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Inflammatory Disorders of the Skull Base: a Review

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Abstract

Purpose of Review In recent years, literature on neuroinflammatory disorders has dramatically expanded, as have options for treatment. However, few reviews have focused on skull-based manifestations of inflammatory disorders.

Recent Findings Here, we review the clinical manifestations, etiologies, diagnostic workup, and treatment of both systemic and localized inflammatory diseases of the skull base with a focus on recent updates to the literature.

Summary This review aims to guide the workup and management of this complex set of diseases.

Keywords Sarcoidosis · IgG4-related disease · Pachymeningitis · Hypophysitis · Orbit

Introduction

Disorders of the skull base are diverse, spanning both localized syndromes, such as Tolosa-Hunt syndrome, and focal manifestations of systemic diseases, such as sarcoidosis (Table 1). Because of the eloquent nature of the area, signs and symptoms related to skull base involvement may also represent the earliest indications of a systemic process. Recognizing these findings is crucial to early diagnosis and accurate treatment, as deficits may be reversible with rapid intervention. Here we review the findings, diagnostic workup, etiologies, clinical manifestations, and treatment of inflammatory diseases of the skull base with the goal of facilitating clinical decision-making.

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Diagnostic Principles

The anatomy of the skull base is complex, with multiple vital neurovascular structures transiting the channels and foramina at the base of the skull, including the cranial nerves. Between the orbits and the paranasal sinuses lies the anterior skull base, while the central skull base contains the pituitary stalk and gland, optic canal, orbital apex, and cavernous sinus, through which cranial nerves III, IV, V1, V2, and VI pass [1]. Within the posterior skull base is the foramen magnum (containing the cervicomedullary junction, vertebral arteries, anterior and posterior spinal arteries, and cranial nerve XI), the internal auditory canal (cranial nerves VII and VIII and the internal auditory artery), the jugular foramen (cranial nerves IX, X, and XI), and the hypoglossal canal (cranial nerve XII).

History and Physical Examination

Presenting symptoms of disorders affecting the skull base are diverse but structure-specific, and a detailed history and systematic examination can often suggest a specific localization. History should include questions about ocular irritation, redness, vision changes, diplopia, headache, dizziness, hearing loss, tinnitus, dysphagia, and dysarthria. Anosmia can be a clue to sinonasal involvement. Pain with eye movements is an important symptom of irritation of the meninges, optic nerve sheath, or extraocular muscles. Clues to pituitary or hypothalamic involvement may include appetite changes, amenorrhea, loss of libido, gynecomastia, galactorrhea, diabetes, acromegalic changes, polydipsia, and skin changes such as striae.

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Table 1 Inflammatory disorders of the skull base

	Focal disorders	Systemic associations
Orbit	Orbital pseudotumor Orbital myositis Dacryoadenitis Posterior scleritis Optic perineuritis	Sarcoidosis IgG4-related disease ANCA vasculitis Thyroid eye disease Infection Malignancy
Cavernous sinus	Tolosa-Hunt syndrome Isolated cranial neuritis	Sarcoidosis IgG4-related disease ANCA vasculitis Infection Malignancy
Sellar area	Primary hypophysitis Iatrogenic hypophysitis	Sarcoidosis IgG4-related disease Langerhans cell histiocytosis Erdheim-Chester disease Infection Malignancy
Pachymeninges	Hypertrophic pachymeningitis	Sarcoidosis IgG4-related disease Giant cell arteritis Granulomatous polyangiitis Rheumatoid arthritis Sjögren's syndrome Infection Malignancy

The physical examination should include a detailed external ophthalmic exam to evaluate for ecchymosis, injection, periorbital swelling, proptosis, and eyelid abnormalities such as ptosis or lid retraction. Digital palpation of the globe can reveal tenderness from scleritis or focal tender spots, or resistance to retropulsion, suggesting an orbital mass or thyroid eye disease. Visual function needs to be examined in order to assess for involvement of the optic nerves or chiasm and should include acuity testing, color vision, visual fields, and fundus examination.

Neurological examination should focus on a thorough assessment of the cranial nerves, particularly extraocular movements, pupils, facial sensation, and facial movement. A Horner's syndrome can be an important clue to carotid or cavernous sinus involvement. The lacrimal and salivary glands are preferentially affected in several systemic syndromes, including sarcoidosis, Sjögren's syndrome, IgG4-related disease, ANCA-associated vasculitis, and lymphoma. Because the skull base drains through regional lymphatic vessels, palpation for lymphadenopathy within the neck should be performed. Given the predilection of systemic diseases including sarcoidosis, IgG4-related disease (IgG4-RD), and vasculitides for the skull base, a general physical examination should be performed with particular attention to the dermatologic and pulmonary examinations. Sarcoidosis may present with a diverse range of cutaneous manifestations, including erythema nodosum and lupus pernio [2]. Cutaneous involvement by IgG4-RD most often involves the skin of the head and neck [3].

