less than 1% of all pituitary disorders. Compared to patients with a pituitary adenoma who rarely have neuroendocrine dysfunction, most patients with pituitary abscess have hypopituitarism [38, 73]. Patients will present with neurological signs and symptoms of headache and visual disturbances, signs of neuroendocrine dysfunction (anterior hypopituitarism, diabetes insipidus), and symptomatology related to infection like fever and leukocytosis [5, 73]. Unfortunately, imaging studies, including CT scan and MRI, are unable to distinguish between pituitary abscess and pituitary adenoma. As a result, for most patients, the diagnosis is made at the time of surgical exploration [135].

Gao et al. report a case series of 66 cases collected over a period of ~23 years. The study described anterior pituitary hypopituitarism in 81.8% and diabetes insipidus in 47.9% of patients. Isolated hypogonadism occurred in 9.3%, isolated ACTH deficiency in 3.7%, isolated hypothyroidism in 1.8%, and combined hypogonadism and ACTH deficiency in 1.8% of patients. The clinical workup could identify the source of the pituitary infection in 14 out of 66 patients (sepsis, sinusitis, pulmonary tuberculosis) [38].

The infective source causing the abscess can be hematogenous dissemination or direct extension from surrounding structures as in conditions such as meningitis, sphenoid sinusitis, or cavernous sinus thrombophlebitis. A pituitary abscess can be acute, subacute (course less than 1 month),

or chronic (duration longer than 1 month). In another case series of 24 patients, 16 (67%) presented with symptoms and physical findings consistent with pituitary mass, while only eight had features suggestive of infections (fever, leukocytosis, meningismus). These infective manifestations have been reported in the acute and subacute phases of the disease, while the chronic stage has an indolent course [135]. It is worthy of mentioning that pituitary surgery and immunocompromised individuals are also at risk for pituitary abscess.

Intraoperative detection of pus and postoperative histological analysis built the diagnosis for this grave condition. Transsphenoidal surgery or, less frequent, transcranial methods are the preferred surgical approach [38]. Pus is found in the sella intraoperatively, or in patients with secondary pituitary abscesses, the sphenoid sinus is the most common area of extrasellar invasion [2, 5, 140].

Figure 19.4 below shows a representative coronal and sagittal MRI of a patient with a pituitary abscess.

In most cases, the etiological agents could not be isolated. In the most extensive study on pituitary abscesses reported, only 19.7% of patients had positive results on gram staining or bacterial

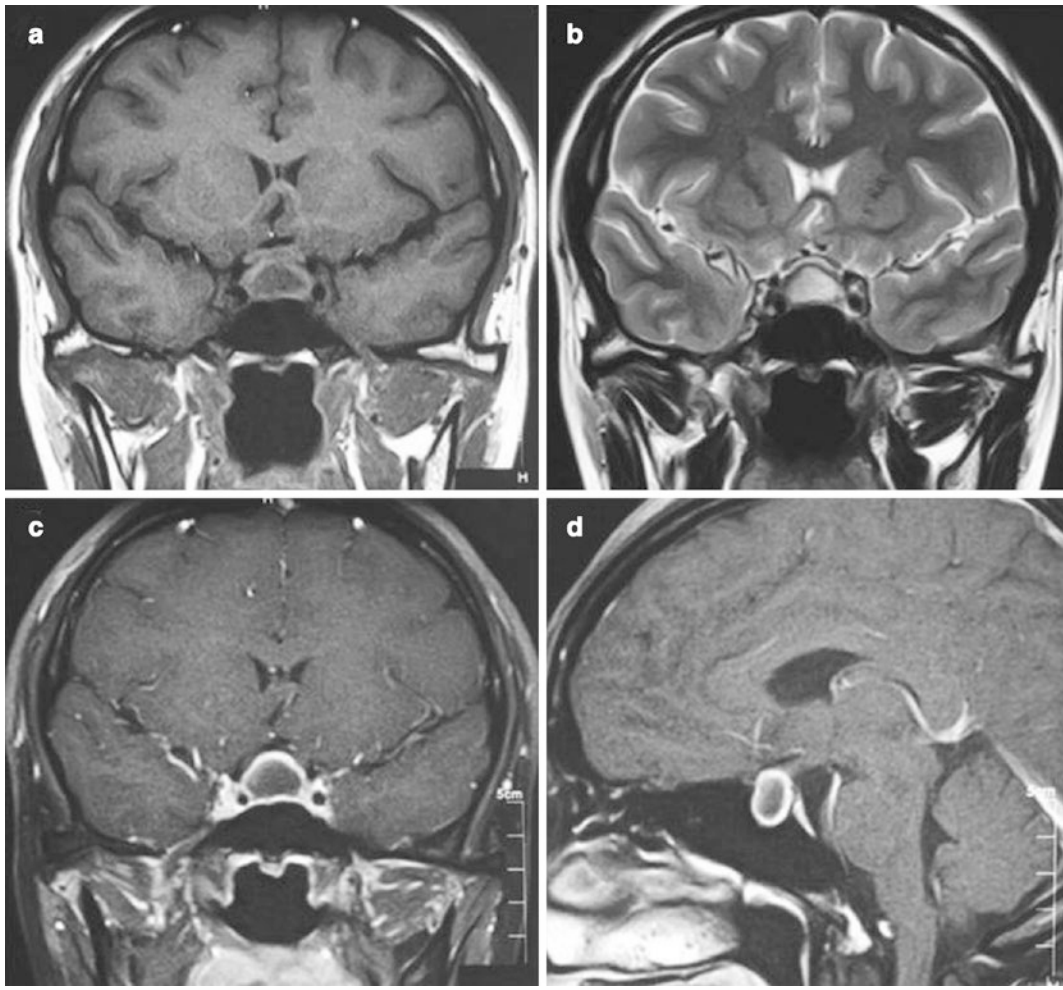

Fig. 19.4 Typical MRI findings in a patient with a pituitary abscess. (**a**) T1-weighted MRI shows hypointense and isointense signals (coronal). (**b**) T2-weighted MRI shows hyperintense and isointense signals (coronal). (**c**) Rim enhancement after gadolinium injection (coronal). (**d**) Rim enhancement after gadolinium injection (sagittal). (Reproduced with permission from [38])

cultures [38]. Table 19.2 summarizes the microorganisms detailed in the two most extensive case series [5, 38]. Histopathology shows evidence of acute or chronic inflammation [38].

Although pituitary abscesses are diagnosed by sampling them, MRI is still an essential tool in their recognition. 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. Other necessary sequences are T1-weighted imaging with hypointense or isointense and T2-weighted imaging with hyperintense or isointense sellar mass [121].

Treatment of the pituitary abscesses includes resection and intravenous and oral antibiotics to prevent a recurrence. Some cases need reintervention. Vates et al. report in their series that in the patients with healthy endocrine function before surgery, few had transient diabetes insipidus after surgery and no other permanent endocrine deficits [135]. In most cases, neuroendocrine dysfunction and diabetes insipidus are irreversible findings, but multiple hormone deficiencies or panhypopituitarism will likely result in needing long term hormone replacement.

Table 19.3 below details the observed endocrine deficits observed in an aggregate set of case series of patients with pituitary abscesses.

Table 19.2 Summary of reported organisms isolated from pituitary abscesses

Organism	N
Acinetobacter baumannii	1
Aspergillus	1
Bacteroides	1
Citrobacter sp.	1
G- cocci	1
G+ cocci, −ve cultures	1
G+ cocci. −ve cultures	1
Gram-negative cocci	1
Group A *Streptococcus* + *Staphylococcus epidermidis*	1
Mucormycosis	1
Mycobacterium fortuitum	1
Mycobacterium tuberculosis	1
Proteus mirabilis and *Pseudomonas aeruginosa*	1
Pseudomonas aeruginosa	1
Pseudomonas fluorescens	1
Staphylococcus aureus	1
Staphylococcus epidermidis	1
Sensitive *Staphylococcus aureus*	1
Staphylococcus haemolyticus	1
Staphylococcus lugdunensis	1
Streptococcus alpha-hemolytic	1
Streptococcus faecalis	1
Streptococcus pneumoniae	1
Toxoplasma gondii	1
β-Hemolytic *Streptococcus*	1
Escherichia coli	2
Gram-negative bacteria	2
Staphylococcus epidermidis	2
Streptococcus alpha-hemolytic, *Neisseria* sp., *Micrococcus* sp., *S. epidermidis*	2
Aspergillus fumigatus	4
MRSA	4
Sensitive *S. aureus*	6
Negative	63
Total	110

Aggregate data from [5, 38, 135]
MRSA methicillin-resistant *Staphylococcus aureus*

Table 19.3 Summary of endocrine outcomes after pituitary abscess

Outcome Endocrine deficit	Number of patients
Died	8
No data	2
Normal	1
Multiple hormones	4
Panhypo	1
Full recovery	34
No data	11
Normal	7
P ↑	2
GH↑	1
Multiple hormones	5
Panhypo	8
Hormone replacement	64
No data	1
Normal	1
P ↑	1
TSH↑	1
ACTH↓	1
Multiple hormones	5
Panhypo	54
Lost FU	4
Multiple hormones	2
Panhypo	2
Grand total	110

Aggregate data from [5, 135, 38]

Neuroborreliosis (Lyme Disease)

Borrelia burgdorferi is the causal agent of neuroborreliosis. It is a spirochete transmitted through a tick that can invade the CNS in up to 15% of the affected patients. The clinical course is highly variable, and symptoms include headache, cranial nerve palsies, and lancinating pain [52, 92, 116]. Meningoradiculitis (Bannwarth's syndrome) is the most frequent presentation in Europe, while myelitis and encephalitis are rare clinical manifestations. The symptoms of neuroborreliosis might be unspecific and mimic other neurological conditions [45, 116].

Patients are categorized into acute neuroborreliosis (symptoms duration <6 months) and late manifestation/chronic neuroborreliosis (symptoms duration > 6 months). Chronic encephalitis or acute stroke-like symptoms also occur, but the most frequent onset is subacute with progression over weeks [43, 87, 92, 128].

The medical history, clinical finding, and serological and cerebrospinal fluid analysis (pleocytosis and detection of Borrelia specific antibodies in CSF) support the diagnosis [91]. Patients treated with antibiotics will have a favorable outcome, although a small number of patients will relapse or remain with residual symptoms [29, 30, 35, 75, 91, 100].

Strokes are rare complications of neuroborreliosis [39], and they can involve the hypothalamus [3].

Reported cases show SIADH occurring with acute Lyme infection and improvement of the SIADH after antibiotic treatment [99, 111, 114]. However, it is not sure that the involvement of the hypothalamus was the cause of the SIADH in these cases as MRI was unrevealing [114] or did not show hypothalamic lesions in-spite of showing multiple other T2 hyperintensities [99].

Patients affected with neuroborreliosis commonly complain of persistent and unspecific symptoms after treatment. Endocrine dysfunction could be the cause of these symptoms. Schafer et al. did not find corticotropic insufficiency in the four patients Lyme neuroborreliosis in their study of patients with previous infectious diseases of the CNS [108]. Tjernberg et al. found a high proportion (40%) of LNB patients suffer from persistent pronounced symptoms 2–3 years posttreatment and that the severity of their symptoms correlated with absolute cortisol increment after ACTH ($r = 0.68$; $p = 0.001$) which was independent of IL-6 production [127].

Hypothalamic Pituitary Viral Infections

Viral infections of the CNS causing hypopituitarism can occur in the acute phase of meningitis and encephalitis or the late stage of these diseases [108, 123, 124, 131]. In the cases studied by Schafer et al., one of the patients with corticotropic deficiency had a history of enterovirus meningitis. The other three of the four patients with a corticotropic deficiency in Schafer's study had a history of meningitis of unknown etiology. The two patients with a history of herpes meningitis and varicella meningitis had no endocrine findings [108].

Central diabetes insipidus (CDI) developed in five infants with congenital cytomegalovirus infection [79] and in a five-year-old boy with encephalitis caused by Coxsackievirus B1 after resuscitation [67]. CDI can also happen in immunocompromised patients with encephalitis caused by cytomegalovirus [84], herpes simplex [67, 77, 109, 129], and varicella-zoster virus [132]. In these cases, the immunosuppression was due to HIV infection, Cushing's syndrome, lymphoma, and immunosuppressive therapy. Moses et al. found direct cytomegalovirus invasion of the hypothalamus and reduction in the number of arginine vasopressin oxytocin cells [84]. Lipsett et al. reported a case of a six-year-old child who, 6 weeks after recovering from varicella developed lethargy, persistent fever of unknown etiology, and twenty-pound weight gain, died from intractable fever. The boy's autopsy showed healthy brain tissue except for gliosis and lymphocytic infiltration of the hypothalamus, particularly in the tuber cinereum and supraoptic nuclei. The meninges showed arachnoiditis along the base of the brain and pituitary stalk [72].

Hypothalamic viral infections are very sporadic. We could find only one case of an otherwise female patient who developed diabetes insipidus 3 weeks after acute herpes simplex encephalitis [18].

Hantavirus

Hantaviruses are the cause of hemorrhagic fever with renal syndrome (HFRS). The disease is endemic in Europe (Balkans, Finland, and Germany) and Asia (Korea). Farmers and soldiers are exposed to the virus by inhalation of infected rodent urine, feces, or saliva. Hantavirus infiltrates the vascular system causing increase capillary permeability, renal failure, thrombocytopenia, hemorrhage, fever, hypotension, and shock [96].

The virus is well known to affect the pituitary. Autopsy findings reported a slightly enlarged pituitary with ischemia/infarction, hemorrhage, and necrosis [46, 61, 133]. Hypophysitis with direct viral invasion in the pituitary gland also occurs [46].

Hypothalamic-pituitary dysfunction happens during the acute phase or after long-term follow-up [1, 37, 58, 71, 94, 96, 110, 118]. Sellar MRI imaging in patients with hypopituitarism shows an edematous pituitary gland or increased signal intensity in the pituitary due to hemorrhage during the acute phase, while pituitary atrophy and secondary empty sellar develops months and years after the acute infection [51, 95, 96]. High-resolution CT in patients with hantavirus infection shows a progressive decrease in the size of the pituitary gland that correlates with decreased pituitary reserve for follicle-stimulating hormone, cortisol, and growth hormone [71]. These cases did not have evident direct involvement of the hypothalamus.

The involvement of the hypothalamus at the level of the pituitary stalk occurs in rare cases during the acute infection resulting in central diabetes insipidus [1, 23, 66]. *Puumala hantavirus* causes a milder form hemorrhagic fever with renal syndrome that can result in the development of hypophysitis, hypopituitarism, and central diabetes insipidus that appears to be due to late-onset autoimmune reaction [125].

Von Economo's Encephalitis Lethargica

Constantin Von Economo described in 1916–1917 several patients with somnolence varying from mild sleepiness to constant sopor that they could always, at least transiently wake up from after being called or stimulated. He discovered that these patients had gliosis in the posterior lateral walls of the third ventricle extending into the hypothalamus [137]. Von Economo classified the acute manifestations into three categories, the somnolent-ophthalmoplegic form, the hyperkinetic form, and the amyostatic-akinetic form [33]. From his pathological clinical correlations, von Economo recognized two centers in the hypothalamus: one in the anterior hypothalamus promoting sleep and one in the posterior hypothalamus maintaining wakefulness [126]. The epidemic coincided with the influenza pandemic, but the causal agent for encephalitis lethargica was never identified [33].

Hypothalamic-Pituitary Parasitic Infections

Toxoplasmosis

Toxoplasma gondii causes toxoplasmosis, the most common central nervous system infection in immunocompromised patients like HIV patients. CNS toxoplasmosis resulted in hypopituitarism, accompanied by focal neurological deficits, headache, and fever [44], but without direct evidence of hypothalamic involvement.

Human African Trypanosomiasis (HAT)

Trypanosoma brucei, an extracellular parasite, causes African human trypanosomiasis, also known as sleeping sickness. Sixty-five million

people are at risk for this disease. Tsetse flies (Glossina sp.), endemic to sub-Saharan Africa, transmit the disease. Because successful programs identifying cases early and targeted vector control decreased the number of cases by 95% from 2000 to 2018, efforts had been underway to eradicate HAT by 2020 [130], but challanges remain [9] including the difficulties of eliminating cattle and human reservoirs [56]. The disease is usually fatal, although some people may be resistant or tolerant to the infection [56].

There are two subspecies of *Trypanosoma brucei*, *T. brucei rhodesiense*, and *T. brucei gambiense.* The two subspecies cause similar disease but with different time courses. The *T. brucei rhodesiense* form is particularly aggressive, causing death within 6 months, while *T. brucei gambiense* form is more protracted and can last several years and accounts for 97% of the prevalent cases.

The tsetse fly bites an infected individual, and the parasites move from the blood meal to the midgut of the insect, where they will become lifelong residents. The fly then goes on to bite other humans or cattle. Upon entering the skin of a new host, the parasites divide asexually invading the bloodstream and lymphatic system spreading into the liver, spleen, heart, endocrine organs, and visual system. The trypanosomes coordinate their reproduction, ensuring that hordes of parasites enter the circulation in coordinated waves [34]. The parasites continuously switch on and off 9000 genes coding for variant glycoproteins expressed on the parasitic surface, ensuring that each wave has a new set of antigens that evade round after round of immunoglobulins produced by the host. This masterpiece of immunological camouflage makes vaccination impossible [85].

Since the adaptive immune system is unable to deal with trypanosomes, humans evolved innate an innated defense protein system consisting of apolipoprotein A1, apolipoprotein L1, and haptoglobin-related protein. *Trypanosoma brucei rhodesiense* and *T. brucei gambiense* developed additional mechanisms to evade these defenses allowing to infect humans [19].

The invasion of the blood is the hemolymphatic stage of the disease characterized by intermittent fever, lymphadenopathy, pruritus, and particular deep pain sensations. The parasites cross the blood-brain barrier, initiating the meningoencephalitic stage. Animal models suggest that the trypanosomes invade the brain through areas of the brain that lack a blood-brain barrier. The lack of a blood-brain barrier makes the choroid plexus, the circumventricular organ, and peripheral ganglia the initial port of entry into the brain. The median eminence of the hypothalamus is one of the circumventricular organs which the parasites use as their beachhead. The trypanosomes can move very fast; they can advance 10 times their length in a second [8]. They use their speed for rushing from the median eminence into the arcuate nucleus hypothalamus upsetting the mechanisms regulating sleep and circadian rhythm. The rapid invasion process also occurs across the circumventricular organs and basal ganglia from where the parasites hastily invade the white matter following the large extracellular spaces.

Autopsy studies of patients with meningoencephalitic trypanosomiasis show inflammatory infiltrates consisting of lymphocytes, plasma cells, and macrophages involving the meninges, choroid plexus, and perivascular spaces of the white matter [55]. The basal ganglia, thalamus, and hypothalamus around the third ventricle also show marked perivascular infiltrates [78]. Mott cells, thought to be modified plasma cells containing eosinophilic inclusions of IgM, are pathognomonic. The widespread changes do not readily explain the specific clinical features of HAT, and interestingly, at autopsy, neurons have been reported as relatively undamaged [55]. For yet unclear reasons, autopsy studies very rarely show the parasites [78].

Animal model experiments show that the *Trypanosoma* targets orexin wake-promoting neurons in the lateral hypothalamic nuclei. The parasite also targets the suprachiasmatic nucleus disrupting the circadian pacemaker and also targets the peptidergic cell populations of the lateral hypothalamus that help maintain wakefulness [126]. Patients with HAT lose the circadian sleep-wake cycle pattern falling asleep multiple times equally throughout day and night. The sleep

architecture of infected patients is also altered with REM sleep occurring within 15 minutes or less after sleep onset, sudden onset of REM [17]. The alterations in the sleep-wake cycle and sleep architecture become more severe as the disease worsens and may constitute a reliable indicator that parasite invasion of the CNS has occurred [17]. Hypocretin levels in the CSF are reduced during the meningoencephalitic stage of HAT but do not to the same extent as in people with narcolepsy and don't entirely correlate with the degree of alteration of sleep architecture [27].

The proximity of the suprachiasmatic nuclei and lateral hypothalamic nuclei to the median eminence makes it likely the inflammatory mediators, including interferon-γ, TNF-α, and IL-1 triggered by the parasitic infection, affecting the suprachiasmatic and lateral hypothalamic neurons [78].

Emerging evidence suggests the *Trypanosoma* itself can phase shift molecular clocks. The sleep-wake pattern in mice infected with *T. brucei* becomes face shifted [106]. Cells from peripheral tissues show a phase shift in their molecular clocks evident because when the cells from infected animals grow in vitro, there is a phase shift Per1/Per2 and Cry1/Cry2 gene expression. Other parasitic infections in the same model do not have this effect [76, 106].

Besides the sleep disturbance, trypanosomiasis also disrupts other hypothalamic functions. Impotence, amenorrhea, and infertility are frequent, and patients with HAT have abnormal sex steroids and gonadotropin levels [105]. Prolactin secretion and cortisol circadian secretion are also disrupted [103].

Pentamidine is the first choice for the treatment of the hemolymphatic phase. Fexinidazole is a new, highly effective, promising oral therapy for the first-stage *T. brucei gambiense* infection.

Drug interventions for the meningoencephalitic stage are more complex and toxic. For this stage, drugs need to be able to cross the blood-brain barrier at sufficient concentrations to be effective. Current treatment consists of a combination of a 10-day course of oral nifurtimox with a 7-day twice-daily, intravenous of eflornithine developed by the Drugs for Neglected Diseases Initiative [80]. A new drug fexinidazole is a promising oral therapy that appears to be as effective as the intravenous combination therapy [81].

Melarsoprol is now the second-line option.

Unfortunately, treatment for *T. brucei rhodesiense* human African trypanosomiasis still requires toxic regimens [15]. For the hemolymphatic phase, Suramin is the first choice due to its high efficacy, but it requires a test dose because of frequent anaphylactic reactions. Pentamidine is also useful.

For the second stage of the disease, the main option is daily melarsoprol injections (2.2 mg/kg) for 10 consecutive days. This arsenic based compound is highly active at lysing parasites and thus even the low serum and tissue concentrations achieved in the CNS still have adequate therapeutic efficacy [15]. The most dreaded complication is the encephalopathic syndrome likely due to the immune system storm triggered by parasite lysis. There are no predictive factors to anticipate this complication. Fever, headache, bullous eruption, and systolic hypotension herald the onset of the reaction, which can present with psychosis, seizures, and coma [12]. Other severe toxicities from the arsenic include arrhythmias, peripheral neuropathy, and hepatitis [15]. Encephalopathic syndrome incidence after treatment is 11.2, with an overall mortality rate of 8.4%[63].

Travelers are far more likely to present with the rhodesiense form of the disease and usually within the hemolymphatic phase. One should suspect trypanosomiasis in a febrile traveler returning from Africa's game parks. Microscopy on thick blood preparation confirms the diagnosis. Treatment with pentamidine is usually the only intervention needed. Confirming the meningoencephalitic phase diagnosis requires a spinal tap. Because therapy for the meningoencephalitic phase is highly toxic, it is best to delay spinal tap until 2–3 days after the first dose of pentamidine to prevent a misdiagnosis due to contamination of the CSF with blood parasites.

Hopefully, human African trypanosomiasis becomes a thing of the past. In the meantime, the ability of this parasite to cause such havoc in the hypothalamic timekeeping mechanisms remains a terrible but fascinating disease.

Hypothalamic-Pituitary Fungal Infections

Candida [117] and *Aspergillus* [48, 70, 74, 93, 136] can cause a pituitary abscess, but in these cases, it was not clear that the hypothalamus was directly involved. Fungal sellar abscesses may present with neurological signs and symptoms (headache, visual disturbances) and hypothalamic-pituitary dysfunction. Histopathological finding, cultivation, or PCR identification of fungus DNA help confirm the diagnosis. Treatment consisted of antifungal therapy with amphotericin B, itraconazole, voriconazole, or Caspofungin, and transsphenoidal drainage.

HIV Infection and Acquired Immunodeficiency Syndrome (AIDS)

HIV infection progresses in two phases. Initially, a robust T-cell response controls the viral invasion. As CD-4 cells progressively die, the virus is unchecked, and the viral loads rise sharply. The depletion of the immune system in this second phase results in AIDS [22].

Hypercortisolemia and cortisol hypersensitivity are prominent features of HIV infection [139]. Patients infected with HIV, as shown by five prospective and retrospective studies, have high serum cortisol and ACTH [21]. In advanced HIV infection without AIDS, patients start losing their adrenal reserve [6]. The hyperactivity of the HPA axis has several causes. Proinflammatory cytokines produced by the immune system trying to control the disease stimulate the HPA axis. The HIV envelope protein gp-120 directly stimulates the release of CRH by the hypothalamus [24]. The structural viral protein R induces glucocorticoid hypersensitivity [60]. Cells infected with HIV actively secrete the Tat viral protein. There is an active transported for the Tat protein in the brain that is most active in the hypothalamus [7]. Tat induces neurotoxicity in neurons, mainly by glutamate excitotoxicity [59]. Thus, the hypothesis that the hypothalamus is affected by neurotoxicity due to the Tat protein is a source of future study questions.

Patients with AIDS have a 40% lower number of oxytocin cells in the paraventricular nucleus of the hypothalamus compared with controls without any inflammatory changes [65, 101]. The decrease in oxytocin appears to be due to post-transcription mechanisms as oxytocin mRNA expression is preserved [42]. HIV encephalitis was present in the hypothalamus of some patients that died from AIDS. These patients had altered levels of enzymes metabolizing the thyroid hormone in the hypothalamus [65]. The virus persists in the brain with most antiretroviral therapies because they have reduced penetrance across the blood-brain barrier, so the involvement of the hypothalamus is likely to continue even after starting antiretroviral treatment. Fortunately, now, many patients start therapy early on in their infection and may have less colonization of the brain with the virus.

Reported cases of people with AIDS and hypothalamic involvement include hyperprolactinemia, central diabetes insipidus, and changes in the HPA axis. Men with AIDS have elevated FSH and LH levels [25].

CMV infection in patients with AIDS can involve the hypothalamus [119]. Some patients with CMV encephalitis can have adipsic hypernatremia, probably due to the destruction of the osmolarity sensing cells in the hypothalamus [57]. *Cryptococcus* sp., *Aspergillus* sp., *Toxoplasma* sp., and *Pneumocystis* sp. can also infect the hypothalamus in patients with AIDS [120].

Antiretroviral therapy affects the endocrine system at multiple levels causing the emergence of AIDS-related insulin resistance and lipodystrophy syndrome. This syndrome, although labeled as "Cushing-like," does not have high cortisol levels [22].

References for Infectious Diseases Section

1. 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(3):382–7. https://doi.org/10.1007/s13365-018-0624-6.
2. Al Salman JM, Al Agha R, Helmy M (2017) Pituitary abscess. BMJ Case Rep 2017. doi:https://doi.org/10.1136/bcr-2016-217,912
3. Almoussa M, Goertzen A, Fauser B, Zimmermann CW (2015) Stroke as an unusual first presentation of Lyme disease. Case Rep Neurol Med. 2015.
4. Arunkumar MJ, Rajshekhar V. Intrasellar tuberculoma presenting as pituitary apoplexy. Neurol India. 2001;49(4):407–10.
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(3):469–76. https://doi.org/10.1007/s11060-013-1285-1.
6. Azar ST, Melby JC. Hypothalamic-pituitary-adrenal function in non-AIDS patients with advanced HIV infection. Am J Med Sci. 1993;305(5):321–5.
7. Banks WA, Robinson SM, Nath A. Permeability of the blood–brain barrier to HIV-1 Tat. Exp Neurol. 2005;193(1):218–27.
8. Bargul JL, Jung J, McOdimba FA, Omogo CO, Adung'a VO, Krüger T, Masiga DK, Engstler M. Species-specific adaptations of trypanosome morphology and motility to the mammalian host. PLoS Pathog. 2016;12(2):e1005448.
9. Barrett MP. The elimination of human African trypanosomiasis is in sight: Report from the third WHO stakeholders meeting on elimination of gambiense human African trypanosomiasis. PLoS Negl Trop Dis. 2018;12(12):e0006925.
10. Behari S, Shinghal U, Jain M, Jaiswal AK, Wadwekar V, Das K, Jha S. Clinicoradiological presentation, management options and a review of sellar and suprasellar tuberculomas. J Clin Neurosci. 2009;16(12):1560–6.
11. Benzick AE, Wirthwein DP, Weinberg A, Wendel GD, Alsaadi R, Leos NK, Zeray F, Sánchez PJ. Pituitary gland gumma in congenital syphilis after failed maternal treatment: a case report. Pediatrics. 1999;104(1):e4.
12. Blum J, Nkunku S, Burri C. Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Trop Med Int Health. 2001;6(5):390–400.
13. Bommakanti K, Panigrahi M, Yarlagadda R, Sundaram C, Uppin MS, Purohit A. Optic chiasmatic-hypothalamic gliomas: Is tissue diagnosis essential? Neurol India. 2010;58(6):833.
14. 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. https://doi.org/10.1155/2014/961913.
15. Bottieau E, Clerinx J. Human African Trypanosomiasis progress and stagnation. Infect Dis Clin. 2019;33(1):61–77.
16. 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(8):2837–40. https://doi.org/10.1210/jc.2015-2049.
17. Buguet A, Bisser S, Josenando T, Chapotot F, Cespuglio R. Sleep structure: a new diagnostic tool for stage determination in sleeping sickness. Acta Trop. 2005;93(1):107–17.
18. Canton A, Simo R, Mesa J, Molina C, Rovira A, Montalban X. Central diabetes insipidus: a complication of herpes simplex encephalitis. J Neurol Neurosurg Psychiatry. 1996;61(3):325–6. https://doi.org/10.1136/jnnp.61.3.325.
19. Capewell P, Cooper A, Clucas C, Weir W, Macleod A. A co-evolutionary arms race: trypanosomes shaping the human genome, humans shaping the trypanosome genome. Parasitology. 2015;142(S1):S108–19.
20. CDC. Syphilis – 2018 sexually transmitted diseases surveillance. 2019. https://www.cdc.gov/std/stats18/syphilis.htm.
21. Christeff N, Gherbi N, Mammes O, Dalle M-T, Gharakhanian S, Lortholary O, Melchior J-C, Nunez EA. Serum cortisol and DHEA concentrations during HIV infection. Psychoneuroendocrinology. 1997;22:S11–8. https://doi.org/10.1016/S0306-4530(97)00015-2.
22. Chrousos GP, Zapanti ED. Hypothalamic-pituitary-adrenal axis in HIV infection and disease. Endocrinol Metab Clin. 2014;43(3):791–806.
23. Chung SK, Yang DW, Noh SH, Koh HI. One case of panhypopituitarism and central diabetes insipidus as a sequelae of hemorrhagic fever with renal syndrome. Kidney Res ClinPract. 1996;15(4):634–9.
24. Costa A, Nappi RE, Polatti F, Poma A, Grossman AB, Nappi G. Stimulating Effect of HIV-1 Coat Protein gp120 on Corticotropin-Releasing Hormone and Arginine Vasopressin in the Rat Hypothalamus: Involvement of Nitric Oxide. Exp Neurol. 2000;166(2):376–84. https://doi.org/10.1006/exnr.2000.7502.
25. Croxson TS, Chapman WE, Miller LK, Levit CD, Senie R, Zumoff B. Changes in the hypothalamic-pituitary-gonadal axis in human immunodeficiency virus-infected homosexual men. J Clin Endocrinol Metab. 1989;68(2):317–21. https://doi.org/10.1210/jcem-68-2-317.
26. Cushing H. The Pituitary Body and its Disorders. Philadelphia. London: Lippincott; 1912.