Laboratory Evaluation

Laboratory testing should typically include at least a complete blood count (CBC) and differential, comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), and c-reactive protein (CRP). If neuroendocrine symptoms or radiographic pituitary involvement are present, an appropriate laboratory evaluation should be performed, which may include measurement of prolactin, thyroid stimulating hormone, insulin-like growth factor 1, sex hormones, cortisol, and adrenal function tests. Depending on other clinical manifestations, additional studies may include testing for anti-nuclear antibodies (ANA), anti-Ro/La antibodies, anti-neutrophilic cytoplasmic autoantibodies (ANCA), complement levels, angiotensin-converting enzyme (ACE), lactate dehydrogenase (LDH), IgG subclasses, and tumor markers alpha-fetoprotein and human chorionic gonadotrophin. Lumbar puncture is often necessary, with cerebrospinal fluid (CSF) analyzed for cell counts, protein, glucose, oligoclonal bands, and IgG index. In cases with concern for infectious or neoplastic processes, testing for infectious pathogens and analysis of flow cytometry and cytopathology may also be informative. However, in many cases, CSF analysis may be unrevealing if inflammation is limited to the extradural space, without subarachnoid involvement.

Imaging

Radiographic abnormalities of skull base structures may be subtle and can be missed on routine imaging studies. Although computed tomography (CT) images remains essential for visualizing bony structures of the skull base, magnetic resonance imaging (MRI) is superior for evaluation of evaluation of soft tissue, cranial nerves, and intracranial extent of disease. Because of the complexity and density of the structures of the skull base, use of a high field strength (3 Tesla or 7 Tesla) should be considered [4]. Sequences should include axial and coronal T1- and T2-weighted sequences; post-Gadolinium T1 sequences; and high-resolution, heavily T2-weighted imaging to improve visualization of the cranial nerves. CT or MR angiography should also be considered to evaluate for vascular involvement. In cases of orbital involvement, contrast-enhanced and fat-suppressed axial and coronal MRI of both the brain and the orbits should be obtained. Given the propensity of skull-base inflammatory disorders for crossing anatomic boundaries, a radiologic examination should be anatomically informed. In particular, involvement of the orbit, pachymeninges, and sellar contents may occur in isolation or in various combinations; thus, the extent of the inflammatory problem must be delineated. The cranial nerves

should be traced longitudinally along their entire path, including important branches.

Because of the frequency of associated systemic disease, full-body imaging, including contrast-enhanced CT imaging of the chest, abdomen, and pelvis, may be helpful in facilitating a diagnosis or selecting a site for biopsy. In evaluation of sarcoidosis, vasculitides, and malignancy, growing evidence suggests that fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT of the body has a high sensitivity for detection of occult lesions and identification of an optimal biopsy site [5].

Focal Disorders of the Skull Base

Focal syndromes of the skull base often represent diagnoses of exclusion and can be challenging to identify given the absence of supportive systemic findings. Diagnosis of these syndromes requires exclusion of systemic syndromes that may have overlapping manifestations.

Orbit: Pseudotumor and Its Variants

First described in 1905, orbital pseudotumor is a benign, idiopathic intraorbital process that accounts for 10% of orbital masses on biopsy [6, 7]. More recently, one-third of cases previously thought to represent isolated and idiopathic orbital pseudotumor have been re-classified as IgG4-RD, and the differential diagnosis for this process includes orbital infections, lymphoid and other neoplasms, and thyroid eye disease [8]. Orbital pseudotumor typically presents with periorbital edema, erythema, proptosis, ptosis, diplopia, and pain with eye movements. MRI findings include diffuse orbital mass; proptosis; thickening and contrast enhancement of the sclera; and enlargement and contrast enhancement of the optic nerve, optic nerve sheath, and extraocular muscles (Fig. 1a) [9]. Diagnosis is by orbital biopsy, and histopathology most often shows granulomatous inflammation [10]. Unlike IgG4-RD, sarcoidosis, and other multisystem inflammatory diseases that may involve the orbit, primary orbital pseudotumor is typically isolated to the orbit and is most often unilateral. Treatment requires prompt initiation of corticosteroids to prevent ocular complications.