27. Dauvilliers Y, Bisser S, Chapotot F, Vatunga G, Cespuglio R, Josenando T, Buguet A. Hypocretin and Human African Trypanosomiasis. Sleep. 2008;31(3):348–54. https://doi.org/10.1093/sleep/31.3.348.
28. Davies H. Modern medicine, vol. v. 1; 1907. Lea Bros. & Company
29. Dersch R, Sarnes AA, Maul M, Hottenrott T, Baumgartner A, Rauer S, Stich O. Quality of life, fatigue, depression and cognitive impairment in Lyme neuroborreliosis. J Neurol. 2015a;262(11):2572–7.
30. Dersch R, Töws I, Sommer H, Rauer S, Meerpohl JJ. Methodological quality of guidelines for management of Lyme neuroborreliosis. BMC Neurol. 2015b;15(1):242.
31. Dhanwal DK, Kumar S, Vyas A, Saxena A. Hypothalamic pituitary dysfunction in acute non-mycobacterial infections of central nervous system. Indian J Endocrinol Metab. 2011;15(Suppl 3):S233–7. https://doi.org/10.4103/2230-8210.84873.
32. Dhanwal DK, Vyas A, Sharma A, Saxena A. Hypothalamic pituitary abnormalities in tubercular meningitis at the time of diagnosis. Pituitary. 2010;13(4):304–10. https://doi.org/10.1007/s11102-010-0234-7.
33. Dickman MS. von Economo Encephalitis. Arch Neurol. 2001;58(10):1696. https://doi.org/10.1001/archneur.58.10.1696.
34. Duszenko M, Figarella K, Macleod ET, Welburn SC. Death of a trypanosome: a selfish altruism. Trends Parasitol. 2006;22(11):536–42.
35. Eikeland R, Ljostad U, Mygland A, Herlofson K, Lohaugen GC. European neuroborreliosis: neuropsychological findings 30 months post-treatment. Eur J Neurol. 2012;19(3):480–7. https://doi.org/10.1111/j.1468-1331.2011.03563.x.
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. https://doi.org/10.11604/pamj.2015.20.308.6538.
37. 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(1):87–90. https://doi.org/10.1111/j.1365-2796.1992.tb00555.x.
38. 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(2):189–94. https://doi.org/10.1007/s11102-016-0757-7.
39. Garkowski A, Zajkowska J, Zajkowska A, Kułakowska A, Zajkowska O, Kubas B, Jurgilewicz D, Hładuński M, Łebkowska U. Cerebrovascular manifestations of lyme neuroborreliosis—a systematic review of published cases. Front Neurol. 2017;8:146. https://doi.org/10.3389/fneur.2017.00146.
40. 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. https://doi.org/10.1186/1472-6823-14-80.
41. Gordon A, Parsons M. The place of corticosteroids in the management of tuberculous meningitis. Br J Hosp Med. 1972;7(65):1–655.
42. Guldenaar SE, Swaab DF. Estimation of oxytocin mRNA in the human paraventricular nucleus in AIDS by means of quantitative in situ hybridization. Brain Res. 1995;700(1–2):107–14.
43. Halperin JJ. Nervous system Lyme disease. Infect Dis Clin North Am. 2015;29(2):241–53. https://doi.org/10.1016/j.idc.2015.02.002.
44. Hamdeh S, Abbas A, Fraker J, Lambrecht JE. Intracranial toxoplasmosis presenting as panhypopituitarism in an immunocompromised patient. Am J Emerg Med. 2015;33(12):1848.e1–2. https://doi.org/10.1016/j.ajem.2015.04.071.
45. Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985–1990. A prospective study of 187 patients with Borrelia burgdorferi specific intrathecal antibody production. Brain J Neurol. 1992;115(Pt 2):399–423. https://doi.org/10.1093/brain/115.2.399.
46. Hautala T, Sironen T, Vapalahti O, Paakko E, Sarkioja 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(1):96–101. https://doi.org/10.1086/340859.
47. Hinman AR. Tuberculous meningitis at Cleveland Metropolitan General Hospital 1959 to 1963. Am Rev Respir Dis. 1967;95(4):670–3.
48. Hong W, Liu Y, Chen M, Lin K, Liao Z, Huang S. Secondary headache due to aspergillus sellar abscess simulating a pituitary neoplasm: case report and review of literature. Springerplus. 2015;4:550. https://doi.org/10.1186/s40064-015-1343-6.
49. Husain N, Husain M, Rao P. Pituitary tuberculosis mimicking idiopathic granulomatous hypophysitis. Pituitary. 2008;11(3):313–5. https://doi.org/10.1007/s11102-007-0068-0.
50. Jain A, Dhanwal DK, Kumar J. A rare case of pituitary tuberculoma-diagnosed and managed conservatively. Pituitary. 2015;18(4):579–80. https://doi.org/10.1007/s11102-014-0577-6.
51. Jovanovic D, Kovacevic Z, Dragovic T, Petrovic M, Tadic J. Anterior pituitary lobe atrophy as late complication of hemorrhagic fever with renal syndrome. Vojnosanit Pregl. 2009;66(2):166–8. https://doi.org/10.2298/vsp0902166j.
52. Kaiser R. Neuroborreliosis. J Neurol. 1998;245(5):247–55. https://doi.org/10.1007/s004150050214.
53. 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):1–7. https://doi.org/10.1007/s11102-013-0547-4.
54. Kennedy DH, Fallon RJ. Tuberculous Meningitis. JAMA. 1979;241(3):264–8. https://doi.org/10.1001/jama.1979.03290290032021.
55. Kennedy PG. Diagnostic and neuropathogenesis issues in human African trypanosomiasis. Int J Parasitol. 2006;36(5):505–12.
56. Kennedy PG. Update on human African trypanosomiasis (sleeping sickness). J Neurol. 2019;266:2334–7.
57. Keuneke C, Anders H-J, Schlöndorff D. Adipsic hypernatremia in two patients with AIDS and cytomegalovirus encephalitis. Am J Kidney Dis. 1999;33(2):379–82.
58. 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(3):355–9. https://doi.org/10.3346/jkms.2001.16.3.355.
59. King J, Eugenin E, Buckner C, Berman JW. HIV tat and neurotoxicity. Microbes Infect. 2006;8(5):1347–57.
60. Kino T, Chrousos GP. Human immunodeficiency virus type-1 accessory protein Vpr: a causative agent of the AIDS-related insulin resistance/lipodystrophy syndrome? Ann N Y Acad Sci. 2004;1024:153–67. https://doi.org/10.1196/annals.1321.013.
61. Klebanov Iu A. Analysis of fatal outcome in hemorrhagic fever with renal syndrome. Klin Med (Mosk). 1990;68(12):64–7.
62. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiane SG, Ishikawa N, Le L-V, Newman-Owiredu M, Nagelkerke N. Global burden of maternal and congenital syphilis and associated adverse birth outcomes—Estimates for 2016 and progress since 2012. PLoS One. 2019;14(2):e0211720.
63. Kuepfer I, Schmid C, Allan M, Edielu A, Haary EP, Kakembo A, Kibona S, Blum J, Burri C. Safety and efficacy of the 10-day melarsoprol schedule for the treatment of second stage Rhodesiense sleeping sickness. PLoS Negl Trop Dis. 2012;6(8):e1695.
64. Lam KS, Sham MM, Tam SC, Ng MM, Ma HT. Hypopituitarism after tuberculous meningitis in childhood. Ann Intern Med. 1993;118(9):701–6. https://doi.org/10.7326/0003-4819-118-9-199,305,010-00007.
65. Langford D, Baron D, Joy J, Del Valle L, Shack J. Contributions of HIV infection in the hypothalamus and substance abuse/use to HPT dysregulation. Psychoneuroendocrinology. 2011;36(5):710–9. https://doi.org/10.1016/j.psyneuen.2010.10.005.
66. Lee JS, Ahn C, Oh HY, Kim S, Lee M, Kim YI. Panhypopituitarism and central diabetes insipidus as a complication of hemorrhagic fever with renal syndrome (Korean hemorrhagic fever). 1986.
67. Lee Y-J, Yang D, Shyur S-D, Chiu N-C. Neurogenic diabetes insipidus in a child with fatal Coxsackie virus B1 encephalitis. J Pediatr Endocrinol Metab. 1995;8(4):301–4.
68. Leonard JM. Central nervous system tuberculosis. Microbiol Spectr. 2017;5(2):1–10. https://doi.org/10.1128/microbiolspec.TNMI7-0044-2017.
69. Leonard JM. Central nervous system tuberculosis. Waltha: UpToDate; 2019.
70. Lim JC, Rogers TW, King J, Gaillard F. Successful treatment of pituitary sella Aspergillus abscess in a renal transplant recipient. J Clin Neurosci. 2017;45:138–40. https://doi.org/10.1016/j.jocn.2017.07.005.
71. 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. AJNR Am J Neuroradiol. 1986;7(4):633–7.
72. Lipsett M, Dreifuss F, Thomas L. Hypothalamic syndrome following varicella. Am J Med. 1962;32(3):471–5.
73. 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 (Oxf). 2011;74(1):79–88. https://doi.org/10.1111/j.1365-2265.2010.03890.x.
74. Liu W, Chen H, Cai B, Li G, You C, Li H. Successful treatment of sellar aspergillus abscess. J Clin Neurosci. 2010;17(12):1587–9.
75. Ljostad U, Mygland A. Remaining complaints 1 year after treatment for acute Lyme neuroborreliosis; frequency, pattern and risk factors. Eur J Neurol. 2010;17(1):118–23. https://doi.org/10.1111/j.1468-1331.2009.02756.x.
76. Lundkvist GBS, Sellix MT, Nygård M, Davis E, Straume M, Kristensson K, Block GD. Clock Gene Expression during Chronic Inflammation Induced by Infection with Trypanosoma brucei brucei in Rats. J Biol Rhythms. 2010;25(2):92–102. https://doi.org/10.1177/0748730409360963.
77. Madhoun ZT, DuBois DB, Rosenthal J, Findlay JC, Aron DC. Central diabetes insipidus: a complication of herpes simplex type 2 encephalitis in a patient with AIDS. Am J Med. 1991;90(5):658–9.
78. Masocha W, Kristensson K. Human African trypanosomiasis: How do the parasites enter and cause dysfunctions of the nervous system in murine models? Brain Res Bull. 2019;145:18–29.
79. Mena W, Royal S, Pass RF, Whitley RJ, Philips JB. Diabetes insipidus associated with symptomatic congenital cytomegalovirus infection. J Pediatr. 1993;122(6):911–3.
80. Mesu VKBK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, Delhomme S, Bernhard S, Kuziena W, Lubaki J-PF. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. The Lancet. 2018a;391(10116):144–54.

81. Mesu VKBK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, Delhomme S, Bernhard S, Kuziena W, Lubaki J-PF, Vuvu SL, Ngima PN, Mbembo HM, Ilunga M, Bonama AK, Heradi JA, Solomo JLL, Mandula G, Badibabi LK, Dama FR, Lukula PK, Tete DN, Lumbala C, Scherrer B, Strub-Wourgaft N, Tarral A. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. The Lancet. 2018b;391(10116):144–54. https://doi.org/10.1016/s0140-6736(17)32758-7.
82. Mohammed H, Goyal MK, Dutta P, Sharma K, Modi M, Shah F, Shree R, Jain A, Jain G, Khandelwal N, Sharma N, Lal V. Hypothalamic and pituitary dysfunction is common in tubercular meningitis: A prospective study from a tertiary care center in Northern India. J Neurol Sci. 2018;395:153–8. https://doi.org/10.1016/j.jns.2018.10.011.
83. 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. https://doi.org/10.1016/j.jns.2017.06.015.
84. 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 Metabol. 2003;88(1):51–4.
85. Mugnier MR, Stebbins CE, Papavasiliou FN. Masters of disguise: antigenic variation and the VSG coat in Trypanosoma brucei. PLoS Pathog. 2016;12(9):e1005784.
86. Murray PR, Rosenthal KS, Pfaller MA. Treponema, Borrelia, and Leptospira. Medical Microbiology: Elsevier; 2019.
87. Mygland A, Ljostad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol. 2010;17(1):8–16, e11–14. https://doi.org/10.1111/j.1468-1331.2009.02862.x.
88. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, Stevens G, Gottlieb S, Kiarie J, Temmerman M. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PLoS One. 2015;10(12):e0143304. https://doi.org/10.1371/journal.pone.0143304.
89. Noblett J, Roberts E (2015) The importance of not jumping to conclusions: syphilis as an organic cause of neurological, psychiatric and endocrine presentations. BMJ Case Rep. 2015. doi:https://doi.org/10.1136/bcr-2014-207,900
90. Oelbaum M. Hypopituitarism in male subjects due to syphilis: with a discussion of androgen treatment. QJM Int J Med. 1952;21(3):249–64.
91. Ogrinc K, Lusa L, Lotric-Furlan S, Bogovic P, Stupica D, Cerar T, Ruzic-Sabljic E, Strle F. Course and Outcome of Early European Lyme Neuroborreliosis (Bannwarth Syndrome): Clinical and Laboratory Findings. Clin Infect Dis. 2016;63(3):346–53. https://doi.org/10.1093/cid/ciw299.
92. Oschmann P, Dorndorf W, Hornig C, Schafer C, Wellensiek HJ, Pflughaupt KW. Stages and syndromes of neuroborreliosis. J Neurol. 1998;245(5):262–72. https://doi.org/10.1007/s004150050216.
93. 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(2):e86–8. https://doi.org/10.1097/scs.0000000000001288.
94. 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(2):141–5.
95. Partanen T, Koivikko M, Leisti P, Salmela P, Paakko 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 (Oxf). 2016;84(1):85–91. https://doi.org/10.1111/cen.12863.
96. Pekic S, Cvijovic G, Stojanovic M, Kendereski A, Micic D, Popovic V. Hypopituitarism as a late complication of hemorrhagic fever. Endocrine. 2005;26(2):79–82. https://doi.org/10.1385/endo:26:2:079.
97. Pekic S, Miljic D, Popovic V. Infections of the Hypothalamic-Pituitary Region. In: Anawalt B, Boyce A, et al., editors. Feingold KR. South Dartmouth (MA): Endotext. MDText.com, Inc.; 2000.
98. Pekic S, Miljic D, Popovic V (2018) Infections of the hypothalamic-pituitary region. In: Endotext [Internet]. MDText. com, Inc.,
99. Perkins MP, Shumway N, Jackson WL Jr. Lyme neuroborreliosis presenting as the syndrome of inappropriate antidiuretic hormone secretion. MedGenMed. 2006;8(3):71.
100. Picha D, Moravcova L, Lasikova S, Holeckova D, Maresova V. Symptoms of post-Lyme syndrome in long-term outcome of patients with neuroborreliosis. Scand J Infect Dis. 2006;38(8):747–8. https://doi.org/10.1080/00365540600810000.
101. Purba JS, Hofman MA, Portegies P, Troost D, Swaab DF. Decreased number of oxytocin neurons in the paraventricular nucleus of the human hypothalamus in AIDS. Brain J Neurol. 1993;116(Pt 4):795–809. https://doi.org/10.1093/brain/116.4.795.
102. Quarterly Epitome of American Practical Medicine and Surgery (1883). vol. 4. W. A. Townsend,
103. Radomski M, Buguet A, Bogui P, Doua F, Lonsdorfer A, Tapie P, Dumas M. Disruptions in the secretion of cortisol, prolactin, and certain cytokines in human African trypanosomiasis patients.

Bulletin de la Societe de pathologie exotique (1990). 1994;87(5):376–9.
104. Reuter H, Wood R, Schaaf HS, Donald PR (2009) Chapter 34 - Overview of extrapulmonary tuberculosis in adults and children. In: Schaaf HS, Zumla AI, Grange JM et al. (eds) Tuberculosis. W.B. Saunders, Edinburgh, pp. 377–390. doi:https://doi.org/10.1016/B978-1-4160-3988-4.00034-2
105. Ridet J. Etude des troubles du cycle menstruel chez la femme trypanosomée à l'aide de frottis vaginaux. Med Trop. 1953;13:514–9.
106. Rijo-Ferreira F, Carvalho T, Afonso C, Sanches-Vaz M, Costa RM, Figueiredo LM, Takahashi JS. Sleeping sickness is a circadian disorder. Nat Commun. 2018;9(1):62.
107. Saranac L, Bjelakovic B, Djordjevic D, Novak M, Stankovic T. Hypopituitarism occurring in neonatal sepsis. J Pediatr Endocrinol Metab. 2012;25(9–10):847–8. https://doi.org/10.1515/jpem-2012-0172.
108. 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. 2008a;158(1):3–9. https://doi.org/10.1530/eje-07-0484.
109. Scheinpflug K, Schalk E, Reschke K, Franke A, Mohren M. Diabetes insipidus due to herpes encephalitis in a patient with diffuse large cell lymphoma. A case report. Exp Clin Endocrinol Diabetes. 2006;114(1):31–4. https://doi.org/10.1055/s-2005-873,014.
110. Settergren B, Boman J, Linderholm M, Wistrom J, Hagg E, Arvidsson PA. A case of nephropathia epidemica associated with panhypopituitarism and nephrotic syndrome. Nephron. 1992;61(2):234–5. https://doi.org/10.1159/000186883.
111. Shamim EA, Shamim SA, Liss G, Nylen E, Pincus JH, Yepes M. Constipation heralding neuroborreliosis: an atypical tale of 2 patients. Arch Neurol. 2005;62(4):671–3.
112. 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(2):72–7. https://doi.org/10.1016/s0303-8467(00)00063-9.
113. Sia IG, Wieland ML. Current concepts in the management of tuberculosis. Mayo Clin Proc. 2011;4:348–61.
114. Siddiqui N, St. Peter DM, Marur S. Ticks and salt: an atypical case of neuroborreliosis. J Commun Hosp Intern Med Perspect. 2017;7(6):358–62.
115. 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. https://doi.org/10.1186/1471-2334-13-481.
116. Stiernstedt G, Gustafsson R, Karlsson M, Svenungsson B, Skoldenberg B. Clinical manifestations and diagnosis of neuroborreliosis. Ann N Y Acad Sci. 1988;539:46–55. https://doi.org/10.1111/j.1749-6632.1988.tb31837.x.
117. 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;109:467–70.
118. Suh DC, Park JS, Park SK, Lee HK, Chang KH. Pituitary hemorrhage as a complication of hantaviral disease. AJNR Am J Neuroradiol. 1995;16(1):175–8. discussion 179–180
119. Sullivan WM, Kelley GG, O'Connor PG, Dickey PS, Kim JH, Robbins R, Shulman GI. Hypopituitarism associated with a hypothalamic CMV infection in a patient with AIDS. Am J Med. 1992;92(2):221–3.
120. Swaab D (2004) The human hypothalamus. Basic and clinical aspects: part II: Neuropathology of the human hypothalamus and adjacent brain structures. Handb Clin Neurol. 95–99.
121. Takao H, Doi I, Watanabe T. Diffusion-weighted magnetic resonance imaging in pituitary abscess. J Comput Assist Tomogr. 2006;30(3):514–6. https://doi.org/10.1097/00004728-200,605,000-00028.
122. 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(10):1247–51. https://doi.org/10.2169/internalmedicine.54.3435.
123. 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(6):489–91. https://doi.org/10.1007/BF03346395.
124. 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;15(4):579–88. https://doi.org/10.1007/s11102-011-0371-7.
125. Tarvainen M, Makela S, Mustonen J, Jaatinen P (2016) Autoimmune polyendocrinopathy and hypophysitis after Puumala hantavirus infection. Endocrinol Diabetes Metab Case Rep. 2016. doi:https://doi.org/10.1530/edm-16-0084
126. Tesoriero C, Del Gallo F, Bentivoglio M. Sleep and brain infections. Brain Res Bull. 2019;145:59–74.
127. Tjernberg I, Carlsson M, Ernerudh J, Eliasson I, Forsberg P. Mapping of hormones and cortisol responses in patients after Lyme neuroborreliosis. BMC Infect Dis. 2010;10(1):20. https://doi.org/10.1186/1471-2334-10-20.
128. Topakian R, Stieglbauer K, Nussbaumer K, Aichner FT. Cerebral vasculitis and stroke in Lyme neuroborreliosis. Two case reports and review of current knowledge. Cerebrovasc Dis. 2008;26(5):455–61. https://doi.org/10.1159/000155982.

129. Torres M, Analyn M, Kazee M, Marie A, Simon M, Howard KM, Paul E, Weinstock M, PhD RS. Central diabetes insipidus due to herpes simplex in a patient immunosuppressed by Cushing's syndrome. Endocr Pract. 2000;6(1):26–8.
130. Trypanosomiasis, human African (sleeping sickness). 2019.
131. Tsiakalos A, Xynos ID, Sipsas NV, Kaltsas G. Pituitary insufficiency after infectious meningitis: a prospective study. J Clin Endocrinol Metab. 2010;95(7):3277–81. https://doi.org/10.1210/jc.2010-0144.
132. 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(1):155–61. https://doi.org/10.3109/14397595.2014.948981.
133. Valtonen M, Kauppila M, Kotilainen P, Lahdevirta J, Svartback CM, Kosunen O, Nurminen J, Sarkkinen H, Brummer-Korvenkontio M. Four fatal cases of nephropathia epidemica. Scand J Infect Dis. 1995;27(5):515–7. https://doi.org/10.3109/00365549509047057.
134. Vani K, Shankar S, Das S, Asha T, Rao TV. Involvement of hypothalamous in tuberculous meningitis, pathological changes at autopsy. Indian J Tuberc. 1991;38:149–53.
135. Vates GE, Berger MS, Wilson CB. Diagnosis and management of pituitary abscess: a review of twenty-four cases. J Neurosurg. 2001;95(2):233–41. https://doi.org/10.3171/jns.2001.95.2.0233.
136. 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. https://doi.org/10.1111/tid.12129.
137. von Economo C. Sleep as a problem of localization. J Nerv Ment Dis. 1930;71(3):249–59.
138. WHO (2018) World Health Organization. https://www.who.int/gho/tb/tb_text/en/.
139. Zapanti E, Terzidis K, Chrousos G. Dysfunction of the hypothalamic-pituitary-adrenal axis in HIV infection and disease. Hormones. 2008;7(3):205–16.
140. 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(7):957–61. https://doi.org/10.1016/j.clineuro.2012.02.020.

Inflammatory Conditions of the Hypothalamus

20

Jesus Lovera, Olinda Verdecie Feria, and Vaniolky Losada Leon

Hypophysitis

Hypophysitis, inflammation of the hypophysis and the pituitary stalk, is a rare condition with an estimated prevalence of one in nine million [30], but its actual prevalence may be much higher because of underdiagnosis. Seventy percent of the cases are due to infiltration by lymphocytes, lymphocytic hypophysitis [27]. Granulomatous infiltration with giant cell and granuloma formation is a less common cause of hypophysitis, representing approximately 18% of cases. Xanthomatous infiltration consisting of hyaline deposits is the rarest type of hypophysitis, accounting for 3%. IgG4 plasmacytic 1% or necrotizing 0.7% forms can also occur. Common clinical features include headache, nausea, vomiting, and visual field deficits [29, 100, 116]. Recent weight gain occurs in 18% of patients [100] and is more severe when there is the involvement of the hypothalamus and pituitary stalk. Rare but more severe cases include cavernous sinus invasion and carotid occlusion [116] and can mimic meningitis or pituitary apoplexy.

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Immune checkpoint inhibitors are a rising cause of hypophysitis [27]. Other autoimmune diseases occur in 16% of cases, with Hashimoto's thyroiditis and Graves' disease being the most common [100].

Lymphocytic Hypophysitis

Three topographic variants of hypophysitis are known. Lymphocytic pan-hypophysitis (LPH) involves the whole gland, lymphocytic adenohypophysitis (LAH) affects only the adenohypophysis, and lymphocytic infundibuloneurohypophysitis (LINH) compromises only the neurohypophysis and pituitary stalk. It is unclear if the inflammation of the infundibulum and the neurohypophysis, anterior hypophysis, or the whole hypophysis are part of the same disease or different entities [30].

The most common complaints with all forms of hypophysitis are headaches, which don't correlate with the size of the gland [142]. The pain may be the result of alterations of the hypothalamic neuroendocrine system or due to inflammatory mediators rather than a result of the mass effect compressing sensitive structures. Interference with somatostatin may be a cause of the pain because octreotide reduces headaches in patients with acromegaly [271]. CSF can show elevated lymphocyte counts (26.7 ± 19 lymphocytes) [79].

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If the inflammation extends beyond the pituitary or if there is a significant mass effect, then visual field deficits will occur. In rare cases, the cavernous sinus can be involved resulting in paralysis of cranial nerves III and VI, resulting in diplopia, or V resulting in facial pain. If there is inflammation affecting the anterior pituitary, then extensive hormonal dysfunction will occur.

On MRI, hypophysitis will manifest by a rapid intense and homogenous enhancement of the pituitary gland with no apparent stalk deviation [116].

Lymphocytic Adenohypophysitis (LAH)

Lymphocytic adenohypophysitis is the most common form of hypophysitis, representing 65% of cases of hypophysitis [30]. Adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH), and follicle stimulating hormone (FSH) will be deficient either alone or in combination, with ACTH being the most common deficiency. Decreased prolactin secretion is frequent and results in impaired milk production postpartum. Women are six times more likely to be affected by this form of hypophysitis than men. Women during their third trimester of pregnancy are at the highest risk for LAH, with 57% of women developing LAH during pregnancy [30, 116]. Heaney et al. found that HLA DQ8 was present in 87% and DR53 in 80% with sporadic LH [91].

Even though the inflammation localizes mainly to the adenohypophysis, hypothalamic involvement may still be present as hyperprolactinemia or diabetes insipidus. It is important to note that the deficiency in ACTH may mask the diabetes insipidus and SIADH (syndrome of inappropriate antidiuretic hormone secretion) may precede diabetes insipidus [105]. Central diabetes insipidus (CDI) in these patients appears to be due to autoimmune-mediated hypothalamic involvement as antibodies against arginine-vasopressin (AVP) cell antibodies can indicate patients at risk for the development of CDI [46, 234]. Anti-hypothalamic antibodies can also target the corticotropin-releasing hormone (CRH)-secreting cells resulting in ACTH deficiency that occurs concurrently with anti-pituitary antibodies targeting the growth hormone-secreting cells [46].

Lymphocytic Infundibuloneurohypophysitis

In infundibuloneurohypophysitis (INH), the inflammation affects only the posterior pituitary lobe, the pituitary stalk, and the median eminence of the hypothalamus. This form of hypophysitis is much less common than LAH. Men and females are equally affected as opposed to LAH, which mainly affects women [30]. Patients with infundibuloneurohypophysitis present with central diabetes insipidus and swelling of the posterior pituitary or pituitary stalk (>3 mm) on brain MRI. Hyper- or hypoprolactinemia may also occur but is less frequent. Diabetes insipidus in this form of hypophysitis is likely due to direct damage to the hypothalamus as opposed to compression. Polydipsia and polyuria may be the only complaints in infundibuloneurohypophysitis [30]. On rare occasions, the lesions can be large, extending into the pons and cavernous sinus [121].

Some of the cases of infundibuloneurohypophysitis reported in the past were associated with recurrent optic neuritis [2, 6]. Anti-aquaporin-4 antibodies were not available at this time, thus the exact pathophysiology of these cases was unknown and may have been patients with NMOSD (neuromyelitis optica spectrum disorder). However, AQP4-negative cases also occur [2, 190]. It is crucial to consider optic neuritis as the cause of visual loss as the loss of eyesight may trigger the clinician to pursue surgery, thinking that the mass effect is responsible for the visual loss [277].

Patients with infundibuloneurohypophysitis and central diabetes insipidus will frequently show loss of the posterior pituitary bright spot on MRI. The current thought is that the high phospholipid concentration of the antidiuretic hormone and neurosecretory oxytocin granules give the high T1 signal on MRI to the posterior pituitary spot [38]. A symmetric dural tail, where the lesion enhancement continues into the adjacent dura, is also a helpful radiological finding that can differentiate inflammation from malignancy [211]. When there is no deviation of the stalk on

MRI, then cancer is less likely. Increasing thickness of the pituitary stalk over serial scans makes malignancy more likely. Only 20% of pituitary stalk lesions were inflammatory in a retrospective case series of 152 patients, while 32% were neoplastic. Although there is an intrinsic bias toward neoplastic lesions in retrospective studies suggesting that malignancies are more common, in many situations, it will be impossible to exclude cancers such as germinomas without obtaining a tissue biopsy. The scoring system created by Gutenberg et al. helps predict the likelihood of hypophysitis. Relation to pregnancy, pituitary mass volume and symmetry, signal intensity and signal intensity homogeneity after gadolinium administration, posterior pituitary bright spot presence, stalk size, and mucosal swelling are the items contributing to the score [80].

Iwama et al. detected antibodies against rabphilin-3A in 22 of 29 (76%) patients with infundibuloneurohypophysitis, including all of the 4 biopsy-proven samples with LINH, and 2 of 18 (11.1%) patients with biopsy-proven lymphocytic adenohypophysitis [111]. The posterior pituitary and hypothalamic vasopressin neurons express rabphilin-3A but not the anterior pituitary [112]. Furthermore, rabphilin-3A immunization triggers lymphocytic infiltration of the hypophysis in mice suggesting that autoimmunity against this antigen may be pathogenic [273]. Treatment of the mice with abatacept, which is a chimeric protein that suppresses T-cell activation, decreased the number of T cells specific for rabphilin-3A [273]. However, anti-rabphilin-3A antibody findings need replication, and the test is not commercially available.

Granulomatous Hypophysitis

Isolated granulomatous infiltration of the hypophysis is extremely rare, initially described in 4 out of 2000 autopsies [227]. Males and females are equally affected [30]. Granulomatous hypophysitis can affect both the anterior hypophysis and the neurohypophysis and pituitary stalk [227]. The thickening of the pituitary stalk is more prominent than in other hypophysitis forms [79]. Patients, in general, have more severe symptoms compared to different types of hypophysitis [100]. Typically, patients present with nausea, vomiting, and pituitary dysfunction. They can be febrile, and pituitary necrosis can be severe, mimicking a pituitary abscess with rapid loss of vision due to chiasmatic compression [128]. Visual field abnormalities are more common than in lymphocytic hypophysitis [79]. Hypothalamic involvement can occur, resulting in diabetes insipidus and hyperprolactinemia [30]. Steroid treatment is less effective than in lymphocytic hypophysitis.

Necrotizing Hypophysitis

Necrosis of significant portions of the hypophysis is very rare [4, 28, 169]. Hypothalamic involvement manifests with diabetes insipidus and thickening of the hypothalamic stalk [4]. In one reported case, acute necrosis of the hypophysis accompanied by headache and compression of the optic pathways occurred 3 years after the development of idiopathic diabetes insipidus with no findings on MRI [169].

Xanthomatous Hypophysitis

Xanthomatous hypophysitis is extremely rare. Symptoms include headache and nausea. Hypothalamic involvement again is manifest by diabetes insipidus and elevated prolactin levels [64] but is far less common than in lymphocytic hypophysitis [64]. Anterior pituitary failure appears to be milder in this form of hypophysitis, and symptoms are frequently present for a long time (up to 14 years) before diagnosis [79]. The mass in the hypophysis is usually biopsied or resected because it mimics neoplasm with ring-enhancing or cystic lesions and deviation on the pituitary stalk. The tissue is a soft liquefied material surrounded by abnormal soft tissue. Pathology shows that the infiltrating cells are CD68 lipid-laden macrophages negative for S-100 and CD1a [50, 64]. Steroid treatment is less effective than lymphocytic hypophysitis [79].

IgG4-Related Hypophysitis

IgG4 is less than 5% of all circulating IgG. IgG4 does not activate complement and has negligible binding to the Fcγ receptors and thus does not seem to be able to activate the immune system upon antigen recognition [232]. The heavy chains of the IgG4 molecule have unstable bonds, and this allows IgG4 chains to separate and recombine randomly into immunoglobulin molecules that can bind to two different antigens [201, 252]. These immunoglobulins may serve as immunoregulators because they can displace normal immunoglobulins from antigen sites and without cross-linking the antigen [172]. IgG4s appear after prolonged antigen exposure in a modified Th2 response where regulatory T cells that produce IL-10 stimulate the production of IgG4 instead of IgE [3].

IgG4-related disease is a systemic disease where IgG4 plasma cells infiltrate multiple organs. Initially reported in the pancreas, IgG4-related disease can affect the liver, biliary system, salivary glands, lacrimal glands, retroperitoneum, lymph nodes, kidneys, aorta, breast, prostate, thyroid, pericardium, and skin [232]. IgG4 plasma cells can infiltrate the pituitary gland and pituitary stalk with clinical findings similar to lymphocytic infundibulohypophysitis, including central diabetes insipidus [225]. Men in their 60s and 70s are more likely to develop IgG4 infundibulohypophysitis [225]. Isolated involvement of the pituitary gland can occur, but most frequently, the pituitary gland involvement occurs along with concurrent infiltration of the retroperitoneum, glands in the head and neck (Mikulicz syndrome), lungs, pancreas, and lymph nodes [225]. Pachymeningitis and pansinusitis are also frequently observed [225]. Serum IgG4 levels are often elevated but may normalize after few doses of steroids. The swelling of the stalk responds to glucocorticoid therapy but frequently recurs with tapering of the steroids [225]. IgG4 may not be rare as it was detected in 30% of cases when systematically screening consecutive cases of hypophysitis for IgG4 plasma cells [14].

In IgG4 hypophysitis, antibodies targeting the corticotrophs in the pituitary are present in approximately 30% of cases, while antibodies against the hypothalamus and posterior pituitary are absent [112].

CTLA-4 Blockers

CTLA-4 is expressed on lymphocytes and binds B7 inhibiting lymphocyte activation. Ipilimumab is a monoclonal antibody targeting CTLA-4 widely used to treat different cancers by releasing the immune system. Autoimmune hypophysitis occurs in about 4% of patients treated with ipilimumab and tends to have a milder course compared to other forms of hypophysitis, and it is exceptionally infrequent for it to cause diabetes or visual deficits [28]. Mild cases only need hormone replacement, but more severe cases may need to stop the CTLA-4 inhibitor and initiate a high dose of steroids.

Treatment

Hypopituitarism and diabetes insipidus need appropriate replacement therapies. Steroids remain the primary treatment, and the hypophysitis tends to be self-limited, usually resolving within 6 months. In cases that relapse with tapering of steroids, azathioprine and rituximab have been helpful. Currently, there are no controlled clinical trials to provide more robust evidence to guide treatment, and the overall rarity of this condition makes it unlikely that we will have such evidence soon. For large masses resulting from pituitary infiltration, surgery or radiotherapy may be necessary [116].

Aquaporin-4 and Neuromyelitis Optica Spectrum Disorder

Aquaporin-4 (AQP4) is the main water channel on the astrocyte end-feet that form the blood-brain barrier and the subpial glia limitans. The astrocytes in the gray matter of the spinal cord also express AQP4 at particularly high levels. This water channel also is strongly expressed in

the ependymal cells lining the ventricles and periaqueductal regions [192]. The supraoptic and paraventricular nuclei of the hypothalamus produce high levels of AQP4, where it appears to serve part of the osmolarity-sensing mechanisms of these neurons by causing rapid changes in cell volume in response to shifts in extracellular osmolarity [119].

The most commonly known lesions resulting from anti-AQP4 antibodies are longitudinally extensive transverse myelitis and bilateral severe optic neuritis, which was described initially as neuromyelitis optica by Devic and Gault. However, a wide array of additional syndromes can occur, and neuromyelitis optica (NMO) spectrum disorders (NMOSD) and typical diencephalic lesions including hypothalamic lesions as well as narcolepsy are part of the core features in the diagnostic criteria for adult patients [272].

Most of the cases of hypothalamic lesions occur in concurrence with other clinical features of NMOSD or after previous attacks, but hypothalamic involvement such as narcolepsy [48] and syndrome of inappropriate antidiuretic hormone secretion (SIADH) [108, 166] can be the presenting symptoms.

Hypothalamic Lesions

The median eminence of the hypothalamus lacking a blood-brain barrier is a critical target for AQP4 antibodies. Bilateral hypothalamic lesions form part of the NMOSD occurring in 2.5–3% of patients positive for AQP4 antibodies [31, 192]. Patients with AQP4 antibodies can present with extensive bilateral hypothalamic involvement resulting in the collapse of multiple hypothalamic functions [213], resulting in fever or hypothermia, hypotension, bradycardia, hypersomnia [236, 259], and anhidrosis [219]. Memory impairment can be irreversible, and hyperphagia and obesity can follow initial recovery from severe hypothalamic involvement [213, 236]. Figure 20.1 shows the typical MRI appearance of a demonstrative case of a patient with AQP4 antibody-positive NMO.

SIADH and Hyponatremia

AQP4 interacts with an osmotically activated ion channel, the transient receptor potential channel, vanilloid subfamily (TRPV4). The circumven-

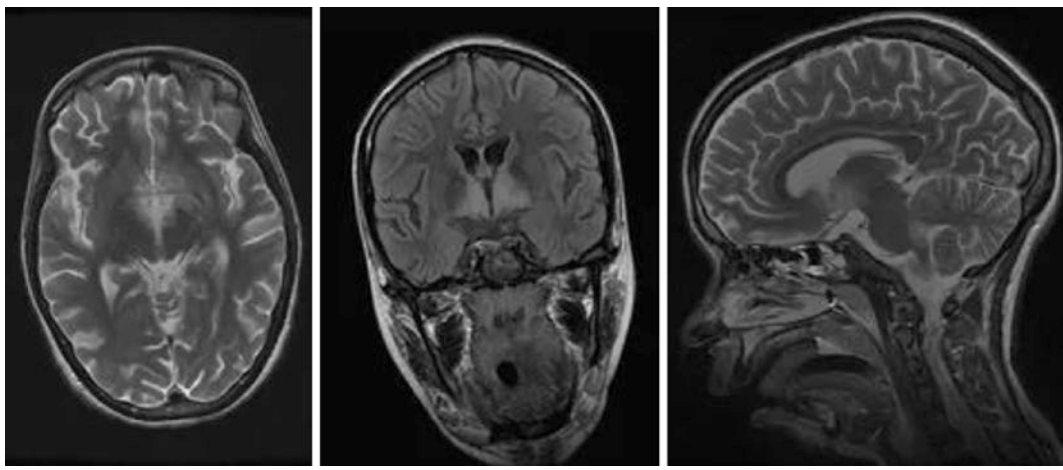

Fig. 20.1 Axial T2, coronal FLAIR, and sagittal T2-weighted MRI demonstrating the characteristic pattern of brain involvement with T2 hyperintensity in the hypothalamus and diencephalon in a patient with AQP4 antibody-positive NMO. (Reproduced with permission from [53])

tricular organs express this channel at high levels, where it serves as a sensor for osmolarity [19]. Hyponatremia fulfilling the criteria for SIADH is not rare in people with NMOSD [114, 236, 268]. Iorio et al. estimate that SIADH occurs in 16% of patients with NMOSD and can be the first symptom of NMOSD [108]. The severe hyponatremia or extension of the lesion to the thalamus resulted in a patient going into coma in a reported case [106]. Although SIADH appears to be the cause of hyponatremia in most of the reported cases, cerebral salt wasting can also occur in rare instances, and it is essential to differentiate salt wasting from SIADH as the treatment is very different. Patients with SIADH need fluid restriction, while patients with central salt wasting need replacement of sodium and volume.

Hormonal Deficiencies

Widespread deficiencies on the hypothalamic-pituitary can take place in NMOSD. Vernant et al. describe two cases of NMO and hyperprolactinemia and secondary amenorrhea [255]. Amenorrhea is the most frequently reported finding, followed by galactorrhea, which can occur with or without amenorrhea [268]. Poppe et al. describe a case presenting with hyponatremia to a nadir of 117 mmol and depressed LH and FSH with normal cortisol and thyroid studies and only mildly elevated prolactin [194]. Fardet et al. describe a case of central hypothyroidism in their report of ten cases with NMO [60].

In children with NMOSD and AQP4 antibodies, endocrinopathies occurred in 60% (15/25) of the cases. Morbid obesity ($n = 8$) occurred most frequently followed by hyperinsulinemia ($n = 5$), hyperandrogenism ($n = 5$), amenorrhea ($n = 5$), hyponatremia ($n = 4$), short stature ($n = 3$), and central hypothyroidism ($n = 2$) [81].

Secondary Narcolepsy

As a consequence of damage to the perifornical area of the hypothalamus, low or undetectable CSF orexin levels resulting in persistent hypersomnia that can fulfill the criteria for narcolepsy can occur [9, 26, 120, 167, 176].

Rapid treatment with high-dose steroids and plasmapheresis can result in significant improvement. Prompt identification and treatment are essential as every day of delay in initiating high-dose steroid treatment results in decreased odds of recovery [231]. Retrospective evidence also suggests that early plasmapheresis/plasma exchange (PLEX) is essential as the probability to regain complete improvement continuously decreases from 50% when patients received PLEX at day 0 to 1–5% when they received PLEX after day 20 [22].

Hypothalamic syndromes, although rare, can be the initial presentation of NMOSD.

Anti-MOG Antibodies Hypothalamic Lesions

Five to 40% of patients with NMOSD do not have antibodies against AQP4. Mader et al. had detected anti-MOG (myelin oligodendrocyte glycoprotein) antibodies in children with recurrent optic neuritis [204] and patients with NMOSD who were negative for AQP4 antibodies [157]. Several other groups reproduced these results [84, 126, 195, 220] and found that about 40% of the patients with NMOSD who are AQP4 antibody-negative have antibodies against MOG. Anti-MOG antibodies also segregate a small subgroup of patients with multiple sclerosis that have severe disease with frequent relapses and prominent brainstem and spinal cord involvement [228].

Hypothalamic involvement in patients with anti-MOG antibodies is not as well as characterized as in AQP4 but seems to occur less frequently. None of the 56 patients studied retrospectively by Sepulveda et al. had hypothalamic involvement [221].

In a retrospective analysis, 1 out of 20 children had hypothalamic involvement [130]. Several reported cases of patients with acute disseminated encephalomyelitis (ADEM) and anti-MOG antibodies included hypothalamic lesions, which is not surprising since ADEM causes widespread areas of inflammation and demyelin-

ation in the central nervous system including deep gray matter structures [10, 11, 138]. Hypothalamic involvement seems to be more frequent in the emerging group of patients with both NMDA and MOG antibodies. Hypothalamic involvement occurred in 4/17 (24%) patients with concurrent MOG and NMDA antibodies in the study by Fan et al. [58] and 1/12 patients in the study by Titulaer et al. [246].

Multiple Sclerosis

Multiple sclerosis (MS) is a common autoimmune demyelinating disease that affects approximately 800,000 people in the United States and 2 million worldwide. Even the first descriptions of MS indicate that MS affects the cortex and deep gray matter structures. Awareness of the importance of gray matter pathology resurged in the last decades.

Hypothalamic Lesions in People with Multiple Sclerosis

The hypothalamus is frequently affected by demyelinating plaques in people with MS [102, 103, 253], and most of these lesions are active with lipid-laden macrophages and microglial activation [102]. Plaques in the hypothalamus are challenging to see macroscopically. They seem to follow the ventricular system and spare the mammillary bodies. As with other gray matter structures, the plaques in the hypothalamus tend to have less inflammation and preponderance of activated microglia [253]. Demyelination in the hypothalamus is more prominent than in other gray matter structures and happens even in the early stages of MS [82].

The inflammation in and around the hypothalamus may affect the endocrine function of the hypothalamus. People with MS show decreased AVP and oxytocin staining in neurons of the paraventricular nucleus (PVN) hypothalamus but preserved numbers of these neurons [197]. Although the content of CRH in paraventricular hypothalamic neurons of patients with MS does not appear to be increased, the number of CRH neurons in the PVN is about 2.4 to 3 times higher than in controls [197] and, the number of cells co-expressing CRH and vasopressin increases 4.5-fold [56]. Hypothalamic lesions contain large numbers of macrophages and glial cells containing IL-1β. Vasopressin or CRH neurons of people with MS as well as controls do not produce IL-1β, but some hypothalamic oxytocin neurons do make IL-1β. However, in people with MS, the expression of IL-1β in hypothalamic neurons is lower than in controls, and the total number of hypothalamic neurons expressing IL-1β is also decreased compared to controls without neurological diseases [104].

MS lesions in the hypothalamus are different from lesions in patients with aquaporin-4 antibodies because the MS lesions are small, triangular or lobulated in shape, and non-Gd-enhancing, while NMO lesions are large and actively enhanced [198]. Thus, plaques in the hypothalamus of people with MS tend not to be very conspicuous on MRI. However, Qui et al., using conventional MRI, did find T2 lesions in the hypothalamus of 18% of 50 consecutive patients with MS who were negative for aquaporin-4 antibodies [198]. Zhang et al. found hypothalamic lesions in 5% of their patients with MS. They also found that hypothalamic lesions were more common in people with MS than in people with ADEM but less common than in people with NMOSD [276]. None of the patients in the study by Qui et al. had clinical symptoms related to hypothalamic dysfunction [198].

Hypothalamic Neurodegeneration

Diffuse neurodegeneration is a second process affecting the hypothalamus in people with MS. Neurodegeneration is manifest in the hypothalamus by reduced neuronal density, acutely injured axons, and oxidation of phospholipids and DNS of neurons [122], axons, and oligodendrocytes. The areas of neurodegeneration show T-cell infiltration, activation of nitric oxide production in microglia, and excessive iron accumulation [82].

There is a loss of hypothalamus volume even after the first attack of MS when whole-brain gray matter atrophy is not evident yet [96]. Hypothalamic damage is visible on MRI with methods sensitive to tissue damage such as T1 relaxation time [275]. The decrease in T1 relaxation time in the hypothalamus correlates with fatigue, and the participants with very high levels of fatigue drove this correlation [275]. Magnetic resonance spectroscopy (MRS) also detects neurodegeneration as NAA (N-acetyl-aspartate) is made only by the mitochondria in neurons. People with MS show decreased NAA/creatine ratios in the hypothalamus, and this happens in people with MS who had experienced only one attack [97, 122]. MRS also shows increased glutamate-glutamine/creatine ratio in the hypothalamus indicating excitotoxicity [97, 122]. The changes in NAA in the hypothalamus correlate with disability, fatigue, and depression [97, 122]. Gliosis is also present in the hypothalamus as the elevated myo-inositol and choline ratios indicate [97]. Whether these correlations with fatigue, cognition, and depression are due to damage to the hypothalamus causing these symptoms or are correlates to widespread brain damage remains to be elucidated.

Hypothalamic-Pituitary Axis Overactivity

The hypothalamic-pituitary axis is overactive in people with multiple sclerosis. Overactivity of the hypothalamus and pituitary is seen at basal conditions [163] and with stimulation tests [61, 93, 163, 199, 274]. People with MS regardless of disease type showed significantly higher cortisol, ACTH, and dehydroepiandrosterone sulfate (DHEAS) plasma concentrations [274].

People with MS have a higher rise in plasma cortisol concentrations in the Dex-CRH test compared to healthy controls [74, 244]. This increase is most pronounced in people with progressive MS with the highest responses in primary progressive multiple sclerosis (PPMS) followed by secondary progressive multiple sclerosis (SPMS) and less elevated in relpasing remitting multiple sclerosis (RRMS) [244]. This overactivity in cortisol production may be a protective mechanism. People with MS that had a higher release of cortisol after the dexamethasone-CRH (DEX-CRH) test had less gadolinium-enhancing lesions. Furthermore, people with smaller ventricular volume had a higher production of cortisol in the dexamethasone-CRH test indicating that the cortisol release is preserving brain tissue [218]. People with RRMS have higher cortisol levels in their morning cortisol awakening response than healthy controls, while people with SPMS have morning cortisol levels similar to those of healthy controls [125]. In RRMS patients, higher morning cortisol output predicts progression over 9 months [125]. However, the overactivity in the hypothalamic-pituitary axis correlates positively with cognitive impairment and disability on the expanded disability status scale (EDSS) scale [61, 93, 94].

In untreated people with MS, CRH-stimulated cortisol secretion slightly increases over time, and lower ACTH secretion mediates this increased cortisol output. This finding indicates that people with RRMS without disease-modifying therapy develop progressive adrenal hypersensitization and hypertrophy due to continuous hypothalamic-pituitary-adrenal overactivity. Furthermore, disease-modifying treatment normalizes this trend [132]. Kumpfel hypothesizes that overactivity of the HPA generates a vicious cycle where increased endogenous steroids desensitize the responses of peripheral immune cells and limit the immune systems' ability to control autoimmunity [132]. Ysrraelit et al. found that lymphocytes of people with MS express similar glucocorticoid receptor numbers to controls; however, binding affinity and glucocorticoid sensitivity of these lymphocytes seem to be reduced [274]. Although the serum cortisol levels are slightly elevated to the upper level of normal, the cortisol levels in the CSF are reduced in people with MS. Poor local activation of cortisone via 11β-hydroxysteroid dehydrogenase type I (11bHSD1) and inactivation via 11bHSD2 may be causing a local cortisol deficit that may explain that the low cortisol CSF levels may be related to plaque formation [95].

Fatigue and the Hypothalamus in People with MS

People with MS suffer from overwhelming fatigue. The hypothesis that increased fatigue is due to hypothalamic damage or dysfunction is attractive. Gottschalk et al. tested 31 participants with MS using the dexamethasone-CRH test and found that people with MS and fatigue exhibited a higher activity of the HPA. In contrast, patients with chronic fatigue with higher fatigue correlates have lower HPA activity [73]. Heesen et al. did not find such correlation and instead found that cytokine levels in the circulation were the main predictors of fatigue [94].

Hanken et al. found another paradoxical result connecting fatigue and the hypothalamus. The posterior hypothalamus contains histaminergic neurons that interact with wake-promoting regions including the dorsal raphe and superior central nuclei in the mesencephalon and the locus coeruleus in the pons, so Hanken et al. hypothesized that damage to these connections would result in higher fatigue. In contrast, they found that in people with MS, lower levels of cognitive fatigue correlate with more significant disruption to the fibers connecting the hypothalamus and the mesencephalon as measured with diffusion tensor imaging [87] mainly on the right [88]. These fibers also include afferents from the vagal nerve to the hypothalamus that mediate sickness behavior. Hanken et al. hypothesize that the disconnection of these fibers may prevent some people affected by MS from experiencing fatigue [87].

Orexin Levels in People with MS

There are few reported cases of people with MS having hypothalamic lesions and low orexin levels in the CSF [123, 181, 258], but some of these cases [123] fit the NMOSD and did not test for aquaporin-4 antibodies or had recently received the H1N1 vaccine [265]. Papuc et al. studied the CSF of 38 patients with MS and 15 healthy controls and found that both groups had similar orexin levels. Contrary to their hypothesis, people with MS and higher levels of fatigue had higher CSF orexin levels [186]. Constantinescu et al. found no correlation between CSF orexin levels and fatigue in people with MS [37].

Thermoregulation in MS

Patients with MS are susceptible to hypothermia. There are reported cases of patients with MS and severe hypothermia who died and had active hypothalamic lesions on autopsy [55] or had new hypothalamic lesions in the preoptic area seen on MRI [269]. Vivid hallucinations accompanied the hypothermia in the patient with the involvement of the preoptic area [235]. Thermoregulatory function studies in two reported cases showed defective vasoconstriction and inadequate thermogenesis suggesting a hypothalamic defect, one of them with concurrent SIADH [235]. However, in other reported cases of patients with MS and hypothermia, detailed histopathology [135] and MRI did not reveal hypothalamic lesions [148], and this is understandable since the control of body temperature relies on a whole network involving the brainstem and spinal cord.

Conclusions

People with MS frequently have lesions in their hypothalamus. People with MS also have overactivity in their HPA that may be a mechanism of protection against inflammation. This defense mechanism may fail as peripheral immune cells in RRMS show diminished glucocorticoid sensitivity. The relationship between hypothalamic lesions and HPA overactivity needs further study. So far, there is not a clear connection between hypothalamic lesions and the hyperactivity of the HPA system. The orexin system does not seem to be widely affected in people with MS and does not seem to be the cause of the increased fatigue that people with MS experience.

Anti-Ma

Anti-neuronal cell antibodies provide antitumor immunity in certain cancers but can cause degenerative neurological disease [209]. Anti-Ma antibodies are well-characterized antibodies, and as such, they allow the diagnosis of "definite paraneoplastic syndrome" even when no tumor is detected [75]. Anti-Ma antibodies recognize a family of highly homologous proteins with shared epitopes. PNMA2 is the primary autoantigen recognized by all patients. Patients can have anti-Ta antibodies (former antibody name: anti-Ma2) that only bind to PNMA2 or anti-Ma antibodies that recognize PNMA1 and PNMA2. The anti-Ma antibodies can also recognize Ma3 (PNMA3) [203]. Reactivity against only Anti-Ma1 is very rare but occurred in one reported case of bladder cancer [184]. Ma2 protein is found only in the brain, Ma1 in the brain and testis, and Ma3 in the brain, testis, and several systemic tissues [203].

The most frequent associated tumors related to anti-Ma2 antibodies are testicular tumors. Men with anti-Ma2 antibodies can have tumors so small that they are undetectable with current imaging. Men with anti-Ma2 antibodies and no detectable tumor may need orchidectomy if there is a history of enlargement of the testicle, cryptorchidism, or microcalcifications on the ultrasound [261]. Anti-Ma1 antibodies occur in patients with tumors outside the testes, including lung and pleural adenocarcinoma, colon cancer, breast cancer, parotid cancer, ovarian cancer, non-Hodgkin lymphoma, renal cell adenocarcinoma, pancreatic cancer, esophageal cancer, and tonsil tumors [40, 184, 263]. The frequency of anti-Ma2 antibody-related paraneoplastic syndromes increased after the introduction of immune checkpoint inhibitors for the treatment of cancers [262].

Patients with anti-Ma antibodies have a plethora of symptoms indicating compromise of the limbic system, diencephalon, brainstem, and cerebellum [40, 98, 184]. Cognitive impairment, amnesia, behavior changes, and refractory temporal lobe epilepsy are common symptoms indicating limbic system involvement. Brainstem involvement manifests with gait disturbance, ocular movement abnormalities, vertical gaze paresis, and external ophthalmoplegia. Isolated cerebellar degeneration can occur in some cases. Atypical parkinsonism and hypokinetic syndrome are the commonly seen symptoms of diencephalic involvement [40]. Distal sensory alteration of the limbs and sensory ataxia are clinical manifestations [184].

Of particular interest to this book is the involvement of the hypothalamus with anti-Ma paraneoplastic syndromes. Hypothalamic and brainstem involvement is characteristic of patients with anti-Ma2 antibodies (Fig. 20.2) [78, 263].

Somnolence, excessive daytime sleepiness, is a frequent clinical presentation, and some patients will have cataplexy, hypnagogic hallucinations, and low hypocretin levels [40]. SIADH, hyponatremia and diabetes insipidus can occur [40, 184]. Cortisol deficiency, hypothyroidism, and panhypopituitarism are also seen [40]. Some patients will have an unexplained weight gain of 20–30 pounds [40], as seen in the case presented in Fig. 20.1 [171]. Hyperthermia frequently occurs [40], and hypothermia is an ominous finding [98]. Usually, the hypothalamic symptoms occur along with limbic or brainstem syndromes, but occasionally, patients with anti-Ma2 antibodies will have isolated hypothalamic involvement [40]. Figure 20.2 shows a representative brain MRI of a patient with anti-MA encephalitis.

Histopathology shows inflammation of the hypothalamus with extensive perivascular infiltration consisting mainly of CD3 and CD8 cells [45]. In some cases, the brain biopsy can be mistaken for a lymphoma. CD45-positive T cells and polyclonal plasma cells can help differentiate the lesions from lymphoma [98].

The most critical component in the diagnosis of paraneoplastic neurological syndromes is the clinical suspicion on the part of the medical team. Analysis of the serum and CSF can detect the presence of paraneoplastic antibodies.

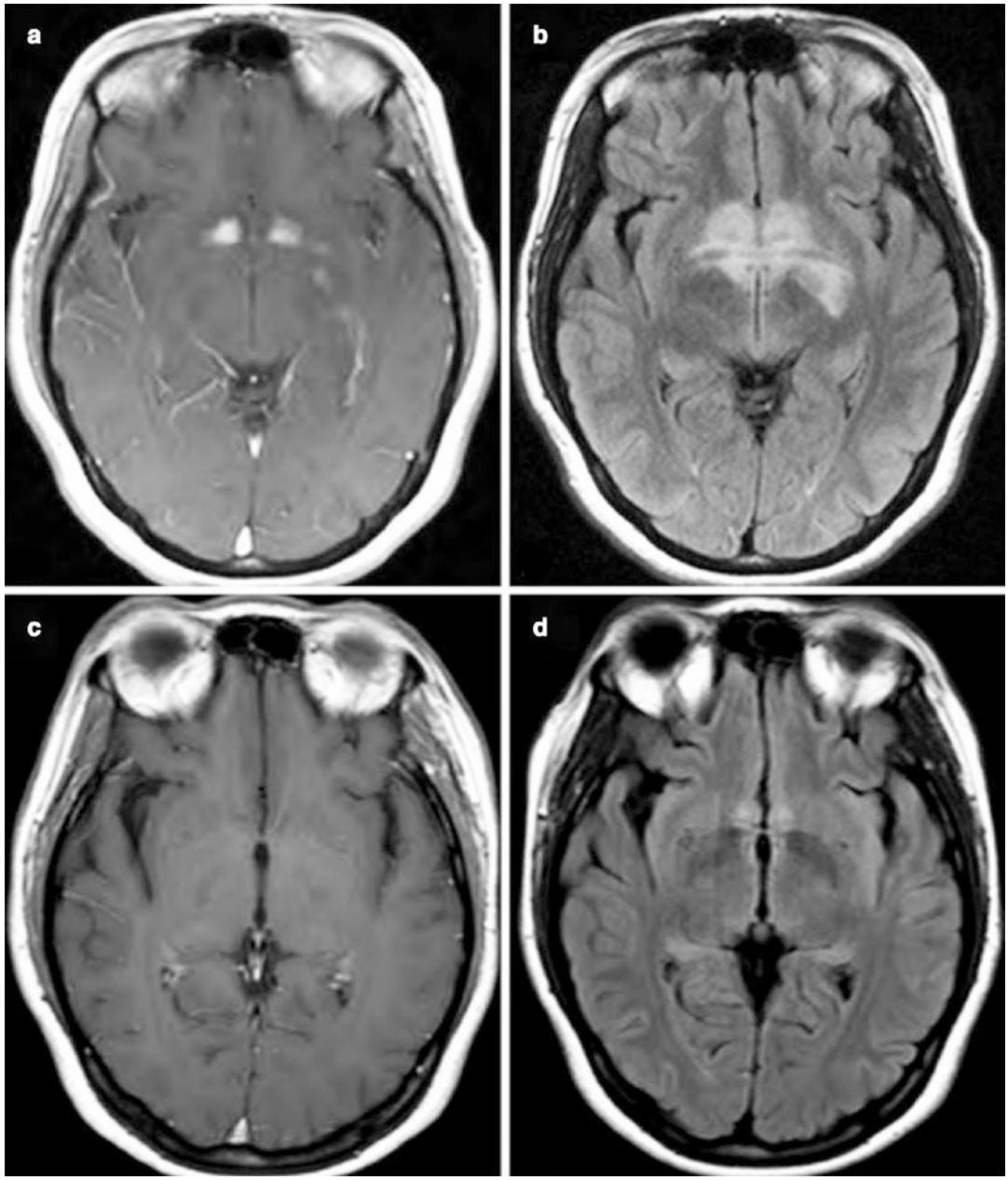

Fig. 20.2 MRI of the brain from a 33-year-old female with recurrence squamous cell carcinoma of the cervix and anti-Ma2 antibodies. Postgadolinium T1 (**a**) and fluid-attenuated inversion recovery (FLAIR) (**b**) sequences obtained upon presentation. Postgadolinium T1 (**c**) and FLAIR (**d**) sequences after treatment with high-dose steroids, chemotherapy, and directed radiation to the involved pelvic lymph nodes. (Reproduced with permission from [171])

Patients with anti-Ma antibodies are more likely to have MRI abnormalities than other patients with paraneoplastic limbic encephalitis due to different antibodies [78]. The most frequent radiological finding is unilateral or bilateral hyperintensity in T2-weighted and FLAIR sequences of the temporal lobes, mainly in the hippocampus and amygdala; diencephalon, thalamus, and hypothalamus; or midbrain. CSF may show slightly to moderately high protein levels and mononuclear pleocytosis.

Treatment consists of corticosteroids, either intravenously or orally, and immunosuppressants. The symptoms may respond to intravenous immunoglobulins (IVIGs) used in association with corticosteroids. Rituximab may also be useful, and in patients with severe symptoms, cyclophosphamide can be effective [184]. Clinical outcomes seem favorable for Ma2 patients, with improvement or stabilization of all symptoms; in contrast, Ma patients have poorer clinical outcomes [75, 203]. These differences may be influenced by the varying percentages of tumor types in each group, as well as by unknown but probably immunological mechanisms [184].

Anti-Voltage-Gated Potassium Channel (VGKC)-Complex Encephalitis

Antibodies against the voltage-gated potassium channel complex (VGKC-complex) cause several autoimmune conditions, including limbic encephalitis. Research into autoimmune encephalitis has significantly advanced recently. In VGKC-complex autoimmune encephalitis, the antibodies target membrane antigens. For many years, the general assumption was that the antibodies detected in a VGKC assay targeted the channel itself. Recent studies proved that most VGKC antibodies directed toward proteins associated with the channel. Irani et al. showed in their study of 96 patients with VGKC antibodies detected by radioimmunoprecipitation that antibodies against the Kv1 subunit of the VGKC channel were rare as only 3/96 (3%) had this specificity. On the other hand, 57% of the patients had antibodies against leucine-rich, glioma-inactivated 1 (LGI1), 33% had antibodies reacting with contactin-associated protein-2 (CASPR 2), 5% had antibodies against contactin-2, and 19% had antibodies with unknown specificity [109].

The identification of the various target antigens led to the identification of more precise syndromes associated with each target antigen. However, the features in patients with different antibodies often overlap. The diversity of autoimmune encephalitis syndromes complicates its recognition. The classical presentation of autoimmune encephalitis consists of a progressive, although sometimes fluctuating, decline over days to weeks in the level of consciousness and cognitive abilities eventually progressing to coma in some cases. Memory, especially the retention of new information, is usually impaired early in the clinical course. Currently, clinicians usually start treatment empirically before specific antibody test results become available because the results of the tests take 1 or 2 weeks to return. Initial treatments may include IVIG, plasmapheresis, and steroids. Second-line therapies include rituximab, cyclophosphamide, or both [136].

We will specify the individual characteristics of some of these encephalopathies, emphasizing the symptoms related to the hypothalamus.

Anti-LGI1 Encephalitis

Anti-LGI1 (leucine-rich, glioma-inactivated 1) encephalitis accounts for most cases of encephalitis previously attributed to VGKC antibodies [109, 134]. The median age is about 60 years. Neoplasms very seldom occur in this disorder, and some of these cancers probably are unrelated random events in these older age patients [136]. Myoclonus and seizures are common. In some cases, faciobrachial dystonic seizures precede other symptoms of the disease by months. The main hypothalamic feature of LGI1 encephalitis is hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion [8, 134], with a reported occurrence of 60%–88% [110, 137]. Co-expression of LGI1 antibodies in the

hypothalamus and kidney may be the mechanism. Generally, hyponatremia is mild to modest and not challenging to rectify [260]. Zhimei et al. found that five (50%) of their patients showed mild to modest hyponatremia and recovered with sodium supplements [145]. However, Weishuai et al. found that hyponatremia occurred in six patients and three presented with refractory hyponatremia [143]. Li et al. report a case of severe refractory hyponatremia, sodium level 126 mmol/L [144].

Anti-Caspr2 Encephalitis

Anti-Caspr2 (contactin-associated protein-like 2) associate with three clinical syndromes: neuromyotonia, Morvan's syndrome, and limbic encephalitis. Neuromyotonia is a peripheral nerve hyperexcitability syndrome characterized by muscle cramps and stiffness. In Morvan's syndrome, autonomic dysfunction, central nervous system dysfunction, and insomnia often occur [109]. The most common phenotype is Morvan's syndrome, but peripheral nerve symptoms may precede or follow encephalitis by months or years. Encephalitis tends to be slower in onset. Thymomas occur in a subgroup of patients with anti-Caspr2 antibodies, and these patients with thymoma are prone to comorbid myasthenia gravis and other autoimmunities found in thymoma patients. The median age is about 60 years, with a male predominance [136]. Hypothalamus involvement can result in profound insomnia and rapid eye movement (REM) sleep behavior disorder (RBD) [226]. The patients respond to immunotherapy but are prone to relapse with the taper of immunotherapy.

Anti-DPPX Encephalitis

Patients with anti-DPPX (dipeptidyl-peptidase-like protein-6) antibodies present with a syndrome of gastrointestinal and central nervous system (CNS) hyperexcitability [247]. Memory loss, seizures, confusion, exaggerated startle response, myoclonus, rigidity, and hyperreflexia also ensue. Patients may have severe diarrhea or constipation. A small group of these patients has tumors such as lymphoma [136]. Considering all previously reported cases in which clinical information was assessable (total 39 patients), 67% developed the triad: weight loss (median 20 kg; range 8–53 kg)/gastrointestinal symptoms, cognitive-mental dysfunction, and CNS hyperexcitability. The increased expression of DPPX in myenteric plexus may explain the frequent gastrointestinal problems. Most patients respond to immunotherapy regardless of the duration of symptoms, suggesting that early diagnosis and treatment may further improve outcome [89]. Hypothalamic dysfunction does not seem to occur.

Anti-IgLON5 Disease

The IgLON family is a subgroup of cell adhesion molecules formed of 5-glycosylphosphatidylinositol-anchored cell adhesion molecules expressed in the blood-brain barrier. IgLON proteins have diverse roles in neuronal development, including neurite outgrowth regulation, dendritic arborization, synapse formation, and expression. IgLONs have three Ig-like C2 domains that perform various cellular interactions. The IgLON family includes the limbic system-associated membrane protein (LSAMP), neurotrimin (NTM), opioid-binding cell adhesion molecule (OPCML), neuronal growth regulator 1 (NEGR1), and IgLON5 [131]. Each IgLON can bind and interact with other members of the family to form dimers. A group of ten pairs of IgLON molecules forms a complex structure in the cell membrane. The IgLON cluster consists of six pairs of IgLON heterodimers, and four homodimers form a complex structure in the cellular membrane [161]. The precise function of IgLON5 and the other members of the family is unclear.

In 2014, Sabater et al. first described anti-IgLON5 disease. This syndrome included a sleep disorder with non-rapid eye movement (NREM) sleep parasomnia and REM behavior disorder, obstructive sleep apnea, and stridor [207]. Sabater et al. observed a 59-year-old man with a slowly

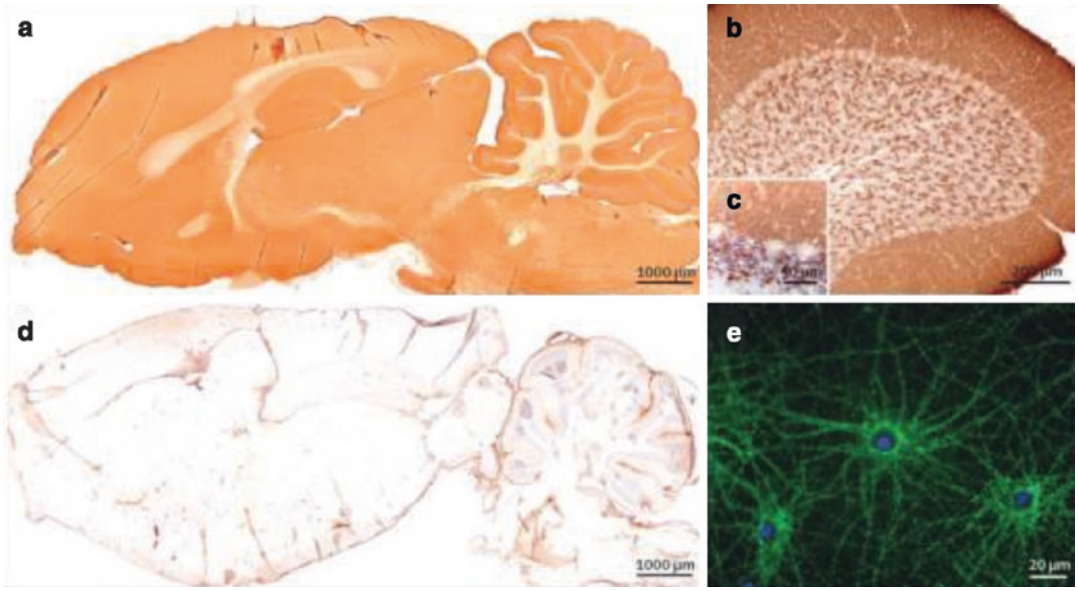

Fig. 20.3 Rat brain slices and cultures of hippocampal neurons showing the IgLON5 reactivity. (**a**) A sagittal rat brain section immunostained with a patient's CSF shows diffuse staining of the neuropil. CSF from controls does not cause staining (**b**). The immunostaining was most prominent in the cerebellum (**c**). In the cerebellum, there was diffuse staining of the molecular layer and synaptic glomeruli of the granular cell layer. (**d**, counterstained with hematoxylin). (**e**) Culture of rat hippocampal neurons incubated (non-permeabilized) with a patient's serum showing intense reactivity with a cell surface antigen. Scale bars: **a** and **b** = 1000 µm, **c** = 200 µm, **d** = 50 µm, and **e** = 20 µm. (Reproduced with permission from [207])

progressive unusual sleep disorder. The patient's serum had a novel antibody against an unknown surface protein demonstrated in the rat brain slices illustrated in Fig. 20.3.

Soon after their first patient, they found three more patients with the same sleep disorder. The patients had excessive daytime sleepiness, and their sleep studies showed abnormal sleep behaviors, sleep apnea, and stridor as demonstrated in Figs. 20.4 and 20.5.

A search through the center's sample collection identified four more patients with similar sleep abnormalities. Besides the sleep problems, some of these patients had gait instability, chorea, and ataxia. Abnormal eye movements, bulbar symptoms, and dysfunction of the autonomic system were frequent. Central hypoventilation was also present and caused the death of several of the patients.

The patients responded poorly to immunotherapy and died within a median of 5 years. On their autopsy, the hypothalamus and the brainstem showed neuronal loss and gliosis. The damage to the neurons was associated with extensive deposits of hyperphosphorylated tau. These tau deposits were most prominent in the tegmentum of the brainstem and hypothalamus as demonstrated by the coronal and transverse brain sections shown in Figs. 20.6 and 20.7 [69, 207]. In other tau pathologies, hyperphosphorylated tau accumulates in glial cells [153]. Patients with anti-IgLON5 antibodies accumulate tau in the neurons but had no accumulation of tau in glial cells and thus would not fit into any of the known tauopathies [207].

Sabater et al. identified the IgLON5 as the target antigen and developed a cell-based assay. All of their patients had IgG4 against IgLON5 on the cell-based assay, and the only control that also had anti-IgLON5 antibodies in over 285 controls had progressive supranuclear palsy [207].

A more extensive study of 22 cases characterized the disease further [67]. At the time of diag-

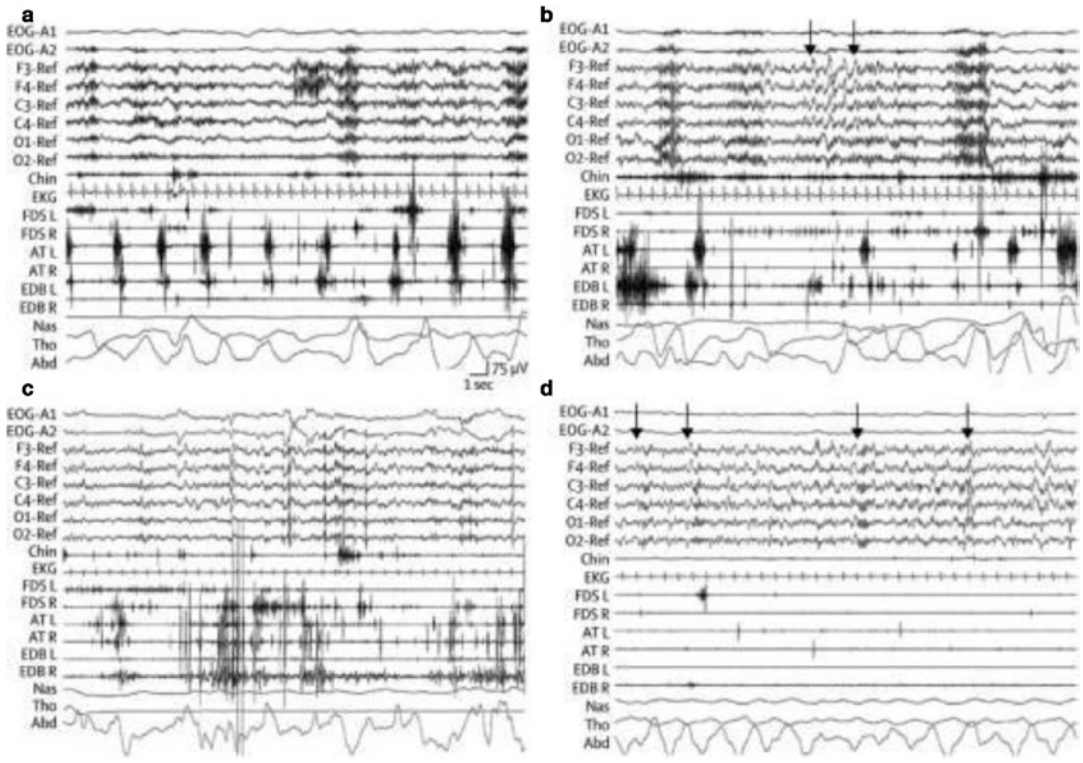

Fig. 20.4 (**a**) Sleep onset characterized by undifferentiated NREM sleep and diffuse theta activity. Rapid periodic leg movements are prominent at the left AT EMG channel; (**b**) N2 sleep with a chain of four consecutive K complexes (arrows) with frequent muscular phasic activity in EMG surface of the limbs that correlate with vocalizations and finalistic movements; (**c**) REM sleep with typical rapid eye movements and EEG features. The EMG shows excessive phasic and tonic muscular activity and body jerks typical of REM sleep behavior disorder; (**d**) N3 with diffuse delta activity and well-defined sleep spindles at 13 Hz (arrows) without body/limb movements. (Reproduced with permission from [207]). Abbreviations: NREM non-rapid eye movement sleep, EMG electromyogram, EEG electroencephalogram, EOG electrooculogram, Chin electromyography of mentalis muscle, EKG electrocardiogram, FDS flexor digitorum superficialis muscle left (L) and right (R), EDB extensor digitorum brevis muscle left (L) and right (R), AT anterior tibialis left (L) and right (R), NAS nasal airflow, THO thoracic respiratory movement, ABD abdominal respiratory motion. Note the calibration mark for 1 second and 75 µV on EEG. (Reproduced with permission from [207])

nosis, the patients with anti-IgLON5 antibodies presented with four types of syndromes. The syndromes were (1) a sleep disorder as described originally, (2) a bulbar syndrome, (3) a syndrome similar to progressive supranuclear palsy, and (4) cognitive decline with or without chorea [67]. Honorat et al. found identical syndromes in their 20 patients [101]. Although these four syndromes are common, additional symptoms and clinical findings can occur [174], including involvement of the peripheral nervous system [174]. Damage to the peripheral nervous system manifests as generalized fasciculations, neuromyotonic discharges, peripheral nerve palsy, atrophy, and cramps [174, 217, 240, 270]. Most cases are slowly progressive, but two reported cases presented sudden-onset encephalitis with dyskinesias [12, 164].