Patients may also present with more limited, structurally specific forms of orbital pseudotumor, including orbital myositis, dacryoadenitis, or trochleitis. Orbital myositis represents a subset of orbital pseudotumor with particular involvement of the extraocular muscles, typically presenting with pain with eye movement and diplopia. Although it may resemble thyroid eye disease, orbital myositis often has a more acute onset, more severe pain, tenderness to palpation over muscle insertions, and a rapid response to corticosteroids [11, 12]. CT or MRI scan typically reveals enlarged extraocular muscles and thickened tendons, whereas tendons are spared in thyroid eye disease (Fig. 1b) [13].

Cavernous Sinus: Tolosa-Hunt Syndrome

First reported in 1954 in a patient with painful ophthalmoplegia and nonspecific granulomatous inflammation of the cavernous sinus, Tolosa-Hunt syndrome is an idiopathic, focal inflammatory syndrome localized to the cavernous sinus [14]. Over half a century later, Tolosa-Hunt syndrome remains both rare and cryptic. Tolosa-Hunt syndrome most often presents with periorbital pain, which can precede ophthalmoplegia by up to a month. In the initial monograph on this syndrome, Edward Tolosa noted that the hallmark feature was "non-specific, chronic inflammation of the septa and wall of the cavernous sinus with the proliferation of fibroblasts an infiltration with lymphocytes and plasma cells" [14]. In a 1961 series of 6 patients, Hunt et al. added that "such inflammatory changes, in a tight connective tissue, may exert pressure upon the penetrating nerves." These include cranial nerves III, IV, V1, V2, and VI and sympathetic nerves. Tolosa-Hunt syndrome is typically relapsing and remitting, with attacks recurring every few months.

Ophthalmoplegia results from involvement of all three ocular motor nerves (oculomotor, trochlear, and abducens) in different combinations. Twenty percent of patients will develop pupillary abnormalities as a result of sympathetic or parasympathetic involvement [15]. In addition to the ophthalmic division of the trigeminal nerve, there are reports of maxillary and mandibular division trigeminal nerve, facial nerve, and optic nerve involvement in rare patients [16, 17]. Dural thickening may also be seen [18].

Neuroimaging is critical, as diagnosis of Tolosa-Hunt syndrome requires exclusion of alternative diagnoses, including infections, vascular lesions (carotid aneurysm or carotid-cavernous fistula), and neoplasm (including lymphoma, meningioma, and perineural metastases). Contrast-enhanced coronal MRI is the study of choice and may reveal thickening and contrast-enhancement of the cavernous sinus, bulging of the normally concave lateral wall of the cavernous sinus, and irregularities in the intracavernous segment of the carotid artery, which may be better visualized on angiography (Fig. 1c) [15, 19]. Symptoms and imaging findings typically resolve with steroids, though prolonged courses may be required, and steroid-sparing agents may be used in refractory cases.

Isolated cranial neuritis, or inflammation of a single cranial nerve, may represent a similar syndrome and can usually be evaluated and treated in the same manner as Tolosa-Hunt syndrome.

Pituitary: Hypophysitis

The pituitary gland is a site of involvement for a number of systemic inflammatory conditions, including sarcoidosis and