MRI may show paramagnetic deposits in the basal ganglia, substantia nigra, and red nucleus [165] as well as symmetrical areas of reduced diffusion restriction in the cerebellum and midbrain tegmentum [240]. Atrophy of the hippocampus, cerebellum, and brainstem are frequently

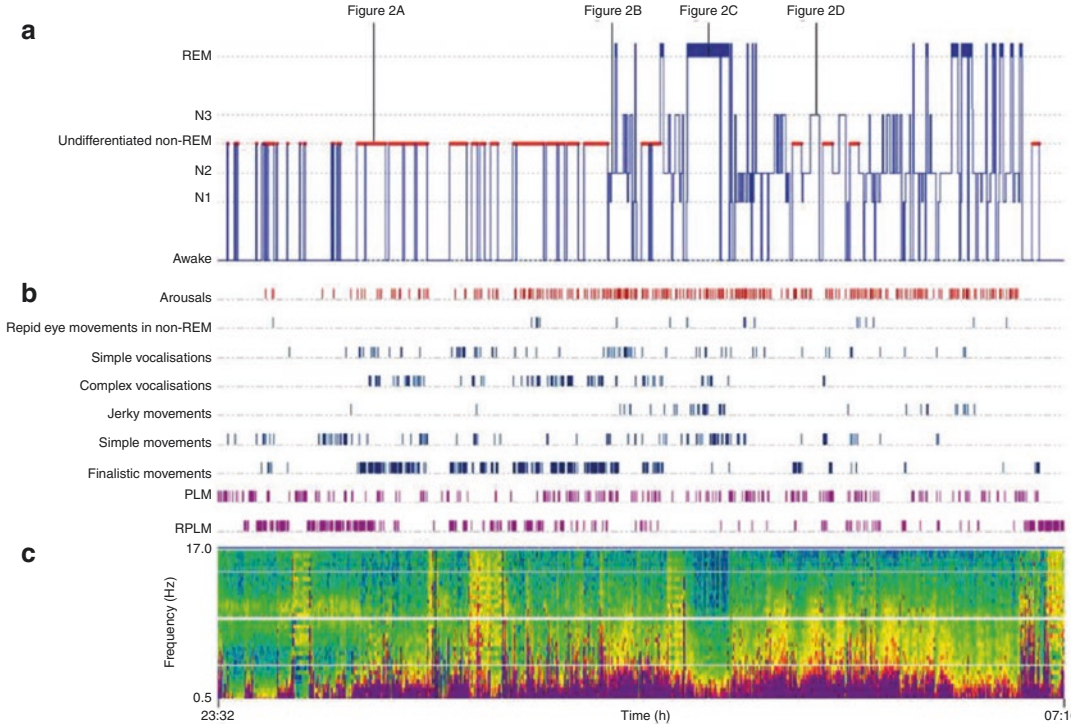

Fig. 20.5 (**a**) Hypnogram. (**b**) Arousals, dissociations, and periodic movements. (**c**) A density spectral array shows the power spectrum of the C3 electrode referenced to electrode O_2. The array shows frequencies in the 0–17 Hz, which are of interest in studying EEG. Warmer colors indicate frequencies that are more dominant than those in cooler tones. Abbreviations: REM rapid eye movements, RBD REM sleep behavior disorder, PLM periodic limb movements, RPLM rapid periodic leg movements. (Reproduced with permission from [207])

present on MRI [174]. The brainstem and thalamus can show T2 hyperintensities [174]. One case showed enhancement of the leptomeninges and the frontotemporal areas [174].

Treatment response in the cases initially reported was very poor. However, Honorat et al. reported better outcomes with immunotherapy in their 20 cases [101]. Several authors describe other cases of response to immunotherapy [21, 23, 83, 150, 165]. Nissen and Blaabjerg report in their comprehensive literature review spanning 58 published cases that the majority of cases responded partially to immunotherapy. Furthermore, untreated cases or cases treated only with steroids had higher mortality [174]. It is possible that very early treatment results in better outcomes.

Four of the eight patients in the original work by Sabater et al. carried the HLA-DRB1*1001 and HLA-DQB1*0501 alleles [207]. The frequency of these haplotypes among the studied population was 1.6% and 14.4% [13], arguing in favor that the association noted in those patients with these alleles represented a genetic susceptibility for autoimmune disease. Gaig et al. confirmed this association with HLA-DRB1*10:01 and HLA-DQB1*05:01 in two additional studies [67, 68].

Gaig et al. also identified an association with the H1/H1 haplotype in the microtubule-associated protein tau (MAPT) gene and anti-IgLON5 disease [66]. Mutations on the MAPT gene cause familial cases of frontotemporal dementia [70]. The H1/H1 haplotype associated with anti-IgLON5 disease is also associated with progressive supranuclear palsy, corticobasal degeneration, and Parkinson's disease [25]. Thus, a combination of the ability to generate anti-

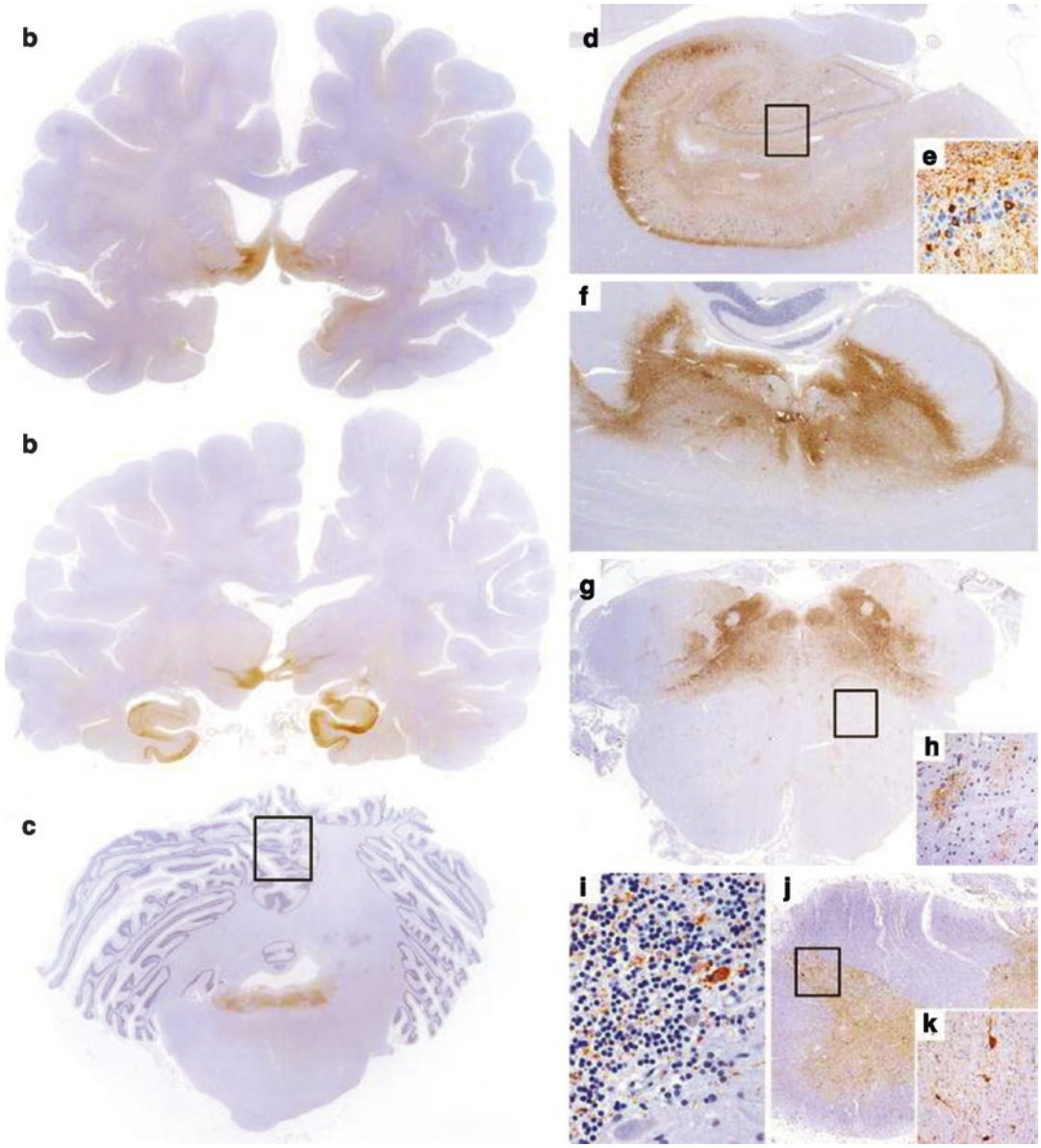

Fig. 20.6 Distribution of tau-related pathology in a patient with anti-IgLON5. (**a**) Coronal sections through the substantia innominata and hypothalamus. (**b**) Coronal sections through **the** thalamus with red nucleus and substantia nigra. (**c**) Cerebellum with pons. (**d**, **e**) Higher magnification of the hippocampus, (**f**) pons, (**g**, **h**) medulla oblongata at the level of the olivary nucleus, (**i**) cerebellar cortex, and (**j**, **k**) cervical spinal cord. The tau pathology mainly affects the hypothalamus and substantia innominata (**a**), the zona incerta and hippocampus (**b**), and the tegmentum of the brainstem **(c)**. Tangles and threads are abundant in the pyramidal layer, with the highest density in the CA2 sector (**d**). Pretangles are also present in the dentate gyrus (*rectangle* in **d** enlarged in **e**). High densities of tangles and threads appear in the tegmentum of pons (**f**) and medulla oblongata (**g**). Bush-like delicate processes accumulating around neurons are visible in the olivary nucleus (*rectangle* in **g** enlarged in **h**). Grain-like processes mainly occur in the vermis of the cerebellar cortex. A few Purkinje cells show a cytoplasmic tau immunoreactivity (*rectangle* in **c** enlarged in **i**). Moderate tau pathology is apparent mainly in the dorsal horn of the spinal cord (**j**, expanded in **k**). (Reproduced with permission from [69])

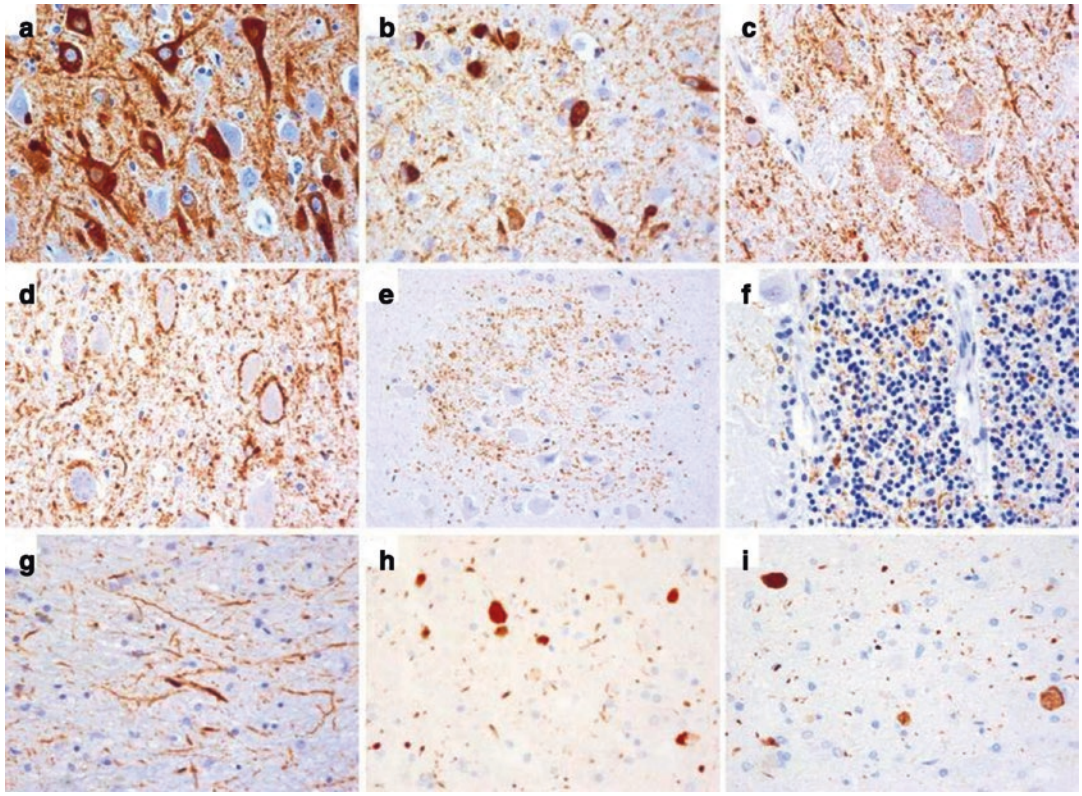

Fig. 20.7 Morphology of tau-related pathology. Tau stains brown on immunostaining. Hyperphosphorylated Tau-related pathologies include the following: neurofibrillary tangles and pretangles (**a** CA2 sector of the hippocampus; **b** substantia innominata), diffuse fine granular cytoplasmic immunoreactivity (**c** gigantocellular nucleus of reticular formation), and numerous somato-synaptic immunoreactivity in the brainstem nuclei (**d** hypoglossal nucleus), bush-like delicate processes accumulating around neurons (**e** olivary nucleus), fine granular synaptic-like deposits (**f** cerebellar cortex), and long coarse and fine threads (**g** substantia innominata). These immunomorphologies stained positive for the three-repeat (**h**) and the four-repeat (**i**) tau isoforms. (**a**–**g**), AT8 × 400; (**h**), 3RT × 400; (**i**), 4RT × 400 [69]

IgLON5 antibodies and a genetic propensity for tau disease may be necessary to cause the anti-IgLON5 disease.

IgG4 anti-IgLON5 antibodies are the most abundant fraction in the serum of patients with anti-IgLON5 disease. However, the IgG1 fraction is responsible for the condition. Anti-IgLON5 IgG1 antibodies cause the IgLON5 clusters in neurons from the hippocampus to move into the cytoplasm. Once removed from the membrane, this cluster loss appears to be irreversible [208]. Anti-IgLON5 disease responds poorly to immunotherapy probably because neurons are not able to replace IgLON5 clusters after binding by IgG1 antibodies, and internalization to the cytoplasm may explain why.

The diffuse involvement of the brainstem nuclei probably explains the sleep breathing disorder, gait instability, bulbar symptoms, as well as the difficulties in the proper order of entering sleep [54, 214].

The hypothalamus has a central role in the regulation of sleep onset and organization. Tau deposition in patients with anti-IgLON antibodies is most severe in the posterior hypothalamus [69]. The dorsomedial and ventromedial nuclei in the posterior hypothalamus are severely affected, while the supraoptic nucleus in the anterior hypo-

thalamus is mostly spared [69]. Hypocretin-1 levels in CSF are normal in anti-IgLON5 disease [68]. The involvement of the hypothalamus probably causes difficulties in the proper order of entering sleep seen in patients with anti-IgLON5 antibodies [207]. Some of the cognitive impairment may be due to the involvement of the mammillary bodies. However, the compromise of brainstem areas probably causes REM behavior disorder and disordered breathing. Studies so far have not investigated the occurrence of damage to hypothalamic functions in anti-IgLON5 disease.

Neurosarcoidosis

Sarcoidosis is a multisystem inflammatory disease whose main characteristic is the formation of noncaseating granulomas. The granulomas affect mainly the lungs and the lymphatic system but can also affect other organ systems. The lesion consists of lymphocytes and mononuclear phagocytes surrounding a noncaseating epithelioid cell granuloma as demonstrated in Fig. 20.8. Although the pathogenesis of sarcoidosis is still uncertain, environmental and genetic factors may contribute substantially to the risk of developing it, leading to an exaggerated granulomatous reaction [264].

Epidemiology of Neurosarcoidosis

Symptomatic neurosarcoidosis occurs in 5–13% of patients with sarcoidosis [33, 34, 177, 229] (with a prospective study of consecutive patients finding a risk as high as 26%) [7]. The risk may not be as high because, as Stern et al. found in their study of 649 patients with sarcoidosis, only

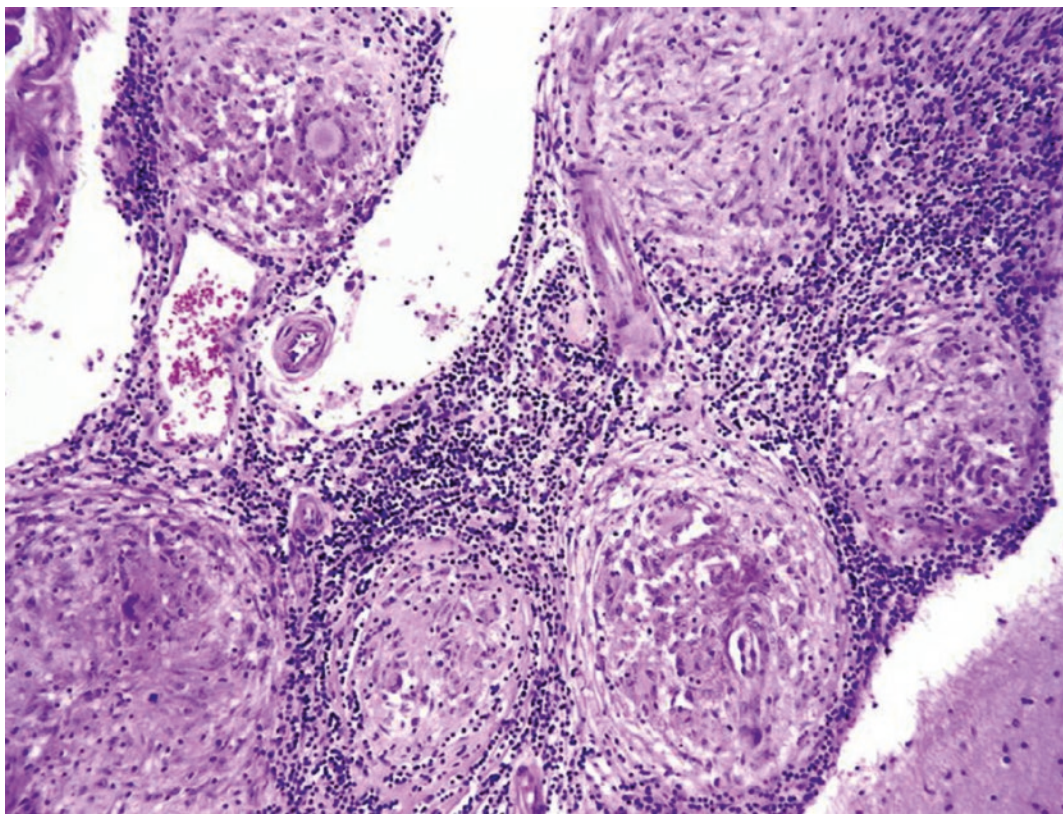

Fig. 20.8 Noncaseating granuloma in the parietal lobe showing the granuloma surrounded by epithelioid cells and nodular inflammatory infiltrates (hematoxylin and eosin 100x. (Reproduced with permission from [133])

55% of patients with neurological problems and sarcoidosis had neurosarcoidosis [229]. The risk of neurosarcoidosis does not depend on race or sex [18, 117, 191]. Fourteen percent of patients with sarcoidosis who had an autopsy done had CNS disease [200]. On imaging, 10% of patients with sarcoidosis had findings indicative of neurosarcoidosis [156]. Approximately half of the patients with neurosarcoidosis present with neurologic difficulties when sarcoidosis is first diagnosed [62, 229].

Clinical Manifestations of Neurosarcoidosis

The clinical signs of neurosarcoidosis are widely variable, as the granulomas can affect the meninges, brain, cranial nerves, spinal cord, and peripheral nerves or any other part of the nervous system. Cranial neuropathy is the most common manifestation occurring in 50–70% of cases of neurosarcoidosis, with facial nerves being the most commonly affected cranial nerve [65, 230]. The optic nerve is the second most frequent site of cranial neuropathy, usually presenting with visual defects. Cranial neuropathies may result in the following manifestations: impaired taste, blindness, blurry vision, double vision, field defects, pupillary abnormalities, dry or sore eyes, slurred speech, impaired swallowing, hoarseness, vertigo, sensorineural deafness, tinnitus, muscle weakness, and tongue deviation.

Meningitis occurs in 8–40% of the patients, typically with infiltration of the basal meninges. Usually, the meningitis is chronic, but in some cases, acute sterile meningitis may develop, leading to fever, stiff neck, and headaches. Cerebrospinal fluid analysis is unrevealing in approximately one-third of people with neurosarcoidosis. CSF may reveal lymphocytosis, elevated protein, and ACE levels, while hypoglycorrhachia develops in one-third of the patients.

Seizures may develop in up to 22% of patients with neurosarcoidosis due to leptomeningeal involvement, granulomas, encephalopathy, or hydrocephalus [177, 242].

Peripheral neuropathy of sarcoidosis may present with a broad clinical spectrum of manifestations. Patients with neurosarcoidosis can have findings similar to Guillain-Barre syndrome that includes severe muscle weakness, pain, paresthesias, dysesthesias, autonomic dysfunction, and abnormal thermal dysfunction [99, 210]. More commonly, peripheral nerve disease presents as a sensory or motor mononeuropathy, mononeuropathy multiplex, or polyneuropathy.

The condition may involve the spinal cord. The presence of spinal lesions on neuroimaging extending more than three spine segments suggests neurosarcoidosis [241].

Hypothalamic Involvement in Neurosarcoidosis

Endocrinopathies

Six to nine percent of patients with neurosarcoidosis will have damage to the neuroendocrine system. The neuroendocrine system is usually affected when the base of the skull has granulomatous infiltration compromising the hypothalamus [57, 188]. Diabetes insipidus (17–90%) [139] and hyperprolactinemia (3–32%) [254] are the most common endocrine disorders in neurosarcoidosis, but multiple other hormonal imbalances or homeostasis dysfunctions can also occur. Hyperprolactinemia usually normalizes with steroid treatment [254].

Water Balance Impairment

Neurosarcoidosis is an important differential diagnosis in patients with central diabetes insipidus. Central diabetes insipidus occurs in 25% of patients with neurosarcoidosis [182]. When contemplating the diagnosis of neurohypophysitis, neurosarcoidosis should remain on the differential as central diabetes insipidus, and hypopituitarism may be the initial presentation of patients with neurosarcoidosis, and some of these patients can have a chest X-ray with no findings [24]. Corticosteroids decrease the size and enhancement of the pituitary gland and stalk but failed to resolve the polyuria even after 8 years of treatment. Thus most patients with central diabetes

insipidus due to neurosarcoidosis will require long-term ADH replacement [237], but in some cases, the diabetes insipidus resolves after prolonged steroid therapy [224]. The granulomatous involvement may involve only the posterior pituitary in adults [151] and children [129].

More profound damage to the hypothalamus can damage the thirst mechanism resulting in adipsic diabetes insipidus [179, 233] or also organic polydipsia. In this case, the patient will have severe hypernatremia with no desire to drink water. Aggressive treatment with infliximab restored thirst perception and resolved the enhancement of the hypothalamus on MRI [180].

Although diabetes insipidus is the most common cause of impaired water balance, inappropriate ADH secretion and primary polydipsia can also occur. Patients with sarcoidosis can develop polyuria due to one or more reasons. In particular, hypercalcemia due to the production of calcitriol by activated macrophages can cause nephrogenic diabetes insipidus [233]. Thus, patients with sarcoidosis and polyuria may require a water restriction test to establish the correct diagnosis.

Endocrine Manifestations

Hypothalamic or pituitary involvement can disrupt the thyroid, gonadal, or adrenal hormonal systems [20, 115]. Galactorrhea develops in many instances since hyperprolactinemia is one of the two most common endocrine abnormalities in people with neurosarcoidosis. It is not unusual to see amenorrhea [149, 238] or other alterations in the menstrual period, impotence, or loss of libido. Patients with neurosarcoidosis and hypothalamic lesions can lose glucose counterregulation. In this case, the patients will have frequent fainting episodes and will have persistent hypoglycemia after glucose intake because they cannot activate the sympathetic system or release glucagon [63]. Even though neurosarcoidosis is not a commonly seen entity from an endocrinology standpoint, it should be considered as part of the diagnosis in patients with panhypopituitarism, especially if there is evidence of multiorgan disease. Figure 20.9 shows the sagittal MRI of a representative patient with neurosarcoidosis and hypothalamic involvement who presented with profound hypothermia.

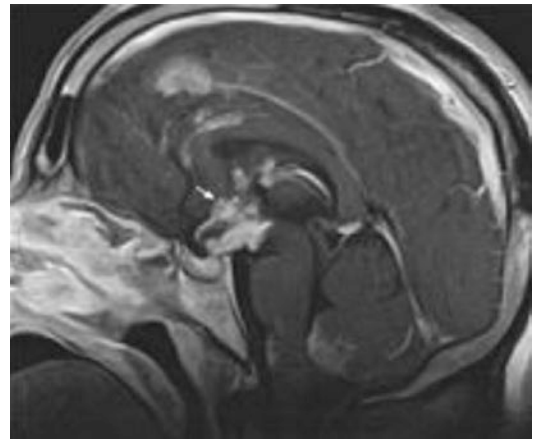

Fig. 20.9 MRI of the brain of a patient with severe hypothermia due to neurosarcoidosis involving the hypothalamus. (Reproduced with permission from [249])

Other Hypothalamic Involvement

More profound hypothalamic deficits will occur in more severe cases when there is deeper infiltration of the hypothalamus. The granulomatous inflammation can lead to a profound disruption of homeostatic functions.

Hypothermia has occurred in several cases where sarcoidosis infiltrated the hypothalamus [90, 127, 185, 223, 249]. The involvement of the hypothalamus can also result in narcolepsy, which can be the presenting symptom of neurosarcoidosis [168, 222]. In one case, narcolepsy responded to whole-brain irradiation [206]. Loss of ventilatory drive can accompany narcolepsy in patients with neurosarcoidosis [71, 159, 160] (Daum 1965, #949).

Obesity is more common in patients with sarcoidosis than in healthy controls, but it is unclear if this increase in obesity is due to hypothalamic involvement or more likely multifactorial (Gvozdenovic 2013, #935). Granulomatous invasion of the ventral medial nucleus of the hypothalamus causes morbid obesity [196, 257]. These patients with neurosarcoidosis and obesity due to hypothalamic involvement have died suddenly, possibly due to impaired ventilatory drive [71, 159]. Profound amnesia and confabulation

occur along with morbid obesity with the involvement of the medial hypothalamus [196]. Paranoid psychosis can occur when sarcoidosis affects the hypothalamus [178].

Diagnosis of Neurosarcoidosis

Although the gold standard for the identification of neurosarcoidosis requires histopathologic confirmation of neural tissue, this is an invasive procedure to avoid if possible. Confirming the diagnosis of sarcoidosis requires histopathologic confirmation. More than 90% of the patients with neurosarcoidosis have granulomas in the lungs or other sites. As a result, superficial biopsy sites like the skin, lacrimal gland, lymph nodes, or lung are preferred [118].

MRI with intravenous gadolinium is the imaging technique of choice that may reveal diffuse, focal, or multifocal central nervous system involvement with a predilection for the basal meninges. Cerebrospinal findings may support the diagnosis. Currently, no biomarkers exist that can identify neurosarcoidosis with sufficient sensitivity and specificity. However, ACE and interleukin-2 receptor may be useful [65]. Positron emission tomography, electroencephalography, electromyography, and nerve conduction studies are other tests that may be useful for diagnosis. PET/CT is not only valuable for identifying neurosarcoidosis but also to find other sites of involvement that are easier to biopsy.

Consensus diagnostic criteria were published in August 2018 by the Neurosarcoidosis Consortium Consensus Group. Clinical findings and diagnostic evaluation suggestive of neurosarcoidosis after thorough evaluation to exclude other causes support the diagnosis. The diagnosis is definite when central nervous system pathology demonstrates neurosarcoidosis, probable when an extraneural biopsy is consistent with sarcoidosis, and possible when no confirmation of granulomatous disease has occurred [230]. Table 20.1 details the formal diagnostic criteria for neurosarcoidosis.

Table 20.1 Diagnostic criteria for neurosarcoidosis [230]

Proposed diagnostic criteria for central nervous system and peripheral nervous system neurosarcoidosis
Possible
1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes
2. There is no pathologic confirmation of granulomatous disease
Probable
1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes
2. There is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis
Definite
1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes
2. The nervous system pathology is consistent with neurosarcoidosis
Type a. Extraneural sarcoidosis is evident
Type b. No extraneural sarcoidosis is evident (isolated CNS sarcoidosis)

Abbreviations: *CSF* cerebrospinal fluid, *EMG* electromyogram, *MRI* magnetic resonance imaging, *NCS* nerve conduction study

Treatment of Neurosarcoidosis

There is no known effective cure for neurosarcoidosis. Spontaneous remission usually happens within the first 6 months of disease, but unfortunately, in contrast to pulmonary sarcoidosis, spontaneous remission of neurosarcoidosis is extremely rare. Isolated cranial nerve disease and aseptic meningitis are the most common scenarios with spontaneous resolution [76, 77]. Thus, long-term immunosuppressive therapy often is required. Corticosteroids are the cornerstone of treatment. For mild to moderate neurosarcoidosis, an initial dose of 20–100 mg/day

prednisone is recommended. An intravenous dose of methylprednisolone 20 mg/kg per day for 3 days, followed by prednisone 1.0–1.5 mg/kg per day, is needed for severe conditions. Relapse is common after steroid dose tapering and requires additional immunosuppressive agents [250, 251]. Hydroxychloroquine, chloroquine, mycophenolate, methotrexate, cyclosporine, and cyclophosphamide may be useful for neurosarcoidosis as steroid-sparing agents. TNF-α blockers like infliximab and adalimumab are necessary for patients with refractory disease [52, 158]. Mass lesions may need neurosurgery or radiotherapy. Radiotherapy is typically a last resort treatment considered if corticosteroid therapy is not successful and at least two alternative agents fail [162].

Narcolepsy and Other Hypersomnias

The hypersomnias of central origin are rare sleep diseases whose common presenting symptom is excessive daytime sleepiness. They include type I and type II narcolepsy and Kleine-Levin syndrome. Medical disorders, psychiatric disorders, and substances also cause hypersomnia. Of particular interest to this section are type I narcolepsy and Kleine-Levin syndrome because of their relationship with the immune system or inflammation.

Type I Narcolepsy

Narcolepsy is a neurological sleep disorder causing a potentially disabling level of daytime sleepiness. People with narcolepsy suddenly fall asleep in unusual situations such as eating, walking, or driving. Individuals with narcolepsy still experience daytime sleepiness even when they sleep well at night. The "sleep attacks" occur in monotonous situations that require no significant active participation of the patient [44].

Type I narcolepsy is a distinct entity characterized by excessive daytime sleepiness and cataplexy. Type I narcolepsy consists of excessive daytime sleepiness without cataplexy [44, 107]. Type I narcolepsy affects about 1 in 2000 people around the world, with a bimodal age of onset, usually between 15 and 35 years of age. The prevalence of type II narcolepsy remains unclear, and its underlying cause is uncertain [43, 107].

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) with the consequent polysomnographic features as shown in Fig. 20.10 means that the person is unable to stay awake and alert during the significant portions of the day when he/she should be awake. People with EDS will nap repeatedly or will fall asleep involuntarily multiple times during the day [17]. Typically, naps are short and considered refreshing by patients. People with severe narcolepsy will have automatic behaviors where they complete complex actions without any awareness. After sleeping at night, they usually wake up refreshed, and waking up in the morning is easy [17].

During episodes of sleepiness, patients can perform automatic activities. For example, people with automatic behaviors will say things out of context in a conversation, write illegibly, or drive to an inappropriate location and have no memory of doing so.

In children, narcolepsy can be slightly different. Weight gain and excessive daytime sleepiness are usually the first symptoms in children. Naps are inconsistently refreshing, and the child may fight against sleep. These children may have difficulty staying still, leading to an erroneous diagnosis of attention deficit hyperactivity disorder [17].

Cataplexy

Cataplexy as demonstrated in Fig. 20.11 consists of a sudden loss of muscle tone with weakness around the knees, face, and neck. Severe episodes can cause patients to collapse. The loss of orexin results in decreased activity in the periaqueductal gray area that inhibits REM sleep. Loss of orexin also increases the activity of neurons in the sublaterodorsal tegmental nucleus that controls atonia during REM sleep [17, 152]. There is no impairment of consciousness during cataplexy.

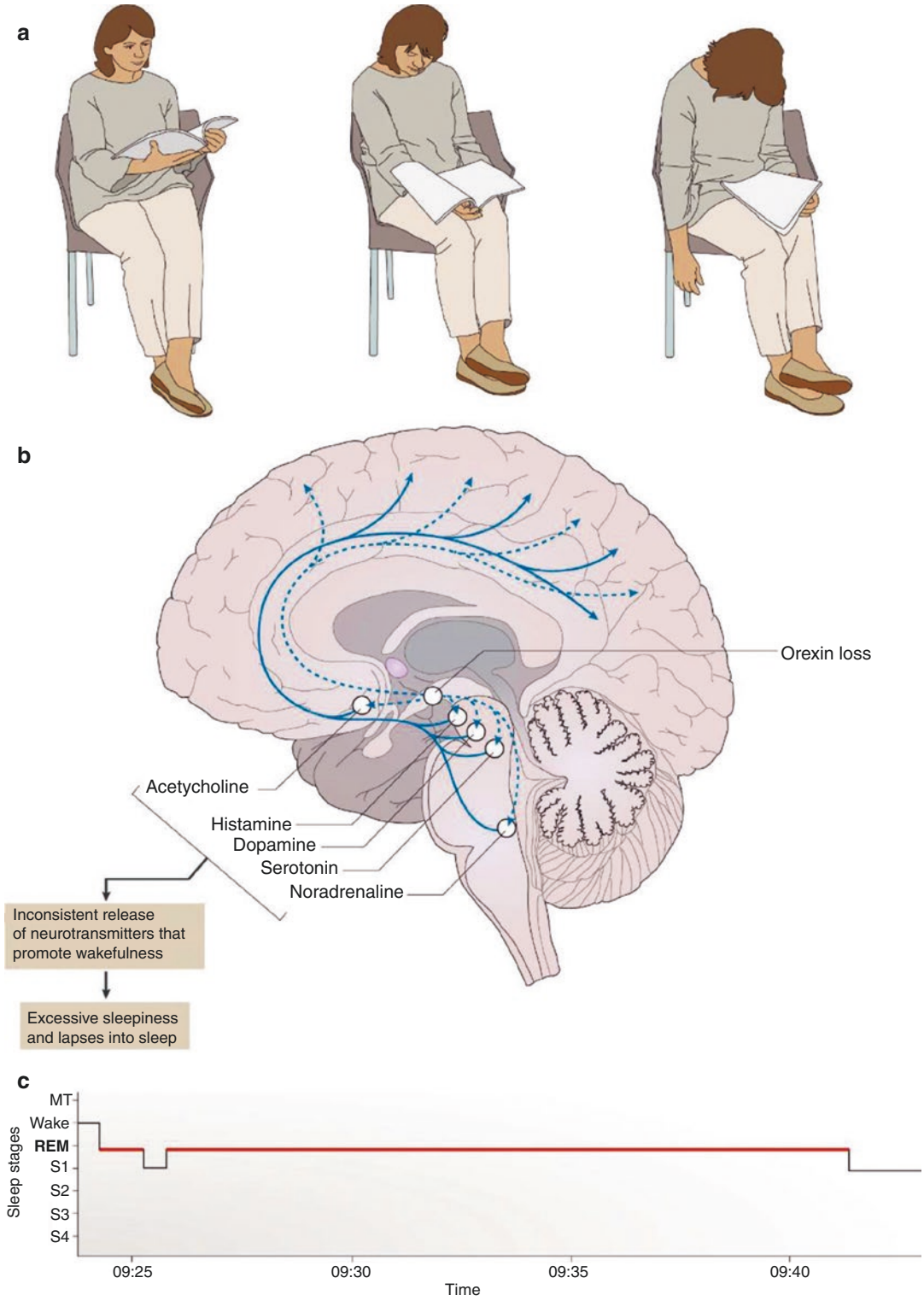

Fig. 20.10 (**a**) An episode of sleep or involuntary nap during quiet reading. Naps can occur in the morning hours and are typically short and refreshing. Sleep episodes are less sudden than cataplexy attacks. (**b**) The specific loss of orexin-producing neurons in type I narcolepsy patients results in the inconsistent firing of the brainstem neurons responsible for arousal. (**c**) Multiple sleep latency test (MSLT) documents the transition from wakefulness to sleep. A shortened sleep latency period is evident, and a so-called sleep-onset rapid eye movement (REM) period (SOREMP) occurs within 15 min. In patients with narcolepsy accompanied by cataplexy, SOREMPs occur in ~50% of sleep episodes (detected by MSLT or nighttime polysomnography). (Reproduced with permission from [17])

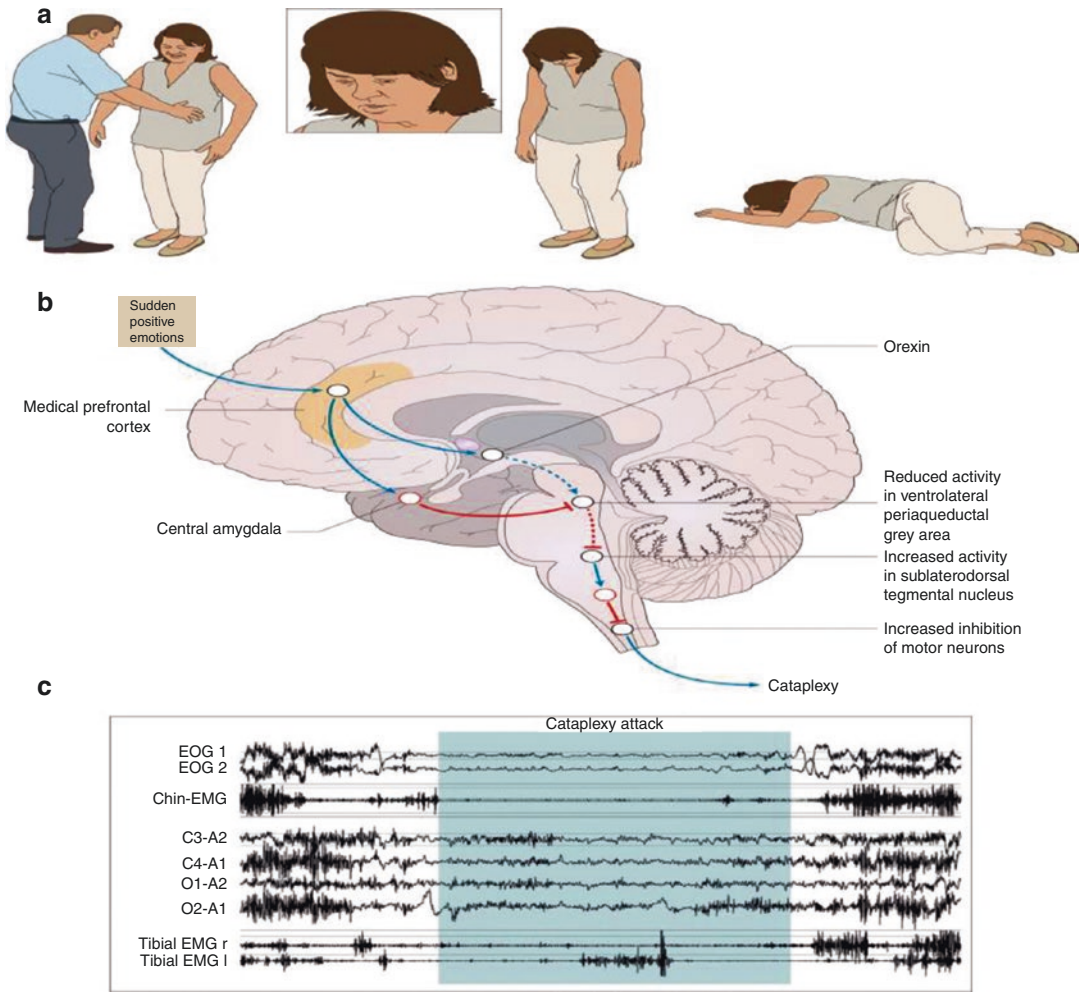

Fig. 20.11 (**a**) A cataplexy attack with rapidly progressive bilateral loss of muscle tone and control of facial, neck, and upper extremity muscles during laughter triggered by tickling. Consciousness is preserved, and muscle twitching or face grimacing can occur. (**b**) Sudden, positive emotions activate neurons in the medial prefrontal cortex that excite orexin neurons in the lateral hypothalamus and the central amygdala. The absence of orexin leads to reduced activity of GABAergic neurons in the periaqueductal gray area that inhibits rapid eye movement (REM) sleep and increases the activity of glutamatergic neurons in the sublaterodorsal tegmental nucleus involved in REM atonia. The imbalance in this pathway results in the activation of descending pathways that inhibit spinal motor neurons and eventually lead to cataplexy. Pathways shown in blue are excitatory; those in red are inhibitory. Open circles indicate neuronal cell bodies. Dotted lines indicate reduced activity. (**c**) An electromyography (EMG) recording during a cataplexy episode (shaded area) documents a loss of muscle tone in multiple channels with superimposed bursts of increased muscle phasic activity (which present clinically as motor phenomena such as muscle twitching and face grimacing). EOG electrooculography channel, l left, r right. (Reproduced with permission from [17])

Strong emotions such as laughter, excitement, or surprise usually are the triggers for cataplexy. Cataplexy can be generalized or partial. In partial cataplexy, only a single limb may fall, the head may drop, or dysarthria can occur. Cataplectic attacks can be different in children because the attacks can appear without a specific triggering factor, can arise during movements, or can occur in anticipation of intense emotions. Children can also have cataplectic facial expressions.

Cataplectic facial expressions are odd facial movements such as raising the eyebrows, opening or closing the mouth, grimacing, lip biting, or tongue protrusion [193].

Nonspecific Symptoms of Type I Narcolepsy

Narcolepsy is frequently associated with sleep paralysis, hallucinations, and disturbed nighttime sleep. These symptoms are not specific for narcolepsy as they may be normal in other contexts or be related to other conditions.

Sleep Paralysis

Sleep paralysis is the inability of a person to speak or move for a few seconds to minutes as he or she falls asleep or wakes up. Sleep paralysis can also involve the feeling of being unable to breathe.

Hallucinations

A hallucination is a sensation or sensory perception experienced without an external stimulus. Hallucinations happen in many conditions. Hypnagogic hallucinations occur while falling asleep, and hypnopompic hallucinations happen while waking up. People with narcolepsy frequently will have hypnagogic and hypnopompic hallucinations. Hallucinations associated with narcolepsy are very vivid and can be very frightening. They tend to produce a feeling of fear or dread and often occur together with sleep paralysis, making them even more disconcerting [44, 146].

Disrupted Nighttime Sleep

Disrupted nighttime sleep is when people wake up frequently during the night. People with narcolepsy often have disrupted nighttime sleep. They wake up frequently and have less total sleep time. Multiple nocturnal arousals and frequent transitions to stage 1 sleep result in fragmented nighttime sleep [44, 205]. The sleep fragmentation can lead to sleep-maintenance insomnia where the patients cannot stay asleep [44].

Hypocretin Orexin System and Type I Narcolepsy

In 1998, Sakurai et al. [212] discovered the orexin peptides. Almost at the same time, de Lecea et al. [47] identified the gene that encodes for the peptides. Thus, the confusing but current nomenclature; Orexin A and B refer to the peptides, and hypocretin (HCRT) refers to the gene and its transcripts [72]. The selective loss of the small population of neurons in the lateral hypothalamus that synthesizes orexin neuropeptides causes type I narcolepsy. Thus, the orexin levels in the cerebrospinal fluid will be very low or undetectable [173]. Orexin A and orexin B are neurotransmitters, ordinarily active during wakefulness. HCRT neurons project to the locus coeruleus (LC), thalamic paraventricular nuclei, periaqueductal gray, septum, bed nucleus of the stria terminalis, raphe peribrachial pontine region, medullary reticular formation, and nucleus of the solitary tract (Fig. 20.1) [17, 113]. These neurons in the cerebral cortex, basal forebrain, brainstem, and hypothalamus produce norepinephrine, dopamine, serotonin, and histamine to maintain alertness throughout the day [17]. Hypocretin neurons also increase activity in the lateral pontine tegmentum suppressing REM sleep. Hypocretin neurons also project to brain regions that regulate metabolism, motivate behaviors (reward-seeking), and regulate the autonomic system [113].

During REM sleep, the cortex is functioning in a similar state to wakefulness. To prevent movements that would cause the person or animal to act out their dreams, atonia neurons in the medial medulla inhibit the spinal cord motor neurons. The REM-on region located in sublaterodorsal nucleus and precoeruleus activates these atonia neurons which are in turn inhibited by neurons in the ventrolateral periaqueductal gray and lateral pontine tegmentum (REM-off region) [17, 152]. Positive emotions activate the medial prefrontal cortex. The medial prefrontal cortex activates the orexin neurons in the hypothalamus and also stimulates the amygdala. The

orexin neurons stimulate the ventrolateral periaqueductal gray neurons (REM-off neurons), and this prevents the activation of atonia neurons. The amygdala inhibits the REM-off neurons, but the orexin neurons antagonize this action, thus preventing the activation of the atonia neurons. People with cataplexy lose the orexin neurons, and this results in the amygdala being able to inhibit the REM-off region, which results in activation of the atonia neurons and the collapse of the person [17, 32, 113].

Diagnosis of Type I Narcolepsy

Multiple sleep latency test (MSLT) is a daytime nap study performed after an overnight polysomnogram. The test measures the time it takes a person to fall asleep during quiet daytime [1].

Most patients with narcolepsy fall asleep at an average of fewer than 8 minutes and often in less than 5 minutes. Patients also enter the stage of rapid eye movement (REM) sleep much faster than normal sleepers [44]. The ICSD-3 [107] defines type I narcolepsy as the presence of excessive daytime sleepiness for more than 3 months, associated with either (a) low hypocretin-1 level or (b) narcolepsy, a mean sleep latency of 8 minutes or fewer on the MSLT, and at least two sleep-onset REM periods during the MSLT. The patient should have a hypocretin-1 level of 110 pg/ml or less in the CSF, which is a highly specific biological measure. Sleep deprivation, obstructive sleep apnea syndrome, circadian rhythm disorders, or the effect of a medication or substance or any other condition explaining the excessive sleepiness cannot be present [107].

Type I Narcolepsy Autoimmunity

Type I narcolepsy is probably an autoimmune disorder, but it has been challenging to prove this with complete certainty because no one has found the smoking gun showing inflammatory cells or antibodies in the hypothalamus. However, multiple substantial clues point to the immune system as the cause of type I narcolepsy.

HLA Haplotype

More than 98% of patients carry the HLA class II HLA-DQB1*0602 allele, compared to only 12% to 30% of the general population [170, 202] making narcolepsy the disorder with the most unambiguous association with an HLA genotype [216]. Other HLA-DQ alleles, HLA-DP, and HLA class I also contribute to genetic susceptibility, as well as genes that affect immune function, such as TCRA, TCRB, P2RY11, EIF3G, ZNF365, IL10RB-IFNAR1, CTSH, and TNFSF4 [59, 85, 183, 216].

H1N1 Vaccination and Childhood Narcolepsy

Childhood narcolepsy had an exceptional increase in incidence in 2010. In 2009, a case of a 7-year-old child developed narcolepsy. He had recently received Pandemrix influenza vaccine. In Finland, 14 instances of additional childhood narcolepsy occurred in 2010. Sweden experienced a similar abrupt increase in cases of narcolepsy in children vaccinated with the H1N1 vaccine in 2010. A study using Finland's hospital discharge registry discovered a 17-fold increase in the number of new cases of narcolepsy in children in 2010 compared to previous years. In this study, 50/54 children who developed narcolepsy in 2010 had received the Pandemrix vaccine. Partinen et al. studied the children in detail, confirming that all 54 children had abnormal multiple sleep latency tests. All of the 34 children who were able to be genotyped had the DQB1*0602/DRB1*15/DR15 – DQ6 genotype [187].

The incidence of narcolepsy in children during 2010 also increased in France [42] and Sweden [175]. This increase in narcolepsy was specific to the H1N1-AS03-P vaccine and did not occur with the other seasonal and pandemic influenza vaccines available that year [16]. In China, there was also a threefold increase in cases following the 2009 H1N1 epidemic, although this was independent of vaccination [86]. These epidemiologic studies all had possible biases [256], but the evidence overall is convincing.

Pathogenic Antibodies

Pathogenic antibodies against orexin neurons may be present in people with narcolepsy, but the evidence is not completely clear. Cvetkovic-

Lopes et al. identified Tribbles homolog 2 (TRIB2) as a potential autoimmune target expressed by hypocretin neurons. TRIB2 is also an autoantigen for autoimmune uveitis. Patients with cataplexy had higher TRIB2-specific antibody titers than healthy controls. Controls with idiopathic hypersomnia, multiple sclerosis, or other inflammatory neurological disorders did not have high titers of TRIB2 antibodies. Patients with a recent onset of narcolepsy had the most elevated anti-TRIB2 titers. The titers decreased in patients who were 2–3 years into the diagnosis but remained higher than controls. Patients still had elevated titers 30 years after their diagnosis [39]. Hiromi et al. also found a higher prevalence of anti-TRIB2 antibodies in their Japanese patients with narcolepsy-cataplexy [248]. Kawashima et al. found anti-TRIB2 antibodies in 25% of patients with cataplexy who had a short duration of disease (<2.3 years) [124]. In 47 cases of narcolepsy ascertained in Sweden during the H1N1 pandemic, there was no difference in antibody titers between patients and controls. However, among the patients younger than 13 years of age, there was a robust correlation between H1N1 antibody titers and TRIB2 [147].

Antibodies against the influenza nucleoprotein receptor cross-react with human hypocretin receptor 2 [5]. Previous work by Tanaka et al. found no difference in autoantibodies against hypocretin or its receptors [239]. Luo et al. also found no anti-hypocretin receptor antibodies in patients with narcolepsy after Pandemrix vaccination [155]. The antibodies may be present in immune complexes as opposed to free circulation, accounting for some of the negative results [49]. Furthermore, some of the antibody responses may not be targeting the relevant antigens in their native conformation. A study in 31 patients post-Pandemrix® found no difference in antibody titers against 9 candidate autoantigens when using conformation-dependent epitopes. The antigens included proteins of the hypocretin transmitter system, preprohypocretin, hypocretin peptides 1 and 2, and hypocretin receptor 2, and proteins previously associated with type I narcolepsy including TRIB2, pro-opiomelanocortin/alpha-melanocyte-stimulating-hormone, and prostaglandin D2 receptor DP1 [266].

T Cells

In mice lacking B and T cells, hypocretin neurons are particularly susceptible to influenza A (H1N1) viral infection. After such H1N1 viral infections, autoreactive cytotoxic C8 + T cells destroyed hypocretin neurons in transgenic mice expressing influenza virus protein hemagglutinin in the hypocretin cells [32, 243].

Latorre et al. and Luo et al. recently found T cells that target HCRT or TRIB2 antigens [140, 154]. The autoreactive T cells in the study by Liu et al. showed cross-reactivity with flu antigens. However, Latorre et al. found no molecular mimicry. Pedersen et al. studied CD8 T cells that recognize hypocretin. They found that these cells were present in patients with narcolepsy and at higher numbers than healthy controls who do not have the HLA-DQB1*06:02 allele. However, healthy controls with the HLA-DQB1*06:02 allele had similar amounts of CD8 autoreactive T cells [189]. Cogswell et al. found that children with type I narcolepsy had higher numbers of CD4 and CD8 autoreactive T-cell responses against orexins, while healthy control children did not. These responses were even higher when they primed the lymphocytes with flu peptides. However, adults with and without narcolepsy had a similar number of autoreactive cells [36]. Thus the abnormal immune response may be very short-lived and only detectable close to the onset of narcolepsy.

Immunotherapy

Except for some interesting anecdotal reports, the evidence for immunotherapy for type I narcolepsy is far from conclusive [15]. Steroids did not improve symptoms in an 8-year-old child treated 2 months after the onset of type I narcolepsy [92].

IVIG has not consistently helped. Extremely early treatment may be necessary. Only one patient so far normalized his hypocretin-1 levels after treatment with IVIG started 2 weeks after the onset of symptoms, cataplexy resolved, and sleepiness moderately improved [41]. Several

additional case reports with IVIG had mixed results with cataplexy appearing to be more amenable to treatment than the excessive daytime sleepiness [15]. The study with the highest number of patients currently reported is a nonrandomized open-label study comparing 22 patients treated with IVIG and 30 control untreated patients. There was no overall reduction in symptoms in the IVIG group [141].

Plasmapheresis improved symptoms in a 60-year-old patient treated 2 months after symptom onset. She improved for a few days after each of the two 5-day courses of plasmapheresis and failed azathioprine and IVIG [35]. Rituximab did not halt the decrease in orexin A levels in a patient 5 months after the onset of cataplexy [267] and improved symptoms markedly but only for 2 months [215]. A patient who had type I narcolepsy for 62 years required treatment with alemtuzumab for low-grade T-cell lymphoma. After treatment with alemtuzumab, his cataplexy resolved, but the rest of his narcolepsy symptoms persisted. The response was long-lived as the patient had no cataplexy until his death 1.8 years later [51].

Symptomatic Treatment

Narcolepsy

Type I narcolepsy requires lifelong treatment, as the destruction of hypocretin neurons is irreversible. Treatment is symptomatic and focuses on improving sleepiness and cataplexy. First-line therapies for excessive daytime sleepiness are modafinil, armodafinil, and sodium oxybate. Second-line options are methylphenidate and pitolisant and third-line amphetamines [15]. Solriamfetol is a recently approved option [245].

Cataplexy

Mild cataplexy often improves with increased alertness following the initiation of wake-promoting therapies. Based on expert consensus, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are off-label options for cataplexy. Venlafaxine is considered first line for patients with concurrent depression [15]. Sodium oxybate is the only medication approved for EDS and cataplexy in adults. For patients with disturbed nighttime sleep and concurrent cataplexy, this is the first-line therapy of choice. Clomipramine is an off-label second-line option, as well as the combination of venlafaxine and sodium oxybate [15].

Conclusions

Type I narcolepsy remains a frustrating disorder. There is convergent evidence of an autoimmune etiology. Genetics points to the immune system. Autoantibodies show mixed inconsistent results. The 2010 spike in cases after the H1N1 vaccination supports the idea of molecular mimicry between the virus and the hypocretin neurons. Autoreactive T cells that circulate in small numbers are present in people with type I narcolepsy, and they are present in higher quantities in children soon after diagnosis. The damage to the hypocretin neurons appears to be very fast. Immunotherapy with IVIG was successful when used in one patient within a few weeks of diagnosis but does not show robust results in patients who are months to years into their disease. Cataplexy seems to be more responsive than excessive daytime sleepiness. The report of a long-lasting response after treatment with alemtuzumab suggests that resetting that occurs after the massive depletion of all types of lymphocytes may be a strategy to consider. However, the safety of such an approach is a significant concern.

References and Bibliography

1. (2019) https://aasm.org/resources/factsheets/narcolepsy.pdf.
2. Tamiya A, Saeki N, Mizota A. Lymphocytic infundibulo-neurohypophysitis associated with recurrent optic neuritis. Br J Neurosurg. 2001;15(2):180–3. https://doi.org/10.1080/02688690151127581.
3. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. Clin Exp Allergy. 2009;39(4):469–77. https://doi.org/10.1111/j.1365-2222.2009.03207.x.
4. Ahmed SR, Aiello DP, Page R, Hopper K, Towfighi J, Santen RJ. Necrotizing infundibulohypophysitis: a unique syndrome of diabetes insipidus and hypopituitarism. J Clin Endocrinol Metabol. 1993;76(6):1499–504.

5. Ahmed SS, Volkmuth W, Duca J, Corti L, Pallaoro M, Pezzicoli A, Karle A, Rigat F, Rappuoli R, Narasimhan V, Julkunen I, Vuorela A, Vaarala O, Nohynek H, Pasini FL, Montomoli E, Trombetta C, Adams CM, Rothbard J, Steinman L. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med. 2015;7(294):294ra105. https://doi.org/10.1126/scitranslmed.aab2354.
6. Al-Mujaini A, Ganesh A, Al-Zuhaibi S, Al-Dhuhli H, Al-Mashani A, Al-Kindi H, Al-Memari A, Al-Futaisi A, Al-Asmi A. Lymphocytic infundibulo-neurohypophysitis: An unusual cause of recurrent optic neuropathy in a child. J AAPOS. 2009;13(2):207–9.
7. Allen RK, Sellars RE, Sandstrom PA. A prospective study of 32 patients with neurosarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20(2):118–25.
8. Andrade DM, Tai P, Dalmau J, Wennberg R. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? Neurology. 2011;76(15):1355–7. https://doi.org/10.1212/WNL.0b013e3182152808.
9. Baba T, Nakashima I, Kanbayashi T, Konno M, Takahashi T, Fujihara K, Misu T, Takeda A, Shiga Y, Ogawa H, Itoyama Y. Narcolepsy as an initial manifestation of neuromyelitis optica with anti-aquaporin-4 antibody. J Neurol. 2009;256(2):287–8. https://doi.org/10.1007/s00415-009-0139-4.
10. Baba T, Shinoda K, Watanabe M, Sadashima S, Matsuse D, Isobe N, Yamasaki R, Kaneko K, Takahashi T, Iwaki T, Kira J-i. MOG antibody disease manifesting as progressive cognitive deterioration and behavioral changes with primary central nervous system vasculitis. Mult Scler Relat Disord. 2019;30:48–50. https://doi.org/10.1016/j.msard.2019.01.053.
11. Baby N, Varghese P, George SK, Aneesh MK. A rare presentation of myelin oligodendrocyte glycoprotein IgG-associated optic neuritis. Pediatr Neurol. 2019;92:78–9. https://doi.org/10.1016/j.pediatrneurol.2018.11.004.
12. Bahtz R, Teegen B, Borowski K, Probst C, Blöcker I-M, Fechner K, Parigger S, Daniel G, Brücke T, Lauenstein A, Schrank B, Stöcker W, Komorowski L. Autoantibodies against IgLON5: two new cases. J Neuroimmunol. 2014;275(1):8. https://doi.org/10.1016/j.jneuroim.2014.08.027.
13. Balas A, Garcia-Sanchez F, Vicario JL. Allelic and haplotypic HLA frequency distribution in Spanish hematopoietic patients. Implications for unrelated donor searching. Tissue Antigens. 2011;77(1):45–53. https://doi.org/10.1111/j.1399-0039.2010.01578.x.
14. Bando H, Iguchi G, Fukuoka H, Taniguchi M, Yamamoto M, Matsumoto R, Suda K, Nishizawa H, Takahashi M, Kohmura E, Takahashi Y. The prevalence of IgG4-related hypophysitis in 170 consecutive patients with hypopituitarism and/or central diabetes insipidus and review of the literature. Eur J Endocrinol. 2014;170(2):161–72. https://doi.org/10.1530/EJE-13-0642.
15. Barateau L, Dauvilliers Y. Recent advances in treatment for narcolepsy. Ther Adv Neurol Disord. 2019;12:1756286419875622. https://doi.org/10.1177/1756286419875622.
16. Barker CI, Snape MD. Pandemic influenza a H1N1 vaccines and narcolepsy: vaccine safety surveillance in action. Lancet Infect Dis. 2014;14(3):227–38. https://doi.org/10.1016/S1473-3099(13)70238-X.
17. Bassetti CLA, Adamantidis A, Burdakov D, Han F, Gay S, Kallweit U, Khatami R, Koning F, Kornum BR, Lammers GJ, Liblau RS, Luppi PH, Mayer G, Pollmächer T, Sakurai T, Sallusto F, Scammell TE, Tafti M, Dauvilliers Y. Narcolepsy — clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat Rev Neurol. 2019;15(9):519–39. https://doi.org/10.1038/s41582-019-0226-9.
18. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, McLennan G, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki B, Weinberger SE, Terrin ML, Knatterud GL, Cherniak R, Case Control Etiologic Study of Sarcoidosis Research G. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10 pt 1):1885–9. https://doi.org/10.1164/ajrccm.164.10.2104046.
19. Benfenati V, Caprini M, Dovizio M, Mylonakou MN, Ferroni S, Ottersen OP, Amiry-Moghaddam M. An aquaporin-4/transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes. Proc Natl Acad Sci. 2011;108(6):2563–8.
20. Bihan H, Christozova V, Dumas JL, Jomaa R, Valeyre D, Tazi A, Reach G, Krivitzky A, Cohen R. Sarcoidosis: clinical, hormonal, and magnetic resonance imaging (MRI) manifestations of hypothalamic-pituitary disease in 9 patients and review of the literature. Medicine (Baltimore). 2007;86(5):259–68. https://doi.org/10.1097/MD.0b013e31815585aa.
21. Bonello M, Jacob A, Ellul MA, Barker E, Parker R, Jefferson S, Alusi S. IgLON5 disease responsive to immunotherapy. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e383.
22. Bonnan M, Valentino R, Debeugny S, Merle H, Ferge JL, Mehdaoui H, Cabre P. Short delay to initiate plasma exchange is the strongest predictor of outcome in severe attacks of NMO spectrum disorders. J Neurol Neurosurg Psychiatry. 2018;89(4):346–51. https://doi.org/10.1136/jnnp-2017-316286.
23. Brunetti V, Della Marca G, Spagni G, Iorio R. Immunotherapy improves sleep and cognitive impairment in anti-IgLON5 encephalopathy. Neurol Neuroimmunol Neuroinflamm. 2019;6(4):e577.
24. Bullmann C, Faust M, Hoffmann A, Heppner C, Jockenhovel F, Muller-Wieland D, Krone W. Five cases with central diabetes insipidus and hypogonadism as first presentation of neurosarcoidosis.

Eur J Endocrinol. 2000;142(4):365–72. https://doi.org/10.1530/eje.0.1420365.
25. Caffrey TM, Wade-Martins R. Functional MAPT haplotypes: bridging the gap between genotype and neuropathology. Neurobiol Dis. 2007;27(1):1–10. https://doi.org/10.1016/j.nbd.2007.04.006.
26. Carlander B, Vincent T, Le Floch A, Pageot N, Camu W, Dauvilliers Y. Hypocretinergic dysfunction in neuromyelitis optica with coma-like episodes. J Neurol Neurosurg Psychiatry. 2008;79(3):333–4. https://doi.org/10.1136/jnnp.2007.135228.
27. Caturegli P, Iwama S. From Japan with love: another Tessera in the hypophysitis mosaic. J Clin Endocrinol Metabol. 2013;98(5):1865–8. https://doi.org/10.1210/jc.2013-1912.
28. Caturegli P, Lupi I, Gutenberg A. Chapter 45 – Autoimmune hypophysitis. In: Rose NR, Mackay IR, editors. The autoimmune diseases. 5th ed. Boston: Academic Press; 2014. p. 633–46.
29. Caturegli P, Lupi I, Landek-Salgado M, Kimura H, Rose NR. Pituitary autoimmunity: 30 years later. Autoimmun Rev. 2008;7(8):631–7. https://doi.org/10.1016/j.autrev.2008.04.016.
30. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. Endocr Rev. 2005;26(5):599–614. https://doi.org/10.1210/er.2004-0011.
31. Chan KH, Tse CT, Chung CP, Lee RL, Kwan JS, Ho PW, Ho JW. Brain involvement in neuromyelitis optica spectrum disorders. Arch Neurol. 2011;68(11):1432–9. https://doi.org/10.1001/archneurol.2011.249.
32. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell. 1999;98(4):437–51.
33. Chen R, McLeod J. Neurological complications of sarcoidosis. Clin Exp Neurol. 1989;26:99–112.
34. Chen RC, McLeod JG. Neurological complications of sarcoidosis. Med J Aust. 1992;156(11):815.
35. Chen W, Black J, Call P, Mignot E. Late-onset narcolepsy presenting as rapidly progressing muscle weakness: response to plasmapheresis. Ann Neurol. 2005;58(3):489–90. https://doi.org/10.1002/ana.20603.
36. Cogswell AC, Maski K, Scammell TE, Tucker D, Orban ZS, Koralnik IJ. Children with narcolepsy type 1 have increased T-cell responses to orexins. Ann Clin Transl Neurol. 2019;6:2566.
37. Constantinescu CS, Niepel G, Patterson M, Judd A, Braitch M, Fahey AJ, Harikrishnan S, Edwards LJ, Tench CR, Bennett GW. Orexin A (hypocretin-1) levels are not reduced while cocaine/amphetamine regulated transcript levels are increased in the cerebrospinal fluid of patients with multiple sclerosis: no correlation with fatigue and sleepiness. J Neurol Sci. 2011;307(1-2):127–31.
38. Côté M, Salzman KL, Sorour M, Couldwell WT. Normal dimensions of the posterior pituitary bright spot on magnetic resonance imaging. J Neurosurg. 2014;120(2):357–62.
39. Cvetkovic-Lopes V, Bayer L, Dorsaz S, Maret S, Pradervand S, Dauvilliers Y, Lecendreux M, Lammers G-J, Donjacour CEHM, Du Pasquier RA, Pfister C, Petit B, Hor H, Mühlethaler M, Tafti M. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. J Clin Invest. 2010;120(3):713–9. https://doi.org/10.1172/JCI41366.
40. Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, Saiz A, Meneses P, Rosenfeld MR. Clinical analysis of anti-Ma2-associated encephalitis. Brain J Neurol. 2004;127(Pt 8):1831–44. https://doi.org/10.1093/brain/awh203.
41. Dauvilliers Y, Abril B, Mas E, Michel F, Tafti M. Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. Neurology. 2009;73(16):1333–4. https://doi.org/10.1212/WNL.0b013e3181bd1344.
42. Dauvilliers Y, Arnulf I, Lecendreux M, Monaca Charley C, Franco P, Drouot X, d'Ortho M-P, Launois S, Lignot S, Bourgin P. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain J Neurol. 2013;136(8):2486–96.
43. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet. 2007;369(9560):499–511.
44. Dauvilliers Y, Barateau L. Narcolepsy and other central hypersomnias. Continuum (Minneap Minn). 2017;23(4):989–1004.
45. Dauvilliers Y, Bauer J, Rigau V, Lalloyer N, Labauge P, Carlander B, Liblau R, Peyron C, Lassmann H. Hypothalamic immunopathology in anti-Ma–associated diencephalitis with narcolepsy-cataplexy. JAMA Neurol. 2013;70(10):1305–10. https://doi.org/10.1001/jamaneurol.2013.2831.
46. De Bellis A, Sinisi AA, Pane E, Dello Iacovo A, Bellastella G, Di Scala G, Falorni A, Giavoli C, Gasco V, Giordano R, Ambrosio MR, Colao A, Bizzarro A, Bellastella A, Italian Autoimmune Hypophysitis Network G. Involvement of hypothalamus autoimmunity in patients with autoimmune hypopituitarism: role of antibodies to hypothalamic cells. J Clin Endocrinol Metab. 2012;97(10):3684–90. https://doi.org/10.1210/jc.2012-2269.
47. De Lecea L, Kilduff T, Peyron C, Gao X-B, Foye P, Danielson P, Fukuhara C, Battenberg E, Gautvik V, Bartlett FN. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci. 1998;95(1):322–7.
48. Deguchi K, Kono S, Deguchi S, Morimoto N, Ikeda M, Kurata T, Ikeda Y, Matsuura T, Kanbayashi T, Takahashi T, Abe K. A patient with anti-aquaporin 4 antibody presenting hypersomnolence as the initial symptom and symmetrical hypothalamic lesions. J Neurol Sci. 2012;312(1–2):18–20. https://doi.org/10.1016/j.jns.2011.08.031.
49. Deloumeau A, Bayard S, Coquerel Q, Dechelotte P, Bole-Feysot C, Carlander B, Cochen De Cock

V, Fetissov SO, Dauvilliers Y. Increased immune complexes of hypocretin autoantibodies in narcolepsy. PLoS One. 2010;5(10):e13320. https://doi.org/10.1371/journal.pone.0013320.
50. Deodhare SS, Bilbao JM, Kovacs K, Horvath E, Nomikos P, Buchfelder M, Reschke K, Lehnert H. Xanthomatous Hypophysitis: a novel entity of obscure etiology. Endocr Pathol. 1999;10(3):237–41.
51. Donjacour C, Lammers GJ. A remarkable effect of alemtuzumab in a patient suffering from narcolepsy with cataplexy. J Sleep Res. 2012;21(4):479–80.
52. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. Chest. 2005;127(3):1064–71. https://doi.org/10.1378/chest.127.3.1064.
53. Downer JJ, Leite MI, Carter R, Palace J, Küker W, Quaghebeur G. Diagnosis of neuromyelitis optica (NMO) spectrum disorders: is MRI obsolete? Neuroradiology. 2012;54(4):279–85. https://doi.org/10.1007/s00234-011-0875-x.
54. Dutschmann M, Menuet C, Stettner GM, Gestreau C, Borghgraef P, Devijver H, Gielis L, Hilaire G, Van Leuven F. Upper airway dysfunction of Tau-P301L mice correlates with tauopathy in midbrain and ponto-medullary brainstem nuclei. J Neurosci. 2010;30(5):1810–21. https://doi.org/10.1523/JNEUROSCI.5261-09.2010.
55. Edwards S, Lennox G, Robson K, Whiteley A. Hypothermia due to hypothalamic involvement in multiple sclerosis. J Neurol Neurosurg Psychiatry. 1996;61(4):419.
56. Erkut ZA, Hofman MA, Ravid R, Swaab DF. Increased activity of hypothalamic corticotropin-releasing hormone neurons in multiple sclerosis. J Neuroimmunol. 1995;62(1):27–33. https://doi.org/10.1016/0165-5728(95)00098-m.
57. Fahoum F, Drory VE, Issakov J, Neufeld MY. Neurosarcoidosis presenting as Guillain-Barre-like syndrome. A case report and review of the literature. J Clin Neuromuscul Dis. 2009;11(1):35–43. https://doi.org/10.1097/CND.0b013e3181ae3be9.
58. Fan S, Xu Y, Ren H, Guan H, Feng F, Gao X, Ding D, Fang F, Shan G, Guan T, Zhang Y, Dai Y, Yao M, Peng B, Zhu Y, Cui L. Comparison of myelin oligodendrocyte glycoprotein (MOG)-antibody disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) when they co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis. Mult Scler Relat Disord. 2018;20:144–52. https://doi.org/10.1016/j.msard.2018.01.007.
59. Faraco J, Lin L, Kornum BR, Kenny EE, Trynka G, Einen M, Rico TJ, Lichtner P, Dauvilliers Y, Arnulf I. ImmunoChip study implicates antigen presentation to T cells in narcolepsy. PLoS Genet. 2013;9(2):e1003270.
60. Fardet L, Genereau T, Mikaeloff Y, Fontaine B, Seilhean D, Cabane J. Devic's neuromyelitis optica: study of nine cases. Acta Neurol Scand. 2003;108(3):193–200. https://doi.org/10.1034/j.1600-0404.2003.02178.x.
61. Fassbender K, Schmidt R, Mößner R, Kischka U, Kühnen J, Schwartz A, Hennerici M. Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: association with cerebral inflammation. Arch Neurol. 1998;55(1):66–72.
62. Ferriby D, de Seze J, Stojkovic T, Hachulla E, Wallaert B, Destee A, Hatron PY, Vermersch P. Long-term follow-up of neurosarcoidosis. Neurology. 2001;57(5):927–9. https://doi.org/10.1212/wnl.57.5.927.
63. Fery F, Plat L, van de Borne P, Cogan E, Mockel J. Impaired counterregulation of glucose in a patient with hypothalamic sarcoidosis. N Engl J Med. 1999;340(11):852–6. https://doi.org/10.1056/NEJM199903183401105.
64. Folkerth RD, Price DL Jr, Schwartz M, Black PM, De Girolami U. Xanthomatous Hypophysitis. Am J Surg Pathol. 1998;22(6):736.
65. Fritz D, Voortman M, van de Beek D, Drent M, Brouwer MC. Many faces of neurosarcoidosis: from chronic meningitis to myelopathy. Curr Opin Pulm Med. 2017;23(5):439–46. https://doi.org/10.1097/MCP.0000000000000401.
66. Gaig C, Ercilla G, Daura X, Ezquerra M, Fernández-Santiago R, Palou E, Sabater L, Höftberger R, Heidbreder A, Högl B, Iranzo A, Santamaria J, Dalmau J, Graus F. HLA and microtubule-associated protein tau H1 haplotype associations in anti-IgLON5 disease. Neurol Neuroimmunol Neuroinflamm. 2019;6(6):e605. https://doi.org/10.1212/nxi.0000000000000605.
67. Gaig C, Graus F, Compta Y, Hogl B, Bataller L, Bruggemann N, Giordana C, Heidbreder A, Kotschet K, Lewerenz J, Macher S, Marti MJ, Montojo T, Perez-Perez J, Puertas I, Seitz C, Simabukuro M, Tellez N, Wandinger KP, Iranzo A, Ercilla G, Sabater L, Santamaria J, Dalmau J. Clinical manifestations of the anti-IgLON5 disease. Neurology. 2017;88(18):1736–43. https://doi.org/10.1212/WNL.0000000000003887.
68. Gaig C, Iranzo A, Cajochen C, Vilaseca I, Embid C, Dalmau J, Graus F, Santamaria J. Characterization of the sleep disorder of anti-IgLON5 disease. Sleep. 2019;42.:zsz133 https://doi.org/10.1093/sleep/zsz133.
69. Gelpi E, Hoftberger R, Graus F, Ling H, Holton JL, Dawson T, Popovic M, Pretnar-Oblak J, Hogl B, Schmutzhard E, Poewe W, Ricken G, Santamaria J, Dalmau J, Budka H, Revesz T, Kovacs GG. Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol. 2016;132(4):531–43. https://doi.org/10.1007/s00401-016-1591-8.
70. Ghetti B, Oblak AL, Boeve BF, Johnson KA, Dickerson BC, Goedert M. Invited review: Frontotemporal dementia caused by microtubule-associated protein tau gene (MAPT) mutations: a chameleon for neuropathology and neuroimaging.

Neuropathol Appl Neurobiol. 2015;41(1):24–46. https://doi.org/10.1111/nan.12213.
71. Gleckman AM, Patalas ED, Joseph JT. Sudden unexpected death resulting from hypothalamic sarcoidosis. Am J Forensic Med Pathol. 2002;23(1):48–51.
72. Gotter AL, Webber AL, Coleman PJ, Renger JJ, Winrow CJ. International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. Pharmacol Rev. 2012;64(3):389–420. https://doi.org/10.1124/pr.111.005546.
73. Gottschalk M, Kumpfel T, Flachenecker P, Uhr M, Trenkwalder C, Holsboer F, Weber F. Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. Arch Neurol. 2005;62(2):277–80. https://doi.org/10.1001/archneur.62.2.277.
74. Grasser A, Möller A, Backmund H, Yassouridis A, Holsboer F. Heterogeneity of hypothalamic-pituitary-adrenal system response to a combined dexamethasone-CRH test in multiple sclerosis. Exp Clin Endocrinol Diabetes. 1996;104(01):31–7.
75. Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, Honnorat J, Smitt PS, Vedeler C, Verschuuren JJ, Vincent A, Voltz R. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75(8):1135–40. https://doi.org/10.1136/jnnp.2003.034447.
76. Gullapalli D, Phillips LH 2nd. Neurologic manifestations of sarcoidosis. Neurol Clin. 2002;20(1):59–83, vi. https://doi.org/10.1016/s0733-8619(03)00054-9.
77. Gullapalli D, Phillips LH 2nd. Neurosarcoidosis. Curr Neurol Neurosci Rep. 2004;4(6):441–7. https://doi.org/10.1007/s11910-004-0066-9.
78. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain J Neurol. 2000;123(7):1481–94. https://doi.org/10.1093/brain/123.7.1481.
79. Gutenberg A, Hans V, Puchner MJA, Kreutzer J, Brück W, Caturegli P, Buchfelder M. Primary hypophysitis: clinical-pathological correlations. Eur J Endocrinol. 2006;155(1):101–7. https://doi.org/10.1530/eje.1.02183.
80. Gutenberg A, Larsen J, Lupi I, Rohde V, Caturegli P. A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. AJNR Am J Neuroradiol. 2009;30(9):1766–72. https://doi.org/10.3174/ajnr.A1714.
81. Hacohen Y, Messina S, Gan HW, Wright S, Chandratre S, Leite MI, Fallon P, Vincent A, Ciccarelli O, Wassmer E, Lim M, Palace J, Hemingway C. Endocrinopathies in paediatric-onset neuromyelitis optica spectrum disorder with aquaporin 4 (AQP4) antibody. Mult Scler. 2018;24(5):679–84. https://doi.org/10.1177/1352458517726593.
82. Haider L, Simeonidou C, Steinberger G, Hametner S, Grigoriadis N, Deretzi G, Kovacs GG, Kutzelnigg A, Lassmann H, Frischer JM. Multiple sclerosis deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron. J Neurol Neurosurg Psychiatr. 2014;85(12):1386. https://doi.org/10.1136/jnnp-2014-307712.
83. Haitao R, Yingmai Y, Yan H, Fei H, Xia L, Honglin H, Chaiyan L, Stöcker W, Liying C, Hongzhi G. Chorea and parkinsonism associated with autoantibodies to IgLON5 and responsive to immunotherapy. J Neuroimmunol. 2016;300:9–10.
84. Hamid SH, Whittam D, Mutch K, Linaker S, Solomon T, Das K, Bhojak M, Jacob A. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. J Neurol. 2017;264(10):2088–94.
85. Han F, Faraco J, Dong XS, Ollila HM, Lin L, Li J, An P, Wang S, Jiang KW, Gao ZC. Genome wide analysis of narcolepsy in China implicates novel immune loci and reveals changes in association prior to versus after the 2009 H1N1 influenza pandemic. PLoS Genet. 2013;9(10):e1003880.
86. Han F, Lin L, Warby SC, Faraco J, Li J, Dong SX, An P, Zhao L, Wang LH, Li QY. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol. 2011;70(3):410–7.
87. Hanken K, Eling P, Kastrup A, Klein J, Hildebrandt H. Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis. Mult Scler Relat Disord. 2015;4(1):39–46.
88. Hanken K, Manousi A, Klein J, Kastrup A, Eling P, Hildebrandt H. On the relation between self-reported cognitive fatigue and the posterior hypothalamic–brainstem network. Eur J Neurol. 2016;23(1):101–9.
89. Hara M, Ariño H, Petit-Pedrol M, Sabater L, Titulaer MJ, Martinez-Hernandez E, Schreurs MW, Rosenfeld MR, Graus F, Dalmau J. DPPX antibody–associated encephalitis: Main syndrome and antibody effects. Neurology. 2017;88(14):1340–8.
90. Hazin R, Saed D, Salem M, Zeyara M, Subei MO. A rare case of neurosarcoidosis presenting as severe hypothermia. Am J Case Rep. 2017;18:512–5. https://doi.org/10.12659/ajcr.901973.
91. Heaney AP, Sumerel B, Rajalingam R, Bergsneider M, Yong WH, Liau LM. HLA markers DQ8 and DR53 are associated with lymphocytic hypophysitis and may aid in differential diagnosis. J Clin Endocrinol Metab. 2015;100(11):4092–7. https://doi.org/10.1210/jc.2015-2702.
92. Hecht M, Lin L, Kushida CA, Umetsu DT, Taheri S, Einen M, Mignot E. Report of a case of immunosuppression with prednisone in an 8-year-old boy with an acute onset of hypocretin-deficiency narcolepsy. Sleep. 2003;26(7):809–10.
93. Heesen C, Gold SM, Raji A, Wiedemann K, Schulz K-H. Cognitive impairment correlates with hypothalamo–pituitary–adrenal axis dysregulation in multiple sclerosis. Psychoneuroendocrinology. 2002;27(4):505–17.

94. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J Neurol Neurosurg Psychiatry. 2006;77(1):34–9. https://doi.org/10.1136/jnnp.2005.065805.
95. Heidbrink C, Hausler SFM, Buttmann M, Ossadnik M, Strik HM, Keller A, Buck D, Verbraak E, van Meurs M, Krockenberger M, Mehling M, Mittelbronn M, Laman JD, Wiendl H, Wischhusen J. Reduced cortisol levels in cerebrospinal fluid and differential distribution of 11beta-hydroxysteroid dehydrogenases in multiple sclerosis: implications for lesion pathogenesis. Brain Behav Immun. 2010;24(6):975–84. https://doi.org/10.1016/j.bbi.2010.04.003.
96. Henry RG, Shieh M, Okuda DT, Evangelista A, Gorno-Tempini ML, Pelletier D. Regional grey matter atrophy in clinically isolated syndromes at presentation. J Neurol Neurosurg Psychiatry. 2008;79(11):1236–44. https://doi.org/10.1136/jnnp.2007.134825.
97. Hnilicova P, Kantorova E, Polacek H, Grendar M, Bittsansky M, Cierny D, Sivak S, Zelenak K, Lehotsky J, Dobrota D, Kurca E. Altered hypothalamic metabolism in early multiple sclerosis – MR spectroscopy study. J Neurol Sci. 2019;407:116458. https://doi.org/10.1016/j.jns.2019.116458.
98. Hoffmann LA, Jarius S, Pellkofer HL, Schueller M, Krumbholz M, Koenig F, Johannis W, la Fougere C, Newman T, Vincent A, Voltz R. Anti-Ma and anti-Ta associated paraneoplastic neurological syndromes: 22 newly diagnosed patients and review of previous cases. J Neurol Neurosurg Psychiatry. 2008;79(7):767–73. https://doi.org/10.1136/jnnp.2007.118588.
99. Hoitsma E, Marziniak M, Faber CG, Reulen JP, Sommer C, De Baets M, Drent M. Small fibre neuropathy in sarcoidosis. Lancet. 2002;359(9323):2085–6. https://doi.org/10.1016/s0140-6736(02)08912-2.
100. Honegger J, Schlaffer S, Menzel C, Droste M, Werner S, Elbelt U, Strasburger C, Störmann S, Küppers A, Streetz-van der Werf C, Deutschbein T, Stieg M, Rotermund R, Milian M, Petersenn S. Diagnosis of primary hypophysitis in Germany. J Clin Endocrinol Metabol. 2015;100(10):3841–9. https://doi.org/10.1210/jc.2015-2152.
101. Honorat JA, Komorowski L, Josephs KA, Fechner K, St Louis EK, Hinson SR, Lederer S, Kumar N, Gadoth A, Lennon VA, Pittock SJ, McKeon A. IgLON5 antibody. Neurological accompaniments and outcomes in 20 patients. Neurol Neuroimmunol Neuroinflamm. 2017;4(5):e385. https://doi.org/10.1212/nxi.0000000000000385.
102. Huitinga I, De Groot CJA, Van der Valk P, Kamphorst W, Tilders FJH, Swaab DF. Hypothalamic lesions in multiple sclerosis. J Neuropathol Exp Neurol. 2001;60(12):1208–18.
103. Huitinga I, Erkut ZA, van Beurden D, Swaab DF. Impaired hypothalamus-pituitary-adrenal axis activity and more severe multiple sclerosis with hypothalamic lesions. Ann Neurol. 2004;55(1):37–45.
104. Huitinga I, van der Cammen M, Salm L, Erkut Z, van Dam A, Tilders F, Swaab D. IL-1beta immunoreactive neurons in the human hypothalamus: reduced numbers in multiple sclerosis. J Neuroimmunol. 2000;107(1):8–20. https://doi.org/10.1016/s0165-5728(00)00248-4.
105. Iida M, Takamoto S, Masuo M, Makita K, Saito T. Transient lymphocytic panhypophysitis associated with SIADH leading to diabetes insipidus after glucocorticoid replacement. Intern Med. 2003;42(10):991–5.
106. Inoue K, Nakayama T, Kamisawa A, Saito J. Syndrome of inappropriate antidiuretic hormone accompanied by bilateral hypothalamic and anterior thalamic lesions with serum antiaquaporin 4 antibody. BMJ Case Rep. 2017;2017:bcr2017219721. https://doi.org/10.1136/bcr-2017-219721.
107. International classification of sleep disorders. 3rd ed. Darien: American Academy of Sleep Medicine; 2014.
108. Iorio R, Lucchinetti CF, Lennon VA, Costanzi C, Hinson S, Weinshenker BG, Pittock SJ. Syndrome of inappropriate antidiuresis may herald or accompany neuromyelitis optica. Neurology. 2011;77(17):1644–6. https://doi.org/10.1212/WNL.0b013e3182343377.
109. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, Peles E, Buckley C, Lang B, Vincent A. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain J Neurol. 2010;133(9):2734–48. https://doi.org/10.1093/brain/awq213.
110. Irani SR, Schott JM, Vincent A, Smith SJ. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? Neurology. 2011;77(24):2140–1; author reply 2141-2143.
111. Iwama S, Sugimura Y, Kiyota A, Kato T, Enomoto A, Suzuki H, Iwata N, Takeuchi S, Nakashima K, Takagi H, Izumida H, Ochiai H, Fujisawa H, Suga H, Arima H, Shimoyama Y, Takahashi M, Nishioka H, S-e I, Shimatsu A, Caturegli P, Oiso Y. Rabphilin-3A as a targeted autoantigen in lymphocytic infundibulo-neurohypophysitis. J Clin Endocrinol Metabol. 2015;100(7):E946–54. https://doi.org/10.1210/jc.2014-4209.
112. Iwata N, Iwama S, Sugimura Y, Yasuda Y, Nakashima K, Takeuchi S, Hagiwara D, Ito Y, Suga H, Goto M, Banno R, Caturegli P, Koike T, Oshida Y, Arima H. Anti-pituitary antibodies against corticotrophs in IgG4-related hypophysitis. Pituitary. 2017;20(3):301–10. https://doi.org/10.1007/s11102-016-0780-8.
113. Jennings KJ, de Lecea L. Chapter 1 – Hypocretins (Orexins): twenty years of dissecting arousal circuits. In: Burk JA, Fadel JR, editors. The orexin/hypocretin system. Academic Press; Cambridge,

Massachusetts, USA. 2019. p. 1–29. https://doi.org/10.1016/B978-0-12-813751-2.00001-2.
114. Jin S, Long Z, Wang W, Jiang B. Hyponatremia in neuromyelitis optica spectrum disorders: literature review. Acta Neurol Scand. 2018;138(1):4–11. https://doi.org/10.1111/ane.12938.
115. Joseph FG, Scolding NJ. Neurosarcoidosis: a study of 30 new cases. J Neurol Neurosurg Psychiatry. 2009;80(3):297–304. https://doi.org/10.1136/jnnp.2008.151977.
116. Joshi MN, Whitelaw BC, Carroll PV. Mechanisms in endocrinology: hypophysitis: diagnosis and treatment. Eur J Endocrinol. 2018;179(3):R151–63.
117. Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29(2):119–27.
118. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, Shigemitsu H, Culver DA, Gelfand J, Valeyre D, Sweiss N, Crouser E, Morgenthau AS, Lower EE, Azuma A, Ishihara M, Morimoto S, Tetsuo Yamaguchi T, Shijubo N, Grutters JC, Rosenbach M, Li HP, Rottoli P, Inoue Y, Prasse A, Baughman RP, Organ Assessment Instrument Investigators TW. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31(1):19–27.
119. Jung JS, Bhat RV, Preston GM, Guggino WB, Baraban JM, Agre P. Molecular characterization of an aquaporin cDNA from brain: candidate osmoreceptor and regulator of water balance. Proc Natl Acad Sci. 1994;91(26):13052–6.
120. Kanbayashi T, Shimohata T, Nakashima I, Yaguchi H, Yabe I, Nishizawa M, Shimizu T, Nishino S. Symptomatic narcolepsy in patients with neuromyelitis optica and multiple sclerosis: new neurochemical and immunological implications. Arch Neurol. 2009;66(12):1563–6. https://doi.org/10.1001/archneurol.2009.264.
121. Kanou Y, Arita K, Kurisu K, Tominaga A, Akimitsu T. Infundibuloneurohypophysitis presenting a large sellar-juxtasellar mass: case report. Surg Neurol. 2004;61(3):278–81.
122. Kantorová E, Poláček H, Bittšanský M, Baranovičová E, Hnilicová P, Čierny D, Sivák Š, Nosáľ V, Zeleňák K, Kurča E. Hypothalamic damage in multiple sclerosis correlates with disease activity, disability, depression, and fatigue. Neurol Res. 2017;39(4):323–30. https://doi.org/10.1080/01616412.2016.1275460.
123. Kato T, Kanbayashi T, Yamamoto K, Nakano T, SfflMizu T, Hashimoto T, Ikeda S-I. Hypersomnia and low CSF hypocretin-1 (orexin-A) concentration in a patient with multiple sclerosis showing bilateral hypothalamic lesions. Intern Med. 2003;42(8):743–5.
124. Kawashima M, Lin L, Tanaka S, Jennum P, Knudsen S, Nevsimalova S, Plazzi G, Mignot E. Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. Sleep. 2010;33(7):869–74. https://doi.org/10.1093/sleep/33.7.869.
125. Kern S, Krause I, Horntrich A, Thomas K, Aderhold J, Ziemssen T. Cortisol awakening response is linked to disease course and progression in multiple sclerosis. PLoS One. 2013;8(4):e60647. https://doi.org/10.1371/journal.pone.0060647.
126. Kitley J, Woodhall M, Waters P, Leite MI, Devenney E, Craig J, Palace J, Vincent A. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. Neurology. 2012;79(12):1273–7.
127. Kohlitz P, Sathiyamoorthy G. 1190: new onset sarcoidosis presenting as hypothermia. Crit Care Med. 2012;40(12):1–328.
128. Kong X, Wang R, Yang Y, Wu H, Su C, Ma W, Li Y, Xing B, Lian W, Xu Z, Yao Y, Ren Z. Idiopathic granulomatous hypophysitis mimicking pituitary abscess. Medicine. 2015;94(28):e1099. https://doi.org/10.1097/MD.0000000000001099.
129. Konrad D, Gartenmann M, Martin E, Schoenle EJ. Central diabetes insipidus as the first manifestation of neurosarcoidosis in a 10-year-old girl. Horm Res Paediatr. 2000;54(2):98–100.
130. Konuskan B, Yildirim M, Gocmen R, Okur TD, Polat I, Kilic H, Saltik S, Ozturk Z, Gucuyener K, Altunbasak S. Retrospective analysis of children with myelin oligodendrocyte glycoprotein antibody-related disorders. Mult Scler Relat Disord. 2018;26:1–7.
131. Kubick N, Brösamle D, Mickael M-E. Molecular evolution and functional divergence of the IgLON family. Evol Bioinformatics Online. 2018;14:1176934318775081. https://doi.org/10.1177/1176934318775081.
132. Kumpfel T, Schwan M, Weber F, Holsboer F, Trenkwalder C, Then Bergh F. Hypothalamo-pituitary-adrenal axis activity evolves differentially in untreated versus treated multiple sclerosis. Psychoneuroendocrinology. 2014;45:87–95. https://doi.org/10.1016/j.psyneuen.2014.03.012.
133. Kurukumbi M, Mehta P, Misra I, Annapurni J. Neurosarcoidosis. In: Eishi Y, editor. Sarcoidosis. London: IntechOpen Limited; 2012. https://doi.org/10.5772/45958.
134. Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R, Cowell JK, Dalmau J. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9(8):776–85. https://doi.org/10.1016/s1474-4422(10)70137-x.
135. Lammens M, Lissoir F, Carton H. Hypothermia in three patients with multiple sclerosis. Clin Neurol Neurosurg. 1989;91(2):117–21. https://doi.org/10.1016/S0303-8467(89)80031-9.
136. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. J Clin Neurol. 2016;12(1):1–13. https://doi.org/10.3988/jcn.2016.12.1.1.

137. Lancaster E, Dalmau J. Neuronal autoantigens—pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012;8(7):380.
138. Lang J, Biebl A, Gruber A, Maier-Hiebl B, Hainfellner JA, Hoftberger R, Gelpi E. Teaching case 5-2018: integrated morphological and immunological work-up of neurosurgical specimen allows accurate diagnosis of neuroinflammatory lesions: an example of acute disseminated encephalomyelitis (ADEM) associated with anti-MOG antibodies. Clin Neuropathol. 2018;37(5):206–8. https://doi.org/10.5414/np301136.
139. Langrand C, Bihan H, Raverot G, Varron L, Androdias G, Borson-Chazot F, Brue T, Cathebras P, Pinede L, Muller G, Broussolle C, Cotton F, Valeyre D, Seve P. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. QJM. 2012;105(10):981–95. https://doi.org/10.1093/qjmed/hcs121.
140. Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, Jovic S, Jarrossay D, Mathis J, Zellini F, Becher B, Lanzavecchia A, Khatami R, Manconi M, Tafti M, Bassetti CL, Sallusto F. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature. 2018;562(7725):63–8. https://doi.org/10.1038/s41586-018-0540-1.
141. Lecendreux M, Berthier J, Corny J, Bourdon O, Dossier C, Delclaux C. Intravenous immunoglobulin therapy in pediatric narcolepsy: a nonrandomized, open-label, controlled, longitudinal observational study. J Clin Sleep Med. 2017;13(03):441–53.
142. Levy MJ, Jäger HR, Powell M, Matharu MS, Meeran K, Goadsby PJ. Pituitary volume and headache: size is not everything. Arch Neurol. 2004;61(5):721–5. https://doi.org/10.1001/archneur.61.5.721.
143. Li W, Wu S, Meng Q, Zhang X, Guo Y, Cong L, Cong S, Zheng D. Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study. BMC Neurol. 2018;18(1):96.
144. Li X, Yuan J, Liu L, Hu W. Antibody-LGI 1 autoimmune encephalitis manifesting as rapidly progressive dementia and hyponatremia: a case report and literature review. BMC Neurol. 2019;19(1):19.
145. Li Z, Cui T, Shi W, Wang Q. Clinical analysis of leucine-rich glioma inactivated-1 protein antibody associated with limbic encephalitis onset with seizures. Medicine. 2016;95(28).
146. Liddon SC. Sleep paralysis and hypnagogic hallucinations: their relationship to the nightmare. Arch Gen Psychiatry. 1967;17(1):88–96. https://doi.org/10.1001/archpsyc.1967.01730250090013.
147. Lind A, Ramelius A, Olsson T, Arnheim-Dahlström L, Lamb F, Khademi M, Ambati A, Maeurer M, Nilsson A-L, Bomfim IL, Fink K, Lernmark Å. A/H1N1 antibodies and TRIB2 autoantibodies in narcolepsy patients diagnosed in conjunction with the Pandemrix vaccination campaign in Sweden 2009–2010. J Autoimmun. 2014;50:99–106. https://doi.org/10.1016/j.jaut.2014.01.031.
148. Linker RA, Mohr A, Cepek L, Gold R, Prange H. Core hypothermia in multiple sclerosis: case report with magnetic resonance imaging localization of a thalamic lesion. Multiple sclerosis (Houndmills, Basingstoke, England). 2006;12(1):112–5. https://doi.org/10.1191/135248506ms1268cr.
149. Lipnick RN, Hung W, Pandian M. Neurosarcoidosis presenting as secondary amenorrhea in a teenager. J Adolesc Health. 1993;14(6):464–7.
150. Logmin K, Moldovan A, Elben S, Schnitzler A, Groiss S. Intravenous immunoglobulins as first-line therapy for IgLON5 encephalopathy. J Neurol. 2019;266(4):1031–3.
151. Loh K-C, Green A, Dillon W, Fitzgerald PA, Weidner N, Tyrrell JB. Diabetes insipidus from sarcoidosis confined to the posterior pituitary. Eur J Endocrinol. 1997;137(5):514–9.
152. Lu J, Sherman D, Devor M, Saper CB. A putative flip–flop switch for control of REM sleep. Nature. 2006;441(7093):589–94. https://doi.org/10.1038/nature04767.
153. Ludolph AC, Kassubek J, Landwehrmeyer BG, Mandelkow E, Mandelkow EM, Burn DJ, Caparros-Lefebvre D, Frey KA, de Yebenes JG, Gasser T, Heutink P, Hoglinger G, Jamrozik Z, Jellinger KA, Kazantsev A, Kretzschmar H, Lang AE, Litvan I, Lucas JJ, McGeer PL, Melquist S, Oertel W, Otto M, Paviour D, Reum T, Saint-Raymond A, Steele JC, Tolnay M, Tumani H, van Swieten JC, Vanier MT, Vonsattel JP, Wagner S, Wszolek ZK, Reisensburg Working Group for Tauopathies With P. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. Eur J Neurol. 2009;16(3):297–309. https://doi.org/10.1111/j.1468-1331.2008.02513.x.
154. Luo G, Ambati A, Lin L, Bonvalet M, Partinen M, Ji X, Maecker HT, Mignot EJ-M. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. Proc Natl Acad Sci. 2018;115(52):E12323–32. https://doi.org/10.1073/pnas.1818150116.
155. Luo G, Lin L, Jacob L, Bonvalet M, Ambati A, Plazzi G, Pizza F, Leib R, Adams CM, Partinen M, Mignot EJ. Absence of anti-hypocretin receptor 2 autoantibodies in post pandemrix narcolepsy cases. PLoS One. 2017;12(12):e0187305. https://doi.org/10.1371/journal.pone.0187305.
156. Lury KM, Smith JK, Matheus MG, Castillo M. Neurosarcoidosis--review of imaging findings. Semin Roentgenol. 2004;39(4):495–504. https://doi.org/10.1016/j.ro.2004.06.006.
157. Mader S, Gredler V, Schanda K, Rostasy K, Dujmovic I, Pfaller K, Lutterotti A, Jarius S, Di Pauli F, Kuenz B. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. J Neuroinflammation. 2011;8(1):184.
158. Marnane M, Lynch T, Scott J, Stack J, Kelly PJ. Steroid-unresponsive neurosarcoidosis successfully treated with adalimumab. J Neurol.

2009;256(1):139–40. https://doi.org/10.1007/s00415-009-0077-1.
159. Mathe JF, Mussini JM, Nomballais F, Friol M, de Kersaint-Gilly A, Feve JR. Unusual involvement of the CNS in a case of neuro-sarcoidosis (author's transl). Rev Neurol (Paris). 1980;136(1):33–41.
160. Mayo MC, Deng JC, Albores J, Zeidler M, Harper RM, Avidan AY. Hypocretin deficiency associated with narcolepsy type 1 and central hypoventilation syndrome in neurosarcoidosis of the hypothalamus. J Clin Sleep Med. 2015;11(9):1063–5. https://doi.org/10.5664/jcsm.5028.
161. McNamee CJ, Youssef S, Moss D. IgLONs form heterodimeric complexes on forebrain neurons. Cell Biochem Funct. 2011;29(2):114–9. https://doi.org/10.1002/cbf.1730.
162. Menninger MD, Amdur RJ, Marcus RB Jr. Role of radiotherapy in the treatment of neurosarcoidosis. Am J Clin Oncol. 2003;26(4):e115–8. https://doi.org/10.1097/01.COC.0000077933.69101.5D.
163. Michelson D, Stone L, Galliven E, Magiakou MA, Chrousos GP, Sternberg EM, Gold PW. Multiple sclerosis is associated with alterations in hypothalamic-pituitary-adrenal axis function. J Clin Endocrinol Metab. 1994;79(3):848–53. https://doi.org/10.1210/jcem.79.3.8077372.
164. Montagna M, Amir R, De Volder I, Lammens M, Huyskens J, Willekens B. IgLON5-associated encephalitis with atypical brain magnetic resonance imaging and cerebrospinal fluid changes. Front Neurol. 2018;9:329. https://doi.org/10.3389/fneur.2018.00329.
165. Moreno-Estébanez A, Garcia-Ormaechea M, Tijero B, Fernández-Valle T, Gómez-Esteban JC, Berganzo K. Anti-IgLON5 disease responsive to immunotherapy: a case report with an abnormal MRI. Mov Disord Clin Pract. 2018;5(6):653–6. https://doi.org/10.1002/mdc3.12679.
166. Nakajima H, Fujiki Y, Ito T, Kitaoka H, Takahashi T. Anti-aquaporin-4 antibody-positive neuromyelitis optica presenting with syndrome of inappropriate antidiuretic hormone secretion as an initial manifestation. Case Rep Neurol. 2011;3(3):263–7. https://doi.org/10.1159/000334129.
167. Nakano T, Fujimoto T, Fukuda Y, Takahashi T, Kanbayashi T. Neuromyelitis optica with syndrome of inappropriate secretion of antidiuretic hormone and hypersomnia associated with bilateral hypothalamic lesions: a case report. Rinsho Shinkeigaku. 2011;51(8):599–602. https://doi.org/10.5692/clinicalneurol.51.599.
168. Nakazato Y, Kondo S, Ohkuma A, Ito Y, Tamura N, Araki N. Neurosarcoidosis presenting as spontaneously remitting hypersomnia. J Neurol. 2009;256(11):1929–31.
169. Nater A, Syro LV, Rotondo F, Scheithauer BW, Abad V, Jaramillo C, Kovacs K, Horvath E, Cusimano M. Necrotizing infundibuloneurohypophysitis: case report and literature review. Endocr Pathol. 2012;23(3):205–11. https://doi.org/10.1007/s12022-012-9214-y.
170. Network BotEN. DQB1 locus alone explains most of the risk and protection in narcolepsy with cataplexy in Europe. Sleep. 2014;37(1):19–25. https://doi.org/10.5665/sleep.3300.
171. Ney DE, Messersmith W, Behbakht K. Anti-Ma2 paraneoplastic encephalitis in association with recurrent cervical cancer. J Clin Neurol. 2014;10(3):262–6.
172. Nirula A, Glaser SM, Kalled SL, Taylora FR. What is IgG4? A review of the biology of a unique immunoglobulin subtype. [miscellaneous article]. Curr Opin Rheumatol. 2011;23(1):119–24. https://doi.org/10.1097/BOR.0b013e3283412fd4.
173. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet. 2000;355(9197):39–40.
174. Nissen MS, Blaabjerg M. Anti-IgLON5 disease: a case with 11-year clinical course and review of the literature. Front Neurol. 2019;10:1056. https://doi.org/10.3389/fneur.2019.01056.
175. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, Himanen S-L, Hublin C, Julkunen I, Olsén P. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One. 2012;7(3):e33536.
176. Nozaki H, Shimohata T, Kanbayashi T, Sagawa Y, Katada S, Satoh M, Onodera O, Tanaka K, Nishizawa M. A patient with anti-aquaporin 4 antibody who presented with recurrent hypersomnia, reduced orexin (hypocretin) level, and symmetrical hypothalamic lesions. Sleep Med. 2009;10(2):253–5. https://doi.org/10.1016/j.sleep.2007.11.022.
177. Nozaki K, Judson MA. Neurosarcoidosis: clinical manifestations, diagnosis and treatment. Presse Med. 2012;41(6):e331–48. https://doi.org/10.1016/j.lpm.2011.12.017.
178. O'Brien G, Baughman R, Broderick J, Arnold L, Lower E. Paranoid psychosis due to neurosarcoidosis. Sarcoidosis. 1994;11(1):34–6.
179. O'Reilly MW, Sexton DJ, Dennedy MC, Counihan TJ, Finucane FM, O'Brien T, O'Regan AW. Radiological remission and recovery of thirst appreciation after infliximab therapy in adipsic diabetes insipidus secondary to neurosarcoidosis. QJM. 2015;108(8):657–9. https://doi.org/10.1093/qjmed/hct023.
180. O'Reilly M, Sexton D, Dennedy M, Counihan T, Finucane F, O'Brien T, O'Regan A. Radiological remission and recovery of thirst appreciation after infliximab therapy in adipsic diabetes insipidus secondary to neurosarcoidosis. QJM. 2013;108(8):657–9.
181. Oka Y, Kanbayashi T, Mezaki T, Iseki K, Matsubayashi J, Murakami G, Matsui M, Shimizu T, Shibasaki H. Low CSF hypocretin-1/orexin-A associated with hypersomnia secondary to hypotha-

lamic lesion in a case of multiple sclerosis. J Neurol. 2004;251(7):885–6.
182. Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. Acta Neurol Scand. 1986;73(3):283–90. https://doi.org/10.1111/j.1600-0404.1986.tb03277.x.
183. Ollila HM, Ravel J-M, Han F, Faraco J, Lin L, Zheng X, Plazzi G, Dauvilliers Y, Pizza F, Hong S-C. HLA-DPB1 and HLA class I confer risk of and protection from narcolepsy. Am J Hum Genet. 2015;96(1):136–46.
184. Ortega Suero G, Sola-Valls N, Escudero D, Saiz A, Graus F. Síndromes neurológicos paraneoplásicos asociados a anticuerpos anti-Ma y anti-Ma2. Neurologia. 2018;33(1):18–27. https://doi.org/10.1016/j.nrl.2016.05.010.
185. Panta R, Batra M, Makdissi A, Chaudhuri AA. Case of hypothalamic-pituitary sarcoidosis with hypothermia. In: 18th European congress of endocrinology. Bioscientifica; Bristol, United Kingdom. 2016.
186. Papuc E, Stelmasiak Z, Grieb P, Pawel G, Rejdak K. CSF hypocretin-1 concentrations correlate with the level of fatigue in multiple sclerosis patients. Neurosci Lett. 2010;474(1):9–12. https://doi.org/10.1016/j.neulet.2010.02.062.
187. Partinen M, Saarenpaa-Heikkila O, Ilveskoski I, Hublin C, Linna M, Olsen P, Nokelainen P, Alen R, Wallden T, Espo M, Rusanen H, Olme J, Satila H, Arikka H, Kaipainen P, Julkunen I, Kirjavainen T. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. PLoS One. 2012;7(3):e33723. https://doi.org/10.1371/journal.pone.0033723.
188. Pawate S, Moses H, Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM. 2009;102(7):449–60. https://doi.org/10.1093/qjmed/hcp042.
189. Pedersen NW, Holm A, Kristensen NP, Bjerregaard A-M, Bentzen AK, Marquard AM, Tamhane T, Burgdorf KS, Ullum H, Jennum P, Knudsen S, Hadrup SR, Kornum BR. CD8+ T cells from patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. Nat Commun. 2019;10(1):837. https://doi.org/10.1038/s41467-019-08774-1.
190. Pena JA, Birchansky S, Lotze TE. Lymphocytic hypophysitis associated with pediatric multiple sclerosis. Pediatr Neurol. 2014;51(4):580–2. https://doi.org/10.1016/j.pediatrneurol.2014.06.005.
191. Pietinalho A, Ohmichi M, Hiraga Y, Lofroos AB, Selroos O. The mode of presentation of sarcoidosis in Finland and Hokkaido, Japan. A comparative analysis of 571 Finnish and 686 Japanese patients. Sarcoidosis Vasc Diffuse Lung Dis. 1996;13(2):159–66. https://doi.org/10.1007/bf00389839.
192. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol. 2006;63(7):964–8. https://doi.org/10.1001/archneur.63.7.964.
193. Plazzi G, Pizza F, Palaia V, Franceschini C, Poli F, Moghadam KK, Cortelli P, Nobili L, Bruni O, Dauvilliers Y, Lin L, Edwards MJ, Mignot E, Bhatia KP. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. Brain J Neurol. 2011;134(12):3480–92. https://doi.org/10.1093/brain/awr244.
194. Poppe AY, Lapierre Y, Melancon D, Lowden D, Wardell L, Fullerton LM, Bar-Or A. Neuromyelitis optica with hypothalamic involvement. Mult Scler. 2005;11(5):617–21. https://doi.org/10.1191/1352458505ms1200cr.
195. Pröbstel A-K, Rudolf G, Dornmair K, Collongues N, Chanson J-B, Sanderson NS, Lindberg RL, Kappos L, de Seze J, Derfuss T. Anti-MOG antibodies are present in a subgroup of patients with a neuromyelitis optica phenotype. J Neuroinflammation. 2015;12(1):46.
196. Ptak R, Birtoli B, Imboden H, Hauser C, Weis J, Schnider A. Hypothalamic amnesia with spontaneous confabulations: a clinicopathologic study. Neurology. 2001;56(11):1597–600. https://doi.org/10.1212/wnl.56.11.1597.
197. Purba JS, Raadsheer FC, Hofman MA, Ravid R, Polman CH, Kamphorst W, Swaab DF. Increased number of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of patients with multiple sclerosis. Neuroendocrinology. 1995;62(1):62–70. https://doi.org/10.1159/000126989.
198. Qiu W, Raven S, Wu J-S, Bundell C, Hollingsworth P, Carroll WM, Mastaglia FL, Kermode AG. Hypothalamic lesions in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2011;82(7):819. https://doi.org/10.1136/jnnp.2009.198192.
199. Reder AT, Lowy MT, Meltzer HY, Antel JP. Dexamethasone suppression test abnormalities in multiple sclerosis: relation to ACTH therapy. Neurology. 1987;37(5):849.
200. Ricker W, Clark M. Sarcoidosis: a clinicopathologic review of three hundred cases, including twenty-two autopsies. Am J Clin Pathol. 1949;19(8):725–49. https://doi.org/10.1093/ajcp/19.8.725.
201. Rispens T, Ooijevaar-de Heer P, Bende O, Aalberse RC. Mechanism of immunoglobulin G4 Fab-arm exchange. J Am Chem Soc. 2011;133(26):10302–11. https://doi.org/10.1021/ja203638y.
202. Rogers AE, Meehan J, Guilleminault C, Grumet FC, Mignot E. HLA DR15 (DR2) and DQB1*0602 typing studies in 188 narcoleptic patients with cataplexy. Neurology. 1997;48(6):1550–6. https://doi.org/10.1212/wnl.48.6.1550.
203. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol. 2001;50(3):339–48.
204. Rostasy K, Mader S, Schanda K, Huppke P, Gärtner J, Kraus V, Karenfort M, Tibussek D, Blaschek A,

Bajer-Kornek B. Anti–myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis. Arch Neurol. 2012;69(6):752–6.
205. Roth T, Dauvilliers Y, Mignot E, Montplaisir J, Paul J, Swick T, Zee P. Disrupted nighttime sleep in narcolepsy. J Clin Sleep Med. 2013;9(09):955–65.
206. Rubinstein I, Gray TA, Moldofsky H, Hoffstein V. Neurosarcoidosis associated with hypersomnolence treated with corticosteroids and brain irradiation. Chest. 1988;94(1):205–6.
207. Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, Contreras A, Giometto B, Compta Y, Embid C, Vilaseca I, Iranzo A, Santamaria J, Dalmau J, Graus F. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol. 2014;13(6):575–86. https://doi.org/10.1016/s1474-4422(14)70051-1.
208. Sabater L, Planagumà J, Dalmau J, Graus F. Cellular investigations with human antibodies associated with the anti-IgLON5 syndrome. J Neuroinflammation. 2016;13(1):226.
209. Sahashi K, Sakai K, Mano K, Hirose G. Anti-Ma2 antibody related paraneoplastic limbic/brain stem encephalitis associated with breast cancer expressing Ma1, Ma2, and Ma3 mRNAs. J Neurol Neurosurg Psychiatry. 2003;74(9):1332–5. https://doi.org/10.1136/jnnp.74.9.1332.
210. Said G, Lacroix C, Plante-Bordeneuve V, Le Page L, Pico F, Presles O, Senant J, Remy P, Rondepierre P, Mallecourt J. Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients. Brain J Neurol. 2002;125(Pt 2):264–75. https://doi.org/10.1093/brain/awf027.
211. Saiwai S, Inoue Y, Ishihara T, Matsumoto S, Nemoto Y, Tashiro T, Hakuba A, Miyamoto T. Lymphocytic adenohypophysitis: skull radiographs and MRI. Neuroradiology. 1998;40(2):114–20. https://doi.org/10.1007/s002340050550.
212. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998;92(4):573–85.
213. Samart K, Phanthumchinda K. Neuromyelitis optica with hypothalamic involvement: a case report. J Med Assoc Thail. 2010;93(4):505–9.
214. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. Neuron. 2010;68(6):1023–42. https://doi.org/10.1016/j.neuron.2010.11.032.
215. Sarkanen T, Alén R, Partinen M. Transient impact of rituximab in H1N1 vaccination–associated narcolepsy with severe psychiatric symptoms. Neurologist. 2016;21(5):85–6.
216. Scammell TE. Narcolepsy. N Engl J Med. 2015;373(27):2654–62. https://doi.org/10.1056/NEJMra1500587.
217. Schroder JB, Melzer N, Ruck T, Heidbreder A, Kleffner I, Dittrich R, Muhle P, Warnecke T, Dziewas R. Isolated dysphagia as initial sign of anti-IgLON5 syndrome. Neurol Neuroimmunol Neuroinflamm. 2017;4(1):e302. https://doi.org/10.1212/nxi.0000000000000302.
218. Schumann EM, Kümpfel T, Then Bergh F, Trenkwalder C, Holsboer F, Auer DP. Activity of the hypothalamic–pituitary–adrenal axis in multiple sclerosis: correlations with gadolinium-enhancing lesions and ventricular volume. Ann Neurol. 2002;51(6):763–7.
219. Sekiguchi T, Ishibashi S, Kubodera T, Fukabori J, Uezato A, Kanbayashi T, Takahashi T, Yokota T, Mizusawa H. Anhidrosis associated with hypothalamic lesions related to anti-aquaporin 4 autoantibody. J Neurol. 2011;258(12):2293–5. https://doi.org/10.1007/s00415-011-6112-z.
220. Sepúlveda M, Armangue T, Martinez-Hernandez E, Arrambide G, Sola-Valls N, Sabater L, Téllez N, Midaglia L, Ariño H, Peschl P. Clinical spectrum associated with MOG autoimmunity in adults: significance of sharing rodent MOG epitopes. J Neurol. 2016;263(7):1349–60.
221. Sepulveda M, Armangue T, Martinez-Hernandez E, Arrambide G, Sola-Valls N, Sabater L, Tellez N, Midaglia L, Arino H, Peschl P, Reindl M, Rovira A, Montalban X, Blanco Y, Dalmau J, Graus F, Saiz A. Clinical spectrum associated with MOG autoimmunity in adults: significance of sharing rodent MOG epitopes. J Neurol. 2016;263(7):1349–60. https://doi.org/10.1007/s00415-016-8147-7.
222. Servan J, Marchand F, Garma L, Seilhean D, Hauw J, Delattre J. Narcolepsy disclosing neurosarcoidosis. Rev Neurol. 1995;151(4):281–3.
223. Sharma OP. Neurosarcoidosis: a personal perspective based on the study of 37 patients. Chest. 1997;112(1):220–8.
224. Shealy CN, Kahana L, Engel FL, McPherson HT. Hypothalamic-pituitary sarcoidosis: a report on four patients, one with prolonged remission of diabetes insipidus following steroid therapy. Am J Med. 1961;30(1):46–55.
225. Shimatsu A, Oki Y, Fujisawa I, Sano T. Pituitary and stalk lesions (infundibulo-hypophysitis) associated with immunoglobulin G4-related systemic disease: an emerging clinical entity. Endocr J. 2009;56(9):1033–41. https://doi.org/10.1507/endocrj.k09e-277.
226. Silber MH. Autoimmune sleep disorders. In: Handbook of clinical neurology. Elsevier; Oxford, England, United Kingdom. 2016;133:317–26.
227. Simmonds M. Über das Vorkommen von Riesenzellen in der Hypophyse. Virchows Arch Pathol Anat Physiol Klin Med. 1917;223(3):281–90.
228. Spadaro M, Gerdes LA, Krumbholz M, Ertl-Wagner B, Thaler FS, Schuh E, Metz I, Blaschek A, Dick A, Brück W, Hohlfeld R, Meinl E, Kümpfel T. Autoantibodies to MOG in a distinct subgroup

of adult multiple sclerosis. Neurol Neuroimmunol Neuroinflamm. 2016;3(5):e257. https://doi.org/10.1212/nxi.0000000000000257.
229. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. Arch Neurol. 1985;42(9):909–17. https://doi.org/10.1001/archneur.1985.04060080095022.
230. Stern BJ, Royal W 3rd, Gelfand JM, Clifford DB, Tavee J, Pawate S, Berger JR, Aksamit AJ, Krumholz A, Pardo CA, Moller DR, Judson MA, Drent M, Baughman RP. Definition and consensus diagnostic criteria for neurosarcoidosis: from the Neurosarcoidosis Consortium Consensus Group. JAMA Neurol. 2018;75(12):1546–53. https://doi.org/10.1001/jamaneurol.2018.2295.
231. Stiebel-Kalish H, Hellmann MA, Mimouni M, Paul F, Bialer O, Bach M, Lotan I. Does time equal vision in the acute treatment of a cohort of AQP4 and MOG optic neuritis? Neurol Neuroimmunol Neuroinflamm. 2019;6(4):e572. https://doi.org/10.1212/NXI.0000000000000572.
232. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366(6):539–51. https://doi.org/10.1056/NEJMra1104650.
233. Stuart CA, Neelon FA, Lebovitz HE. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. N Engl J Med. 1980;303(19):1078–82. https://doi.org/10.1056/NEJM198011063031902.
234. Sugihara H. Review on recent topics in hypophysitis. J Nippon Med Sch. 2017;84(5):201–8. https://doi.org/10.1272/jnms.84.201.
235. Sullivan F, Hutchinson M, Bahandeka S, Moore RE. Chronic hypothermia in multiple sclerosis. J Neurol Neurosurg Psychiatry. 1987;50(6):813. https://doi.org/10.1136/jnnp.50.6.813.
236. Suzuki K, Nakamura T, Hashimoto K, Miyamoto M, Komagamine T, Nagashima T, Izawa N, Kanbayashi T, Takahashi T, Hirata K. Hypothermia, hypotension, hypersomnia, and obesity associated with hypothalamic lesions in a patient positive for the anti-aquaporin 4 antibody: a case report and literature review. Arch Neurol. 2012;69(10):1355–9. https://doi.org/10.1001/archneurol.2012.300.
237. Tabuena RP, Nagai S, Handa T, Shigematsu M, Hamada K, Ito I, Izumi T, Mishima M, Sharma OP. Diabetes insipidus from neurosarcoidosis: long-term follow-up for more than eight years. Intern Med. 2004;43(10):960–6. https://doi.org/10.2169/internalmedicine.43.960.
238. Tamagno G, Murialdo G. Amenorrhea-galactorrhea syndrome as an uncommon manifestation of isolated neurosarcoidosis. Ann Ital Med Int. 2001;16(4):260–6.
239. Tanaka S, Honda Y, Inoue Y, Honda M. Detection of autoantibodies against hypocretin, hcrtrl, and hcrtr2 in narcolepsy: anti-Hcrt system antibody in narcolepsy. Sleep. 2006;29(5):633–8. https://doi.org/10.1093/sleep/29.5.633.
240. Tao QQ, Wei Q, Song SJ, Yin XZ. Motor neuron disease-like phenotype associated with anti-IgLON5 disease. CNS Neurosci Ther. 2018;24(12):1305.
241. Teirstein AS, Judson MA, Baughman RP, Rossman MD, Yeager H Jr, Moller DR, Case Control Etiologic Study of Sarcoidosis Writing G. The spectrum of biopsy sites for the diagnosis of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(2):139–46.
242. Terushkin V, Stern BJ, Judson MA, Hagiwara M, Pramanik B, Sanchez M, Prystowsky S. Neurosarcoidosis: presentations and management. Neurologist. 2010;16(1):2–15. https://doi.org/10.1097/NRL.0b013e3181c92a72.
243. Tesoriero C, Codita A, Zhang MD, Cherninsky A, Karlsson H, Grassi-Zucconi G, Bertini G, Harkany T, Ljungberg K, Liljestrom P, Hokfelt TG, Bentivoglio M, Kristensson K. H1N1 influenza virus induces narcolepsy-like sleep disruption and targets sleep-wake regulatory neurons in mice. Proc Natl Acad Sci U S A. 2016;113(3):E368–77. https://doi.org/10.1073/pnas.1521463112.
244. Then Bergh F, Kumpfel T, Trenkwalder C, Rupprecht R, Holsboer F. Dysregulation of the hypothalamo-pituitary-adrenal axis is related to the clinical course of MS. Neurology. 1999;53(4):772–7. https://doi.org/10.1212/wnl.53.4.772.
245. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, Chen D, Carter LP, Wang H, Lu Y. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol. 2019;85(3):359–70.
246. Titulaer MJ, Höftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, Benson LA, Shu H, Irioka T, Hirano M. Overlapping demyelinating syndromes and anti–N-methyl-D-aspartate receptor encephalitis. Ann Neurol. 2014;75(3):411–28.
247. Tobin WO, Lennon VA, Komorowski L, Probst C, Clardy SL, Aksamit AJ, Appendino JP, Lucchinetti CF, Matsumoto JY, Pittock SJ. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. Neurology. 2014;83(20):1797–803.
248. Toyoda H, Tanaka S, Miyagawa T, Honda Y, Tokunaga K, Honda M. Anti-Tribbles homolog 2 autoantibodies in Japanese patients with narcolepsy. Sleep. 2010;33(7):875–8.
249. Troutman GS, Salamon J, Scharf M, Mazurek JA. Cold at the core: Osborn waves in neurosarcoidosis-induced central hypothermia. Case Rep Cardiol. 2019;2019:5845839. https://doi.org/10.1155/2019/5845839.
250. Ungprasert P, Crowson CS, Matteson EL. Characteristics and long-term outcome of neurosarcoidosis: a population-based study from 1976-2013. Neuroepidemiology. 2017;48(3-4):87–94. https://doi.org/10.1159/000477300.
251. Ungprasert P, Matteson EL. Neurosarcoidosis. Rheum Dis Clin N Am. 2017;43(4):593–606. https://doi.org/10.1016/j.rdc.2017.06.008.

252. van der Neut KM, Schuurman J, Losen M, Bleeker WK, Martínez-Martínez P, Vermeulen E, den Bleker TH, Wiegman L, Vink T, Aarden LA, De Baets MH, van de Winkel JGJ, Aalberse RC, Parren PWHI. Anti-inflammatory activity of human IgG4 antibodies by dynamic fab arm exchange. Science (New York, NY). 2007;317(5844):1554–7. https://doi.org/10.1126/science.1144603.
253. Vercellino M, Masera S, Lorenzatti M, Condello C, Merola A, Mattioda A, Tribolo A, Capello E, Mancardi GL, Mutani R, Giordana MT, Cavalla P. Demyelination, inflammation, and neurodegeneration in multiple sclerosis deep gray matter. J Neuropathol Exp Neurol. 2009;68(5):489–502. https://doi.org/10.1097/NEN.0b013e3181a19a5a.
254. Verhage TL, Godfried MH, Alberts C. Hypothalamic-pituitary dysfunction with adrenal insufficiency and hyperprolactinaemia in sarcoidosis. A case report. Sarcoidosis. 1990;7(2):139–41.
255. Vernant JC, Cabre P, Smadja D, Merle H, Caubarrere I, Mikol J, Poser CM. Recurrent optic neuromyelitis with endocrinopathies: a new syndrome. Neurology. 1997;48(1):58–64. https://doi.org/10.1212/wnl.48.1.58.
256. Verstraeten T, Cohet C, Dos Santos G, Ferreira GL, Bollaerts K, Bauchau V, Shinde V. Pandemrix and narcolepsy: a critical appraisal of the observational studies. Hum Vaccin Immunother. 2016;12(1):187–93. https://doi.org/10.1080/21645515.2015.1068486.
257. Vesely D. Hypothalamic sarcoidosis: a new cause of morbid obesity. South Med J. 1989;82(6):758–61.
258. Vetrugno R, Stecchi S, Plazzi G, Lodi R, D'Angelo R, Alessandria M, Cortelli P, Montagna P. Narcolepsy-like syndrome in multiple sclerosis. Sleep Med. 2009;10(3):389–91.
259. Viegas S, Weir A, Esiri M, Kuker W, Waters P, Leite MI, Vincent A, Palace J. Symptomatic, radiological and pathological involvement of the hypothalamus in neuromyelitis optica. J Neurol Neurosurg Psychiatry. 2009;80(6):679–82. https://doi.org/10.1136/jnnp.2008.157693.
260. Vincent A. Developments in autoimmune channelopathies. Autoimmun Rev. 2013;12(6):678–81.
261. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, Clover L, Parkinson A, Bien CG, Omer S. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain J Neurol. 2004;127(3):701–12.
262. Vogrig A, Fouret M, Joubert B, Picard G, Rogemond V, Pinto A-L, Muñiz-Castrillo S, Roger M, Raimbourg J, Dayen C, Grignou L, Pallix-Guyot M, Lannoy J, Ducray F, Desestret V, Psimaras D, Honnorat J. Increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors. Neurol Neuroimmunol Neuroinflamm. 2019;6(6):e604. https://doi.org/10.1212/nxi.0000000000000604.
263. Voltz R, Gultekin SH, Rosenfeld MR, Gerstner E, Eichen J, Posner JB, Dalmau J. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med. 1999;340(23):1788–95. https://doi.org/10.1056/NEJM199906103402303.
264. Voortman M, Drent M, Baughman RP. Management of neurosarcoidosis: a clinical challenge. Curr Opin Neurol. 2019;32(3):475–83. https://doi.org/10.1097/wco.0000000000000684.
265. Vrethem M, Malmgren K, Lindh J. A patient with both narcolepsy and multiple sclerosis in association with Pandemrix vaccination. J Neurol Sci. 2012;321(1-2):89–91.
266. Wallenius M, Lind A, Akel O, Karlsson E, Svensson M, Arvidsson E, Ramelius A, Törn C, Palm L, Lernmark Å. Autoantibodies in Pandemrix®-induced narcolepsy: nine candidate autoantigens fail the conformational autoantibody test. Autoimmunity. Elsevier; Oxford, England, United Kingdom 2019;52(4):185–91.
267. Wasling P, Malmeström C, Blennow K. CSF orexin-a levels after rituximab treatment in recent onset narcolepsy type 1. Neurol Neuroimmunol Neuroinflamm. 2019;6(6):e613. https://doi.org/10.1212/nxi.0000000000000613.
268. Watanabe M, Furusho K, Takahashi T, Tamaoka A. Galactorrhea in a patient with Aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: a case report and review of the literature. Neurologist. 2015;20(6):101–3. https://doi.org/10.1097/NRL.0000000000000061.
269. Weiss N, Hasboun D, Demeret S, Fontaine B, Bolgert F, Lyon-Caen O, Chabas D. Paroxysmal hypothermia as a clinical feature of multiple sclerosis. Neurology. 2009;72(2):193. https://doi.org/10.1212/01.wnl.0000339102.12168.ee.
270. Wenninger S. Expanding the clinical spectrum of IgLON5-syndrome. J Neuromusc Dis. 2017;4(4):337–9.
271. Williams G, Ball JA, Lawson RA, Joplin GF, Bloom SR, Maskill MR. Analgesic effect of somatostatin analogue (octreotide) in headache associated with pituitary tumours. Br Med J (Clin Res Ed). 1987;295(6592):247–8.
272. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG, International Panel for NMOD. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177–89. https://doi.org/10.1212/WNL.0000000000001729.
273. Yasuda Y, Iwama S, Kiyota A, Izumida H, Nakashima K, Iwata N, Ito Y, Morishita Y, Goto M, Suga H, Banno R, Enomoto A, Takahashi M, Arima H, Sugimura Y. Critical role of rabphilin-3A in the pathophysiology of experimental lymphocytic

neurohypophysitis. J Pathol. 2018;244(4):469–78. https://doi.org/10.1002/path.5046.
274. Ysrraelit MC, Gaitan MI, Lopez AS, Correale J. Impaired hypothalamic-pituitary-adrenal axis activity in patients with multiple sclerosis. Neurology. 2008;71(24):1948–54. https://doi.org/10.1212/01.wnl.0000336918.32695.6b.
275. Zellini F, Niepel G, Tench CR, Constantinescu CS. Hypothalamic involvement assessed by T1 relaxation time in patients with relapsing-remitting multiple sclerosis. Mult Scler. 2009;15(12):1442–9. https://doi.org/10.1177/1352458509350306.
276. Zhang L, Wu A, Zhang B, Chen S, Men X, Lin Y, Lu Z. Comparison of deep gray matter lesions on magnetic resonance imaging among adults with acute disseminated encephalomyelitis, multiple sclerosis, and neuromyelitis optica. Mult Scler J. 2013;20(4):418–23. https://doi.org/10.1177/1352458513499420.
277. Zoeller GK, Benveniste RJ, Farhadi FA, Bruce JH. Lymphocytic hypophysitis in a patient presenting with sequential episodes of optic neuritis. Pituitary. 2012;15(1):101–5. https://doi.org/10.1007/s11102-010-0244-5.

Traumatic and Degenerative Hypothalamic Diseases

21

Roger E. Kelley

Traumatic Brain Injury (TBI)

The effects of TBI on hypothalamic function reflect the severity and pattern of injury. There have been a number of mechanisms cited [1]. These included direct traumatic injury to the hypothalamic-pituitary (H-P) axis, hypoxic insult, vascular injury related to vessel integrity disruption or hypotension, systemic shock with vasospasm, interruption of the portal supply due to raised intracranial pressure (ICP), and compression injury from hemorrhage, as well as localized or generalized edema which can contribute to elevated ICP.

Pituitary infarction is seen in up to 43% of cases of fatal TBI [2]. The blood supply to the H-P axis comes primarily from the internal carotid arteries. The superior hypophyseal arterial supply includes the right and left anterior superior hypophyseal arteries. These vessels supply not only the pituitary body but also provide supply to the optic nerve as well as the hypothalamus [3]. The superior and inferior hypophyseal arteries form both a superficial external and internal plexuses. The internal plexus, composed of capillary loops, contributes to the formation of the hypophyseal portal system. This portal system connects the hypothalamus to the anterior pituitary. The hypophyseal portal system serves for circulatory control of pituitary gland hormone secretion via the transport and exchange of releasing and inhibiting hormones from the hypothalamus [4]. Shearing brain injuries can lead to disruption of this transport system with the degree dependent upon the level of trauma. There can be the secondary or comorbid factors, with hypothalamic-pituitary dysfunction as the end result.

TBI is viewed as a common cause of hypopituitarism with a prevalence rate of up to 27.5% for anterior hypopituitarism [5]. According to a review on this topic [6], predictors of extended hypopituitarism following TBI are not unexpected factors. These include (1) severity on admission, (2) CT brain scan findings, (3) increased ICP, (4) diffuse axonal injury, (5) older age, (6) acute changes in pituitary hormone function, (7) presence of anti-pituitary hormone changes, (8) length of stay in an intensive care unit, and (9) presence of anti-hypothalamic antibodies and basal skull fracture.

There is resultant hormonal disruption. This can include deficiency of growth hormone, hypothyroidism, hypogonadism, hypocortisolism, and central diabetes insipidus. In a prospective study of TBI in adults [7], the authors reported a relationship between hormonal deficiency and Glasgow Outcome Scale score and the presence of empty sella on MR brain imaging. In the acute phase of injury, for the 186 patients reported,

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hormonal dysfunction was reported in 53%. Of the 54 patients who died in the acute setting, 59% had hormonal abnormalities. Three months after the TBI, there was a 55% recovery rate in hormonal function. Obviously, this was for survivors. Another 37% had recovery of hormonal function at 6 months. However, 3 patients developed new hormonal problems with this percentage impacted by 21 patients lost to follow-up. There were persistent hormonal deficiencies seen at 1 year with 20 of 89 patients having clinically significant hormonal disturbance. The results of this study led to the recommendation that serial hormonal monitoring is in order for at least 1 year out from moderate to severe TBI. A large body of evidence, as cited by Benvenga [8], supports the importance of recognizing the association of pituitary hormone deficiency in the setting of TBI.

In a prospective study of 340 patients in a rehabilitation unit following TBI or subarachnoid hemorrhage [9], who were screened for pituitary hormone dysfunction, 37% had hypopituitarism, with hypogonadism in men the most common at 40%. Estradiol was not reported in women in this study. Tanriverdi et al. [6], on the other hand, found growth hormone to be the most common pituitary deficiency after TBI. This was followed by deficiencies in gonadotropin, adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone.

In summary, there is considerable support for the importance of recognizing the association of pituitary hormone deficiency in the setting of TBI. In addition to direct trauma to the H-P axis and vascular injury, secondary effects related to inflammation and autoantibodies might play a role in the pathogenesis. Vijapur et al. [10] looked at potential associations with anti-hypothalamic and anti-pituitary antibodies, as well as inflammatory biomarkers, in TBI. This investigation was inspired by previous work looking at autoantibodies related to TBI to glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), myelin basic protein, and glutamate receptors [11, 12]. There has also been evidence of specific autoantibodies to the H-P axis [13]. The authors reported an association between hormone deficiency and both anti-pituitary and anti-hypothalamic IgM, but not IgG, antibody productions. There was a positive correlation between multiple inflammatory biomarkers, in their inflammatory marker panel, and IgM autoantibody production. Thus, there is a potential cascade of events in TBI that can lead to either direct or secondary effects on the H-P axis function. A summary of potential contributing factors is provided in Table 21.1.

Table 21.1 Potential contributing factors to hypothalamic damage in traumatic brain injury

1.	Direct compression
2.	Shear force injury
3.	Circulatory compromise
4.	Disruption of remote neurocircuitry connections
5.	Excitotoxic neurotransmitter release
6.	Evolving edema with compression
7.	Increased intracranial pressure
8.	Hypoxic insult
9.	Hypothalamic autoantibodies
10.	Generation of post-traumatic inflammation

Subarachnoid Hemorrhage, Ischemic and Hemorrhagic Stroke, TBI, and Brain Edema

There is a well-recognized overlap between the effects of TBI and the effects of aneurysmal subarachnoid hemorrhage (SAH) on the hypothalamic-pituitary dysfunction as pointed out in the review by Schneider et al. [14]. This overlap is not restricted to these two processes as one can see an H-P axis effect with ischemic and hemorrhagic stroke as well. A common mechanism relates to brain edema and how it might be exacerbated by a generic insult to the hypothalamus. In a review of neuroendocrine changes after aneurysmal SAH, Karaca et al. [15] reported that growth hormone deficiency was most common followed by ACTH and then gonadotropin- and thyroid-stimulating hormone. Of particular pertinence in cerebral insults associated with brain edema is the production and regulation of the peptide hormone vasopressin by the hypothalamus. This production is within the paraventricular and supraoptic nucleus of the hypothalamus with

secretion into the circulation through the posterior pituitary gland. Vasopressin is an important regulator of blood pressure, blood osmolality, and blood volume. In pathological conditions, such as TBI, SAH, and ischemic stroke, oversecretion of vasopressin from the pituitary can promote hyponatremia and aggravate brain edema creating a vicious cycle [16]. This may have a particular deleterious effect on ischemic stroke associated with vasopressin hypersecretion [17].

Booji et al. [18] looked at the interplay between various types of brain insult, including stroke, SAH, and TBI with post-event fatigue. They theorized that an effect on the pituitary, or H-P axis, was a contributing factor. Based upon their extensive literature search, they reported that up to 82% of patients were found to have some degree of pituitary dysfunction following stroke with growth hormone deficiency most commonly found. The cumulative prevalence was 49.3% following SAH or TBI. However, they acknowledged significant differences in methodologies for the various studies as well as differing approaches in distinguishing the acute versus chronic phase of the insult.

A study by Boehncke et al. [19] also reported impaired growth hormone secretion, along with secondary adrenal failure, as the most common consequences of acute stroke on pituitary function. Of the 39 patients evaluated prospectively between 66 and 274 days after ischemic stroke, 32 (82%) had pituitary hormonal deficiency to some degree. There was an impaired growth hormone response in 79.5% and secondary adrenal insufficiency in 14.6%. However, they did not observe outcome to be correlated with pituitary function. In contradistinction to this report, Tu et al. [20] reported an association between neuroendocrine biomarkers and prognosis in acute ischemic stroke. Specifically, they looked at baseline brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, cortisol, and copeptin levels following admission for acute ischemic stroke. Plasma levels of these biomarkers were reported to correlate with stroke severity, and the panel helped to predict functional outcome at 90 days better than either the National Institute of Health Stroke Scale or any biomarker alone.

In a study of neuroendocrine changes in patients with spontaneous intracerebral hemorrhage, Huttner et al. [21] looked at thyrotropin, free triiodothyronine, thyroxine, human growth hormone, insulin-like growth factor 1, and testosterone with no significant effect observed. They did find a mild decrease in ACTH and cortisol at day 3 in those patients with large hematomas. They also reported that there were pathologically elevated levels of luteinizing and follicle-stimulating hormone, throughout the observation period, in patients with small hematomas. In addition, prolactin levels were elevated in large hematomas which was an expected finding. Overall, the authors concluded that the rather pronounced neuroendocrine disturbances associated with acute ischemic stroke and SAH were not observed in a consistent fashion in intracerebral hemorrhage.

Cerebral Ischemia

Radak et al. [22] reviewed the potential consequences of transient ischemic attach on the hypothalamic-pituitary-adrenal (HPA) axis. This axis tends to be stimulated by cerebral ischemia, as a stressor, and neuroendocrine alterations can be an early detectable manifestation of the insult [23–25]. One deleterious contributing factor is activation of the autonomic nervous system with catecholamine release. This catecholamine release can contribute to the cerebral ischemic cascade and adversely affect functional outcome [26]. Excessive glutamate release, resulting from cerebral ischemic insult, is an excitatory neurotransmitter. Such a degree of release is excitotoxic on brain cells, and a potential contributor to this cytopathological process is presumably the relatively high concentration of glutamate in hypothalamic nuclei [27].

Other than stimulation of the autonomic nervous system, there are other effects of acute ischemia on brain function including the HPA axis in reaction to the stress of the insult [28]. One effect

is hypercortisolism [29, 30] mediated by corticotropin-releasing hormone as well as glucocorticoid-negative feedback regulation of the HPA axis [31]. The three major features of a stress response of the HPA axis, whatever the mechanism, are a rise in cortisol level, thyroid function depression, and functional depletion of anabolic hormones including growth hormone and insulin [32]. Kreber et al. [33] reported growth hormone deficiency in 54% of middle-aged adults recovering from stroke. They observed that 32% fell into the severe category, and the growth hormone deficiency was seen in association with lower levels of follicle-stimulating hormone, luteinizing hormone, triiodothyronine, and sex hormone-binding globulin, along with higher levels of prolactin.

The hypothalamus itself appears to be a prime mediator of this stress response through its various afferent projections from the brainstem, limbic system, and sympathetic adrenomedullary circuits. In severe experimental stroke, Mracsko et al. [34] observed differential effects between the sympathetic nervous system and the HPA axis on the systemic immune system. They observed elevated glucocorticoid and metanephrine levels were associated with lymphocytopenia. In support of the potential importance of the hypothalamus in acute cerebral ischemia, Brisson and Andrew [35] observed specific protection of a neuronal population within the hypothalamus, in a mouse model of acute ischemic injury, when compared to the neocortex. This purported neuroprotection of the hypothalamus could either translate into a salutary effect in the ischemic cascade, a possible deleterious effect of the stress reaction of the hypothalamus, or both.

Effects of Radiation Therapy on the Hypothalamic-Pituitary Axis

The effects of irradiation are impacted by the protocol used for the neoplastic process [36]. While actively dividing (mitotic) cells, reflective of neoplasia, are more sensitive to direct "single-hit" radiosensitivity response, neuronal tissue cells are more radioresistant but can suffer the consequences of cumulative dosing. Such radiation-induced neurotoxicity on the H-P axis is reflective of the total radiation dose, the fraction size, and the spacing in time between fractions to allow for tissue repair. Fractionation thus is neuroprotective for the integrity of the H-P axis in such a setting.

Survival will obviously dictate the potential for radiation therapy to affect the H-P axis with subsequent hormonal disturbance. A particular pertinent neoplastic process, in this regard, is meningioma affecting the sellar or perisellar region that is managed with a course of cranial irradiation. Such patients typically survive for years, and this allows assessment of the effect of the cranial radiation over an extended period of time as compared to a malignant brain tumor. Lamba et al. [37] have reported on 74 such patients at a single academic center. They reported a 20% risk for hypopituitarism across an H-P axis following radiation therapy with a median follow-up of 43 months. The involvement pattern revealed 24% for thyroid and adrenal, 19% for growth hormone, and 10% for gonadal. The hormonal deficiency was detected from a median time of 11 months, for growth hormone, and 32 months for adrenal insufficiency. The authors noted that both the growth hormone and gonadotropin deficiencies might have been underestimated, in their study, because of lack of routine testing.

Neurodegenerative Disease

The aging process affects all aspects of the central nervous system including hypothalamic function. Neurodegeneration is a complex process, and it can be difficult to distinguish the not unexpected consequences of aging, the so-called "luxury of growing older," versus a neuropathological process. Just as the skin and vascular and musculoskeletal systems show the effects of aging, one typically sees cerebral atrophy in advancing age along with microvascular ischemic disease. Just how one is affected by the various components of neurodegeneration, i.e., the phenotypic expression, is a function of several

key components: (1) genetic, epigenetic, aging, and environmental factors, (2) cellular impairment related to messenger RNA misreading which can result in cellular toxic gain of function or loss of function, and (3) pathological sequelae such as protein misfolding with deposition of toxic material such as beta-amyloid plaques and neurofibrillary tangles. Neurodegenerative disease includes the more common forms of dementia such as Alzheimer's disease, frontotemporal lobe dementia/degeneration, and dementia with Lewy bodies, as well as amyotrophic lateral sclerosis. In addition, neurodegenerative disease includes various extrapyramidal disorders such as Parkinson's disease and multi-system atrophy, related to alpha-synuclein, as well as progressive supranuclear palsy and cortico-basal ganglionic degeneration. Huntington's disease, an autosomal disorder related to an abnormal number of CAG trinucleotide repeats, includes extrapyramidal features along with dementia.

A common mechanism in various neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, and Huntington's disease in alteration of hypothalamic function resulting in abnormal energy metabolism [38]. This encompasses the regulation of food intake along with energy expenditure. With the hypothalamus viewed as the hub for control of energy balance, the various disruptors of hypothalamic function, seen in the various forms of neurodegenerative disease, impact on manifestations and outcome.

Microglia and Macroglia in Neurodegenerative Disease

One key component of neurodegenerative disease involves the microglia. These glial cells are viewed as the macrophages of the central nervous system and serve to monitor and maintain homeostasis of brain tissue through their regulation of local inflammatory responses [39]. The regulation of both inflammation and pain tends to be localized to the lateral hypothalamus [40]. This is related to parasympathetic circuitry which is involved in feeding behavior, wakefulness, as well as the reward system. Orexin neurons are a component of this regulatory system, within the lateral hypothalamus, and are reported to play a role in the modulation of pain transmission associated with various inflammatory diseases.

Macroglia include astrocytes and oligodendrocytes as well as specialized macroglia in the hypothalamus termed tanycytes. Hypothalamic astroglia and tanycytes support neuronal synaptic plasticity which is important for regulation of hormonal release. These include gonadotropin-releasing hormone and oxytocin [41]. Interaction between astrocytes and tanycytes with hypothalamic neurons affects release of various growth factors as well as prostaglandins and progesterone [42].

Disruption of feedback loops between the endocrine glands and the hypothalamus, as part of the natural history of aging, can be an important mechanism of neurodegeneration and loss of neuroendocrine control. This tends to be detected in midlife with progression in a pattern viewed as a "vicious cycle" of damage to neuronal-glial circuitry resulting in dysregulation of the control of endocrine-mediated homeostasis as well as a negative impact on food intake and body metabolism [42]. Microglia appear to be particularly pertinent in the neurodegenerative process involving the hypothalamus. Rosin and Kurrasch [43] propose that hypothalamic microglia may be key regulators of homeostasis through detection and transmission of stimuli to the hypothalamus external to the central nervous system. Neurodegenerative aspects of hypothalamic dysfunction are summarized in Table 21.2.

Table 21.2 Neurodegenerative aspects of hypothalamic dysfunction

1. Hypothalamic atrophy
2. Deposition of beta-amyloid (misfolded protein) plaques
3. Deposition of neurofibrillary tangle resulting from hyperphosphorylated tau protein
4. TDP-43 proteinopathy
5. Granulovacuolar degeneration
6. Neurotransmitter disruption
7. Hormone dysregulation
8. Synaptic disruption

Functional Connectivity and Neurodegeneration

The hypothalamus, as the central regulator of homeostasis, has prominent connectivity with other brain regions. The interaction can be through various neurotransmitter pathways, including dopaminergic, cholinergic, serotonergic, and glutaminergic, as well as through neuroendocrine release and feedback loop. As an example, Kandasamy et al. [44] have proposed a possible hypothalamic-pituitary-hippocampal (HPH) axis. In recognition of the importance of hippocampal atrophy in dementia, they theorize that there is a reciprocal relationship between hippocampal function and aberrant neuroestradiol production which is impacted by an association with both menopause and neurodegeneration. Furthermore, they propose that the promotion of hippocampal neurogenesis, through elevated concentration of neuroestradiol, is reflective of alteration of feedback regulation of this HPH axis.

Liu et al. [45] cited an abnormal functional connectivity between the hypothalamus and the temporal gyrus being involved in underlying depression often seen in patients with Alzheimer's disease. Their hypothesis was based on previous studies of increased HPA axis activity in major depression along with the hypothalamus being a site of deposition of neurofibrillary tangles. They used functional MRI to assess hypothalamic connectivity in 22 Alzheimer's patients with depression and 21 Alzheimer's patients without depression. They reported reduced functional connectivity between the hypothalamus and the right middle and superior temporal gyrus. This led them to suggest that this abnormal functional connectivity was part of the pathophysiology of depression in Alzheimer's disease.

Hypothalamus and Alzheimer's Disease (AD)

It has been proposed that the hypothalamus plays a pivotal role in AD [46]. In a transgenic mouse model of AD [47], the hypothalamus was reported to be a primary brain region of metabolic disturbance. Braak and Braak [48], in their staging study of AD pathology, reported the presence of both beta-amyloid plaques and neurofibrillary tangles throughout the hypothalamus as well as atrophy [49]. This translates into the reduction in various neurotransmitters and neurohormones. A number of studies have reported a disruption of the HPA axis in AD [50–53]. It remains to be determined how much the hypothalamus may play a primary role versus a reactionary role in the pathogenesis of AD. A number of studies have focused on a potential central role. A potential important contributor is the paraventricular nucleus of the hypothalamus. The release of cortico-releasing hormone (CRH), from this nucleus, stimulates release of ACTH from the anterior pituitary gland. This tends to be produced and released in response to biological stress and leads to production and release of cortisol by the adrenal gland cortex. ACTH also appears to play an important role in circadian rhythm.

There is some postulated relationship between thyroid hormone regulation and AD. Both hypothyroidism and hyperthyroidism have been reported to be associated with an increased risk of AD [54]. A potential protection against AD with thyroid-releasing hormone (TRH) as well as thyroid hormone levels was observed in an animal model by Luo and Stropa [55]. This neuroprotective effect was also supported by studies by Faden et al. [56], for a TRH analog, and also, in a mouse model, by administration of L-thyroxine by Fu et al. [57].

Of particular interest, with possible clinical implications, is the possible association of aging-related lower estrogen levels in women and lower testosterone levels in men. This has led to speculation that dysfunction of the feedback loop in the hypothalamic-pituitary-gonadal axis can be associated with cognitive impairment progressing to AD. A reported relationship between low estrogen is women with AD [58] and potential protection by estrogen supplementation [59] generated considerable interest. However, studies looking at potential benefit of estrogen supplement following menopause were disappointing. This prompted the idea of a critical earlier timeframe of administration in which estrogen supplement

was of particular benefit. Two studies which addressed this concept were both disappointing in terms of expected benefit [60, 61]. Similarly, testosterone supplementation has not provided conclusive support, to date, with well-recognized potential risks [62]. Gonadotropin-releasing hormone is released by the hypothalamus resulting in release of luteinizing hormone (LH) by the pituitary gland. Increased levels of LH have been reported to be associated with cognitive decline as well as AD pathology [63, 64]. Inhibition of beta-amyloid and hyperphosphorylation of tau was observed in a transgenic mouse model of AD related to ablation of the LH receptor [65]. Leuprolide is a commercially available gonadotropin-releasing hormone, which reduces estrogen in women and testosterone in men, including reduction of LH. In a phase 2 clinical trial of this hormone, at relatively high dose, and in combination with a cholinesterase inhibitor, there was a reported protection against cognitive decline in mild to moderate AD [66]. Despite this preliminary positive report, no substantial follow-through information is presently available.

The hypothalamus plays an integral role in body weight [67]. It is theorized that hypothalamic involvement in AD may be the culprit in the weight loss often seen in association with AD [68]. Leptin is an adipocyte-derived hormone which helps in the maintenance of body weight and energy reserve through negative feedback on the hypothalamus [69]. Beta-amyloid deposition in the hypothalamus may play a role is alteration of leptin signaling resulting in the not uncommonly observed loss of fat tissue and associated weight loss in AD [46]. However, another possible contributing factor is loss of appetite which would well be related to the commonly observed finding of loss of taste and smell in neurodegenerative disorders such AD and Parkinson's disease [70].

Diabetes mellitus is reported to be associated with an increased risk of dementia [71] although the association may be more closely related to small-vessel ischemic cerebrovascular disease [72] rather than the typical neuropathological changes of AD, specifically beta-amyloid plaques and neurofibrillary tangles. However, the overlap of vascular and neurodegenerative components of AD is well recognized [73]. Insulin resistance may be of particular concern in the evolution of AD with La Monte [74] using the term "type 3 diabetes" to denote sporadic AD. There is impaired insulin signaling observed in AD presumably related to the involvement of the hypothalamus with the neuropathological correlates of hyperphosphorylated tau as well as the misfolded protein of beta-amyloid plaques. This proposed relationship between insulin resistance and impaired signaling could have clinical implications. For example, Claxton et al. [75] reported improvement in cognition in mild cognitive impairment (MCI) and early AD with long-acting intranasal insulin detemir.

There is some data to support caloric restriction as having a salutary effect on AD pathology. The hypothalamus has been cited as being of potentially significant benefit in this goal. Satoh et al. [76] have proposed the dorsomedial and lateral hypothalamus as being particularly important mediators of this caloric restriction effect. However, the question arises clinically as to whether or not an ideal body mass index (BMI), as a means to prevent AD pathology, might complicate matters as one develops AD and has difficulty with excessive weight loss. It is perhaps more relevant for a healthy diet both in terms of protection against atherosclerosis and a neuroprotective effect as suggested by studies of the Mediterranean diet [77] and the MIND diet [78]. It has not yet been addressed how these diets, designed to have antioxidant and anti-inflammatory properties, along with proposed protection against beta-amyloid deposition and apoptosis, impact the hypothalamus if indeed there is a direct effect.

Circadian rhythm disruption is reported to be common in AD [79]. This has obvious implications in reference to the hypothalamus which is the primary regulator of circadian rhythms [80], specifically the suprachiasmatic nucleus of the hypothalamus. Tranah et al. [81] reported that disrupted circadian rhythms were associated with MCI and dementia in older women. This presumably interfaces with the well-recognized association of fragmented and reduced sleep associated with AD [79]. Sleep disturbance might well precede the cognitive decline of AD. This

Table 21.3 Manifestations of Alzheimer's disease related to hypothalamic dysfunction

1. Loss of energy
2. Weight loss
3. Disruption of circadian rhythm
4. Altered sleep-wake cycle
5. Memory loss
6. Depression
7. Agitation with sundowning

has led to studies of the hypothalamic neurohormones involved in the sleep-wake cycle with orexin (also known as hypocretin) felt to play a prominent role [82]. Fronczek et al. [83] reported up to a 40 to 50% reduction in orexin neurons in AD. However, the results of studies on hypothalamic orexin signaling alteration have been somewhat conflicting. It has been suggested that genetic variations in orexin signaling could contribute to the pathogenesis of AD in susceptible individuals by dysregulation of the normal sleep pattern [84]. Hypothalamic factors which may contribute to the manifestations of AD are summarized in Table 21.3.

Hypothalamus-Mediated Aggressive Behavior in Dementia

Unfortunately, behavioral disturbance is not uncommon in dementia. Ballard and Corbett [85], for example, estimated that 20% of community dwellers with AD exhibited agitated and aggressive behavior with the percentage roughly 50% or higher in institutionalized patients. This has a significant deleterious effect on both the patient and caregiver. Patients are often heavily sedated in an effort to protect themselves and their caregivers from physical harm. The so-called "sundowning" effect is a common manifestation of dementia with the behavioral disturbance, along with increased confusion, becoming more pronounced later on during the day and into the evening. The hypothalamus is an important mediator of aggressive behavior [86]. It has been theorized that the increased behavioral disturbance, as part of the sundowning effect, is reflective of disruption of the circadian rhythm and sleep-wake cycle mediated through the suprachiasmatic nucleus of the hypothalamus. It is quite possible that a vicious cycle develops between stress, agitation, and sleep regulation disruption, all mediated through the hypothalamus, and the dementia pathology. This is expanded upon in the next section.

Stress, the Hypothalamus, and Neurodegenerative Disease

A recent report highlighted the association of stress-related disorders, such as PTSD and adjustment disorders, with neurodegenerative diseases [87]. The authors looked specifically at AD, Parkinson's disease, and amyotrophic lateral sclerosis in a population-matched cohort with a median age, at initiation, of 47 years with median follow-up of 4.7 years. A statistically significant association between stress-related disorders was observed for AD but not for the other two. It has been theorized that AD is a stress-related disorder with the HPA axis a potential target of promising therapies [88]. Carroll et al. [89] used a transgenic mouse model of tau pathology, with hyperphosphorylated tau which is an integral part of neurofibrillary tangles, to look at the effect of chronic stress as a potential promoter of AD pathogenesis. They observed a relationship between chronic stress and tau pathology and other neurodegenerative changes as well as learning impairment. This was through a corticotropin-releasing hormone (CRH) receptor-dependent mechanism. Of interest, they reported that this mechanism could be blocked by CRH receptor 1 antagonists and augmented by CRH overexpression.

Corticotropin-releasing hormone (CRH), which plays a primary role in the HPA axis, is reported to be the final common pathway in the stress response. The HPA axis is reported to be hyperactive in depression including strong activation of CRH. This has led to speculation that overlap between depression and neurodegeneration is directly related to the consequences of stress on the HPA axis [90]. The potential inter-

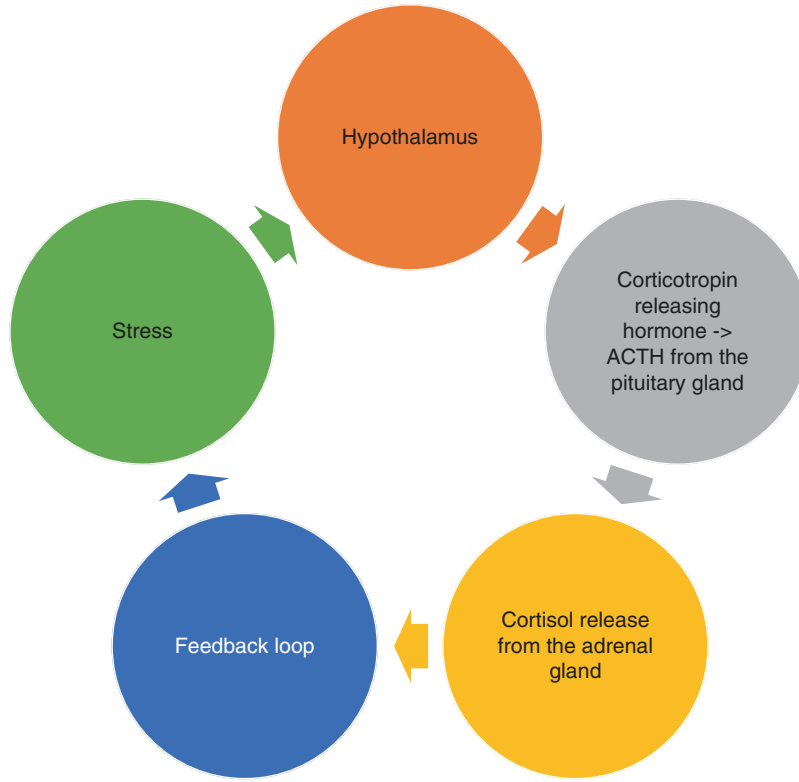

Fig. 21.1 Hypothalamic stress interactions

action of mediators of the stress reaction, in reference to the hypothalamus, is illustrated in Fig. 21.1. Granulovacuolar degeneration (GVD), which can play a role in neurodegeneration, represents cytoplasmic vacuoles within neurons most typically seen in the medial temporal lobe. In a study looking at GVD in different neurodegenerative disorders, there was a reported relationship between the location of GVD and brain regions involved in chronic stress response. However, this was only observed in AD and not in other neurodegenerative disorders such as sporadic Parkinson's disease, progressive supranuclear palsy, or Pick's disease [91].

Hypothalamic Involvement in Parkinson's Disease

Parkinson's disease is a relatively common neurodegenerative disease typically seen in patients 60 years and older, but younger individuals can certainly be affected especially if there is a genetic predisposition or it is the result of a neurotoxic effect. Alpha-synuclein is a naturally occurring neuropeptide believed to be involved in regulation of neurotransmission. Abnormal collections of alpha-synuclein aggregates results in a neurodegenerative process termed an alpha-synucleinopathy. There are three main types: Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multi-system atrophy (MSA). The pathological hallmarks of PD include loss of dopaminergic neurons in the substantia nigra, affecting extrapyramidal system motor function through depletion of the nigrostriatal pathway, as well as intracytoplasmic inclusions of alpha-synuclein aggregates. These neuronal inclusions are eosinophilic and are termed Lewy bodies. These Lewy bodies occur diffusely and can be seen in regions of autonomic regulation including the hypothalamus. They have more recently been implicated in the enteric nervous system with proposed brain-gut-microbiota of pathogenesis spreading from the gut to the brain [92]. There are a number of potential neuroendocrine media-

tors related to the phenotypic expression of PD with the hypothalamus intimately involved [93].

Javoy-Agid et al. [94] called attention to the reduction in dopamine concentration in the hypothalamus in patients with PD. In addition, there is a reported mild to moderate reduction in other neurotransmitters in idiopathic PD including noradrenaline, serotonin, as well as dopamine [95]. Studies with ^{18}Fluoro-dopa positron emission tomography (PET) have demonstrated reduction in monoamine storage capacity, to a significant degree, in PD [96]. This is reflective of presynaptic function of the monoaminergic terminals within the hypothalamus. Postsynaptic dopamine receptor function, specifically dopamine D_2 and D_3 receptors, is expressed throughout the hypothalamic nuclei [97]. ^{11}C-raclopride PET was used in a study by Politis et al. [98]. This was in recognition of this tracer being a marker of dopamine D_2 and D_3 receptor binding [99]. The authors reported reductions in hypothalamic D_2 receptor availability in 14 PD patients compared to 9 controls. However, there was no correlation with disease duration or severity, and it was possible the reduction was related to chronic exposure to levodopa. Despite this, they speculated that this dopaminergic dysfunction may be associated with neuroendocrine, sleep, and autonomic dysfunction in PD.

One particular avenue of research in the interrelationship between PD and the hypothalamus has been related to orexin which is produced exclusively by the hypothalamus and also known as hypocretin. There are two forms of this neurohormone, orexin-A and orexin-B, and they function in sleep regulation and appetite. Sleep disturbance is common in PD and is associated with diurnal excessive sleepiness and fragmented sleep [100]. It is postulated to be related to disruption of the orexin system based upon findings of Fronczek et al. [101] and Thannickal et al. [102]. There has been reported to be selective sparing of orexin-A and orexin-B neurons within the hypothalamus in a macaque model of PD using MPTP [103]. This may be reflective of selective vulnerability for these neurons in PD. This could also be reflective of orexin-A having a neuroprotective effect in a mouse model of PD using MPTP [104]. In addition, when orexin neurons are depleted within the hypothalamus, specifically in the lateral hypothalamus/perifornical region, memory impairment was observed in a rat model of PD [105].

Huntington's Disease and the Hypothalamic-Pituitary-Gonadal Axis

Huntington's disease (HD) is a genetic progressive neurodegenerative disease which is autosomal dominant in transmission. The pathology of this disorder includes the basal ganglia and the limbic system, including the hypothalamus. Two features of HD, which are believed to be related, are hippocampal degeneration and testicular atrophy [106, 107]. Disruption of the hypothalamic-pituitary-gonadal axis, attributed to the effect of the huntingtin gene on steroidogenesis, has been proposed to explain this relationship [108]. Involuntary movement, such as choreoathetosis, is typically seen in HD. As the disease progresses, non-motor manifestations become prominent and can include weight loss, in later stages of the disease, as well as cognitive decline; psychiatric manifestations, with suicide a common cause of mortality; and sleep disturbance. It is felt that progressive loss of energy, tied into metabolic disruption reflective of hypothalamic impairment, is a contributing factor [109]. It is quite possible that hypothalamic involvement also plays a role in the associated weight loss and sleep disturbance as well as possibly an adverse effect on mood.

Amyotrophic Lateral Sclerosis, Frontotemporal Lobar Degeneration, and the Hypothalamus

There is an increasing literature on hypothalamic dysfunction as part of the manifestations of amyotrophic lateral sclerosis (ALS). ALS is a motor neuron disorder typically affecting middle-aged and older adults with combined upper and lower

motor neuron impairment. Thus, one can see the worrisome combination of lower motor neuron findings including atrophy, weakness, and fasciculations along with upper motor neuron features such as spasticity and hyperreflexia.

Unfortunately, there can also be bulbar findings, which impact significantly on prognosis. These include dysarthria and dysphagia and can contribute to respiratory compromise. Reduction in energy homeostasis is a hallmark of ALS with hypothalamic atrophy intimately involved [110]. Reduction in BMI tends to precede the onset of motor symptoms in ALS [111, 112]. This is, at least in part, related to increased metabolic activity seen in ALS [113]. Dysphagia can also play a role as the disease progresses in association with bulbar symptoms.

The pathology of ALS overlaps with frontotemporal lobar degeneration (FTLD). FTLD, also known as frontotemporal dementia (FTD), is the third most common form of neurodegenerative dementia after AD and dementia with Lewy bodies. It tends to present somewhat earlier than AD with behavioral disturbance as a common initial manifestation. The hexanucleotide (GGGCC) repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*) accounts for roughly half of familial ALS cases as well as approximately 10% of sporadic ALS cases [114]. Normally, there are two to ten hexanucleotide GGGGCC repeats in the C9orf72 gene. This *C9orf72* repeat expansion, when in the 100s, is associated with neuronal aberrant misfolded protein aggregations with neurotoxic activity [115]. This includes transactive response DNA-binding protein 43 kDa designated as TDP-43. TDP-43 is an aberrant nuclear protein localized in the cytoplasm. This pathological substrate accounts for roughly 25% of familial FTLD cases [116]. Ubiquitinated TDP-43 can be seen in both FTLD and ALS [117]. It is reported that up to 10–15% of ALS patients have associated FTLD and that 15% of patients with FTLD will display motor features of ALS during the course of their disease [118].

Deficits in energy metabolism and loss of BMI have been reported to be associated with TDP-43 pathology in the basal forebrain of the hypothalamus [119]. Progressive weight loss, with associated muscle wasting, is a significant phenotypic expression of ALS. Vercruysse et al. [120] reported an association with weight loss and a defect in the hypothalamic melanocortin system in mouse model of ALS. Of note, clinically, their findings suggested that drugs expected to promote weight gain would be ineffective in this model of ALS.

It is reported that 5–10% of cases of ALS are familial and dominantly inherited [121]. Roughly 20% of these cases are genetically linked to point mutations in the gene encoding cytosolic Cu/Zn superoxide dismutase (SOD1) [122]. In a mouse model of familial ALS [123], expression of mutant superoxide dismutase 1 was found to be associated with altered transport of vasopressin from the hypothalamo-neurohypophyseal axis. The sleep disturbances observed in ALS and FTLD were the subject of a neuropathological study of patient with *C9orf72*-related disease [124]. Of note, TDP-43 was not noted in either group. However, dipeptide repeat protein aggregates were noted in pinealocytes and, to a lesser extent, in the suprachiasmatic nucleus of the hypothalamus.

It has been theorized that growth hormone deficiency has some potential contribution to the manifestations of ALS. In a study of the growth hormone-insulin-like growth factor system, based upon serum levels of these two factors and associated proteins in 25 ALS patients and 25 healthy subjects who were age-, gender-, and BMI-matched [125], the growth hormone-insulin-like growth factor system was observed to be impaired. However, in a randomized, controlled clinical trial of growth hormone administration in patients with ALS [126], in which 73% of patients had growth hormone deficiency, there was no protective effect observed on progression of the disease.

Summary

Some take-home messages emerge from this summary. The hypothalamus remains somewhat neglected in the grand scheme of brain injury and

neurodegenerative disease despite its inherent importance. As the primary mediator of homeostasis, it has extensive connections to a number of integrated moving parts. With its important role in neuroendocrine balance, hormone deficiencies following traumatic injury must be identified and corrected to meet homeostatic needs including energy demands. Studies reveal varying results in terms of hormone levels, and this is probably, at least in part, related to the stage of the injury as well as the potential for spontaneous recovery. In neurodegenerative disease, the effect of hypothalamic impairment on the BMI, as well as the emotional status and sleep-wake cycle, can be major contributors to progressive functional impairment. There is an increasing literature on how stress can impact hypothalamic function as well as be associated with the pathogenesis of neurodegenerative disease.

Moving forward, neuroimaging, with innovative newer imaging modalities, holds great promise for elucidating the integrity of the hypothalamus following insults related to trauma, cerebral ischemia, or neurodegeneration. Despite major progress with beta-amyloid and tau imaging with PET scan in neurodegenerative disorders such as AD, the small size of the hypothalamus makes visualization limited at this time. Functional neuroimaging with MRI [127] has provided greater imaging ability, but the microcircuitry aspects have been challenging. Evolving techniques, such as miniature fluorescence spectroscopy [128], appear to have great potential in looking at the circuitry connections of cells in deep brain structures in neurodegenerative disease. With the use of animal models of disorders such as ALS and AD, one can assess the level of hyperactivity associated with the neurodegenerative disorder and assess the potential for interventions to interfere with ongoing neural injury.

Innovative therapeutic approaches are on the horizon in reference to neuronal injury. One particularly interesting avenue of research is work being done with the chaperone system. Chaperones are proteins identified as regulators of protein folding. They can help newly produced proteins to fold correctly as well as help repair misfolded proteins and facilitate removal of misfolded proteins that cannot be repaired. This system, responsible for cell protein homeostasis, can be disrupted by various stressors which can lead to pathological rewiring of the chaperone system into what are termed epichaperomes. It is proposed that these rewired structures result in "protein connectivity-based dysfunction" (PCBD) which could well be of pertinence in AD where misfolded beta-amyloid and tau are important contributors to the pathology [129].

From a practical standpoint, protection of the hypothalamus and its interconnections is very much reflective of promotion of a healthy lifestyle. Dietary factors have been reported to be neuroprotective as mentioned above. There has been increasing support for active mental and physical exercise to promote protection against dementia. In a mouse model of hypothalamic neurodegeneration in AD, Do et al. [130] reported a neuroprotective effect of exercise on hypothalamic-mediated neurodegeneration including inflammation, apoptosis, as well as glucose metabolism. Naturally, efforts to protect against head trauma, optimizing radiation therapy approaches, and protection against stroke are also important in the protection of hypothalamic function.

References

1. Temizkan S, Kelestimur F. A clinical and pathophysiological approach to traumatic brain injury. Pituitary. 2019;22:220–8.
2. Salehi F, Kovacs K, Scheithauer BW, Pfeifer EA, Cusiman M. Histologic study of the human pituitary gland in acute brain injury. Brain Inj. 2007;21(6):651–6.
3. Xuereb GP, Prichard MM, Daniel PM. The arterial supply and venous drainage of the human hypophysis cerebri. Q J Exp Physiol Cogn Med Sci. 1954;39:199–217.
4. Sav A, Rotondo F, Syro LV, Serna CA, Kovascs K. Pituitary pathology in traumatic brain injury: a review. Pituitary. 2019;22:201–11.
5. Lauzier F, Turgeon AF, Boutin A, Shemilt M, Cote I, Lachance O, et al. Clinical outcomes, predictors, and prevalence of anterior pituitary disorders following traumatic brain injury: a systematic review. Crit Care Med. 2014;42(3):712–21.

6. Tanriverdi F, Schneider HJ, Aimaretti G, Masel BE, Casanueva FF, Kelestimur F. Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. Endocrine Rev. 2015;36(3):305–42.
7. Krahulik D, Zapletalova J, Frysak Z, Vaverka M. Dysfunction of hypothalamic-hypophysial axis after traumatic brain injury in adults. J Neurosurg. 2010;113:581–4.
8. Benvenga S. The history of pituitary dysfunction after traumatic brain injury. Pituitary. 2019;22:229–35.
9. Kopczak A, Kilimann I, Von Rosen F, Krewer C, Schneider HJ, Stalla GK, Schneider M. Screening for hypopituitarism in 509 patients with traumatic brain injury or subarachnoid hemorrhage. J Neurotrauma. 2014;31:99–107.
10. Vijapur SM, Yang Z, Barton DJ, Vaughan L, Awan N, Kumar RG, et al. Anti-pituitary and anti-hypothalamic autoantibody associations with inflammation and hypogonadotropic hypogonadism in men with traumatic brain injury. J Neurotrauma. 2019;36:21–54.
11. Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, Manley GT. An update on diagnostic and prognostic biomarkers for traumatic brain injury. Expert Rev Mol Diagn. 2018;18:165–80.
12. Yang Z, Zhu T, Weissman AS, Jaalouk E, Rathore DS, Romo P, Shi Y, Wagner AK, Wang KKW. Autoimmunity and traumatic brain injury. Curr Phys Med Rehabil Rep. 2017;5:22–9.
13. Guaraldi F, Grottoli S, Arvat E, Ghigo E. Hypothalamic-pituitary autoimmunity and traumatic brain injury. J Clin Med. 2015;4:1025–35.
14. Schneider HJ, Kreitschmann-Andermaher I, Ghigo E, Stall GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage. A systematic review. JAMA. 2007;298(12):1429–38.
15. Karaca Z, Hacioglu A, Kelestimur F. Neuroendocrine changes after aneurysmal subarachnoid hemorrhage. Pituitary. 2019;22:305–21.
16. Zeynalov E, Jones SM, Eliott JP. Vasopressin and vasopressin receptors in brain edema. In: Vitamins and Hormones. Chap 11. (2020) vol. 113;291–313.
17. Jia S-W, Liu X-Y, Wang SC, Wang Y-F. Vasopressin hypersecretion-associated brain edema formation in ischemic stroke: underlying mechanisms. J Stroke Cerebovasc Dis. 2016;25:1289–300.
18. Booji HA, Gaykema WD, Kuijpers KA, Pouweis MJM, den Herto HM. Pituitary dysfunction and association with fatigue in stroke and other acute brain injury. Endocr Connect. 2018;7:223–7.
19. Boehncke S, Ackermann H, Badenhoop K, Sitzer M. Pituitary function and IGF-I levels following ischemic stroke. Cerebrovasc Dis. 2011;31:163–9.
20. Tu WJ, Dong X, Zhao SJ, Yang DG, Chen H. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischemic stroke. Neuroendocrinology. 2013;25:771–8.
21. Huttner HB, Kiphuth I-C, Teuber L, Lucking H, Kloska SP, Staykov D, et al. Neuroendocrine changes in patients with spontaneous supratentorial intracerebral hemorrhage. Neurocrit Care. 2013;18:39–44.
22. Radak D, Resanovic I, Isenovic ER. Changes in hypothalamic-pituitary-adrenal axis following transient ischemic attack. Angiology. 2014;65(8):723–32.
23. Neidert S, Katan M, Schuetz P, Fluri F, Ernst A, Bingisser R, et al. Anterior pituitary axis hormones and outcome in acute ischemic stroke. J Intern Med. 2011;269(4):420–32.
24. Olsson T, Marklund N, Gustafson Y, Nasman B. Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. Stroke. 1992;23(11):1573–6.
25. Fassbender K, Schmidt R, Mossner R, Daffertshofer M, Hennerici M. Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. Relation to acute confusional state, extent of brain damage, and clinical outcome. Stroke. 1994;25(6):1105–8.
26. Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Prognostic relevance of pathological sympathetic activation after thromboembolic stroke. Neurology. 2001;57(5):833–8.
27. He M, Chen M, Wang J. Relationship between glutamate in the limbic system and hypothalamus-pituitary-adrenal axis after middle cerebral artery occlusion in rats. Chin Med J. 2003;116(10):1492–6.
28. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci. 2006;8(4):383–95.
29. Johansson A, Olsson T, Carlberg B, Karlsson K, Fagerlund M. Hypercortisolism after stroke-partly cytokine mediated? J Neurol Sci. 1997;147(1):43–7.
30. Slowik A, Turaj W, Pankiewicz J, Dziedzic T, Szermer P. Hypercortisolemia in acute stroke is related to the inflammatory response. J Neurol Sci. 2002;196(1–2):27–32.
31. Keller-Wood ME, Dallman MF. Corticosteroid inhibition of ACTH secretion. Endocr Rev. 1984;5(1):1–24.
32. Kreber LA, Mj A, Madel BE, Singh CK, Randle KD, Johnson C, Helvie R, Ashley MJ, Griesbach GS. Prevalence of growth hormone deficiency in middle-age adults recovering from stroke. Brain Inj. 2020;34(2):276–80.
33. Van den Berghe G. The neuroendocrine response to stress is a dynamic process. Best Pract Res Clin Endocrinol Metab. 2001;15(4):405–19.
34. Mracsko E, Liesz A, Karcher S, Zorn M, Bari F, Veltkamp R. Differential effects of sympathetic nervous system and hypothalamic-pituitary-adrenal axis on systemic immune cells after severe experimental stroke. Brain Behav Immun. 2014;41:200–9.
35. Brisson CD, Andrew RD. A neuronal population in hypothalamus that dramatically resists acute ischemic injury compared to the neocortex. J Neurophysiol. 2012;108:419–30.

36. Darzy KH, Shalet SM. Hypopituitarism as a consequence of brain tumors and radiotherapy. Pituitary. 2005;8:203–11.
37. Lamba N, Bussier MR, Niemierko A, Abedi P, Fullerton BC, Loeffler JS. Hypopituitarism after cranial irradiation for meningiomas: a single-institutional experience. Pract Rad Oncol. 2019;9:266–73.
38. Vercruysse P, Vieau D, Blum D, Petersen A, Dupuis L. Hypothalamic alterations in neurodegenerative diseases and their relation to abnormal energy metabolism. Front Mol Neurosci. 2018;11:1–16.
39. Xu L, He D, Bai Y. Microglia-mediated inflammation and neurodegenerative disease. Mol Neurobiol. 2016;53:6709–15.
40. Fakhoury M, Salman I, Najjar W, Merhej G, Lawand N. The lateral hypothalamus: an uncharted territory for processing peripheral neurogenic inflammation. Front Neurosci. 2020;14:1–12.
41. Chowen JA, Argente-Arizon P, Freire-Regatillo A, Frago IM, Horvath TL, Argente J. The role of astrocytes in the hypothalamic response and adaptation in metabolic signals. Prog Neurobiol. 2016;144:68–87.
42. Chowen JA, Garcia-Segura LM. Microglia, neurodegeneration and loss of neuroendocrine control. Prog Neurobiol. 2020;184:1–11.
43. Rosin JM, Kurrasch DM. Emerging roles for hypothalamic microglia as regulators of physiological homostasis. Front Neuroendocrinol. 2019;54:1–14.
44. Kandasamy M, Radhakrishnan RK, Abirami GPP, Roshan SA, Yesudhas A, Balmuthu K, et al. Possible existence of a hypothalamic-pituitary-hippocampal (HPH) axis: a reciprocal relationship between hippocampal specific neuroestradiol synthesis and neuroblastosis in ageing brains with special reference to menopause and neurocognitive disorders. Neurochem Res. 2019;44:1781–95.
45. Liu X, Wei C, Tu Y, Hou H, Huang X, Chen X, Guo Z, Bai G, Chen W. The abnormal functional connectivity between the hypothalamus and the temporal gyrus underlying depression in Alzheimer's disease patients. Front Aging Neurosci. 2018;10:1–7.
46. Ishii M, Iadecola C. Metabolic and non-cognitive manifestations of Alzheimer's disease: the hypothalamus as both the culprit and target of pathology. Cell Metab. 2015;22(5):761–76.
47. Zheng H, Zhou Q, Du Y, Xu P, Lin L, Xiao J, Gao H. The hypothalamus as the primary brain region of metabolic abnormalities in APP/PS1 transgenic mouse model of Alzheimer's disease. Mol Basis Dis. 1864;2018:263–73.
48. Braak H, Braak E. Neuropathology staging of Alzheimer-related changes. Acta Neuropathol. 1991;82:239–59.
49. Callen DJ, Black SE, Gao F, Caldwell CB, Szalai JP. Beyond the hippocampus: MRI volumetry confirms widespread limbic atrophy in AD. Neurology. 2001;57:1669–74.
50. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, Morris JC. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry. 2006;163:2164–9.
51. Rasmuson S, Andrew R, Nasman B, Seckl JR, Walker BR, Olsson T. Increased glucocorticoid production and altered cortisol metabolism in women with mild to moderate Alzheimer's disease. Biol Psychiatry. 2001;49:547–52.
52. Davis KL, Davis BM, Greenwald BS, Mohs RC, Mathe AA, Johns CA, Horvath TB. Cortisol and Alzheimer's disease, I: Basal studies. Am J Psychiatry. 1986;143:300–5.
53. Greenwald BS, Mathe AA, Mohs RC, Levy MI, Johns CA, Davis KL. Cortisol and Alzheimer's disease, II: dexamethasone suppression, dementia severity, and affective symptoms. Am J Psychiatry. 1986;143:442–6.
54. Tan ZS, Vasan RS. Thyroid function and Alzheimer's disease. J Alzheim Dis. 2009;16:503–7.
55. Luo L, Stropa EG. Thyrotropin releasing hormone inhibits tau phosphorylation by dual signaling pathways in hippocampal neurons. J Alzheim Dis. 2004;6:527–36.
56. Faden AI, Movsesyan VA, Knoblach SM, Ahmed F, Cernak I. Neuroprotective effects of novel small peptides in vitro and after brain injury. Neuropharmacology. 2005;49:410–24.
57. Fu AL, Zou CY, Chen X. Thyroid hormone prevents cognitive deficits in a mouse model of Alzheimer's disease. Neuropharmacology. 2010;58:722–9.
58. Manly JJ, Merchant CA, Jacobs DM, Small SA, Bell K, Ferrin M, Mayeux R. Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. Neurology. 2000;54:833–7.
59. Vest RS, Pike CJ. Gender, sex steroid hormones, and Alzheimer's disease. Horm Behav. 2013;63:301–7.
60. Espeland MA, Shumaker SA, Leng I, Manson JE, Brown CM, Leblanc ES, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women ages 50 to 55 years. JAMA Intern Med. 2013;173:1–8.
61. Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-Cognitive and Affective Study. PLoS Med. 2015;12:e1001833.
62. Vigen R, O'Donnell CI, Baron AE, Grunwalk GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310:1829–36.
63. Rodrigues MA, Verdile G, Foster JK, Hogervorst E, Joesbury K, Dhaliwal S, et al. Gonadotropins and cognition in older women. J Alzheim Dis. 2008;13:267–74.
64. Short RA, Bowen RL, O'Brien PC, Graff-Radford NR. Elevated gonadotropin levels in patients with Alzheimer disease. Mayo Clin Proc. 2001;76:906–9.
65. Lin J, Lin X, Yuan F, Lin L, Cook CL, Rao CV, Lei Z. Genetic ablation of luteinizing hormone receptor