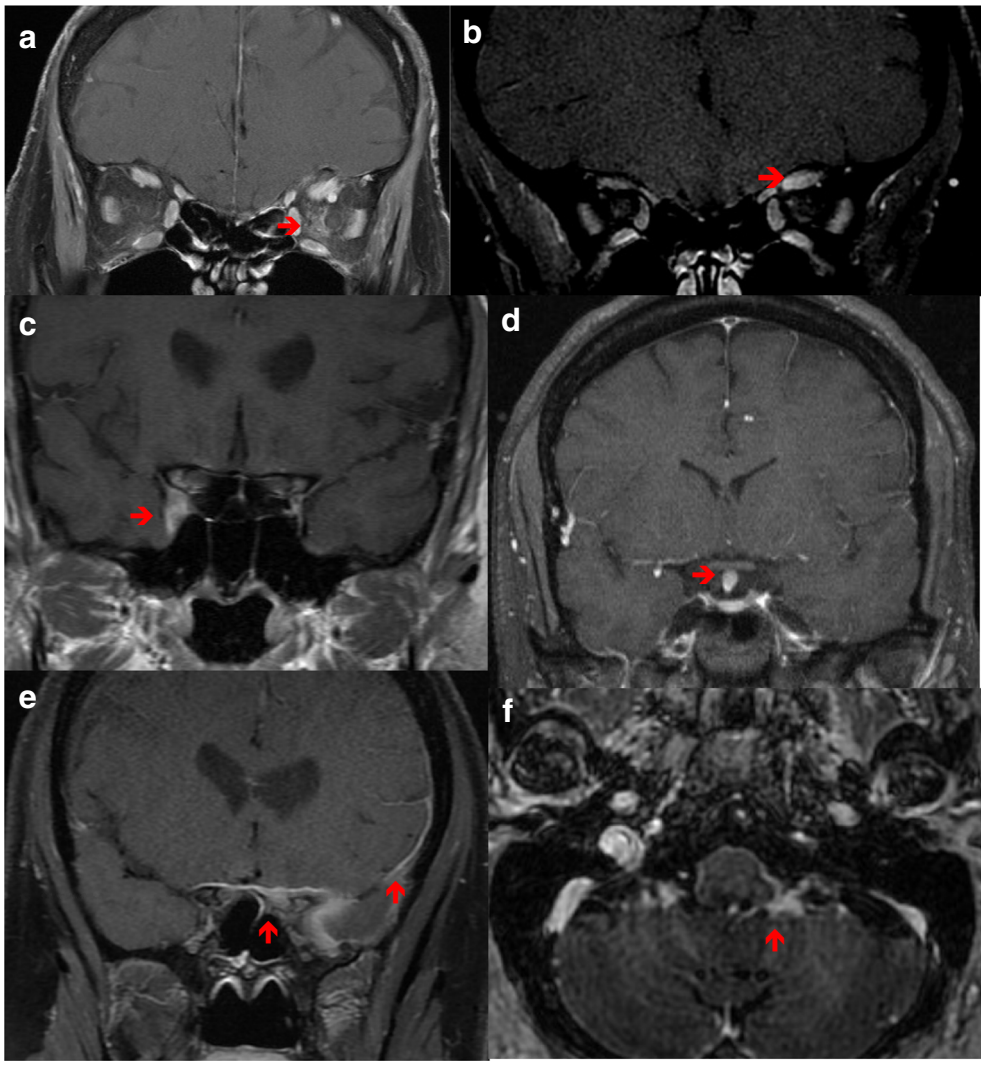

Fig. 1 MRI findings in inflammatory disorders of the skull base. **a**) Orbital fat stranding in left-sided inflammatory pseudotumor. Biopsy showed fibrosis and chronic inflammation without granulomas or features of IgG4RD. **b**) Asymmetric enhancement of left superior rectus in orbital myositis. **c**) Asymmetric contrast enhancement in right anterior cavernous sinus in recurrent Tolosa-Hunt syndrome. **d**) Infundibulohypophysitis in presumed sarcoidosis in a patient with history of recurrent uveitis and erythema nodosum. **e**) Leptomeningeal and optic nerve sheath inflammation in biopsy-proven IgG4RD. **f**) Meningeal nodularity and thickening extending along foramen of Luschka into 4th ventricle in biopsy-proven sarcoidosis

IgG4-RD. In some cases, inflammation of the pituitary can be localized and primary. Primary hypophysitis is categorized based on whether inflammation involves the anterior pituitary gland (adenohypophysitis), posterior gland and/or stalk (infundibuloneurohypophysitis or infundibulohypophysitis), or entire gland (panhypophysitis) (Fig. 1d). Histologic subtypes include lymphocytic, granulomatous, xanthomatous, and plasmacytic hypophysitis [20]. Lymphocytic hypophysitis is seen more commonly than the other histologic subtypes and occurs more frequently among women than men (approximately a 3:1 ratio). Among reproductive-aged women, lymphocytic hypophysitis most often occurs at the end of pregnancy or during the first few months after delivery [21].

Across all subtypes, patients typically present with symptoms related to mass effect from enlargement of the pituitary gland, including headaches and visual symptoms, and pituitary or hypothalamic dysfunction. Cavernous carotid artery occlusion is a rare complication of hypophysitis [22]. In addition to primary hypophysitis, iatrogenic hypophysitis can occur as a complication of a host of new biological and immunomodulatory agents, including anti-cytotoxic T-lymphocyte-associated antigen-4 antibodies and immune checkpoint inhibitors [23•, 24, 25].

The natural history of lymphocytic hypophysitis typically involves progressive pituitary atrophy, sometimes creating the appearance of an empty sella. However, at least partial recovery of pituitary function can occur spontaneously [26, 27]. No prospective controlled studies have examined treatment of primary hypophysitis. However, symptoms from mass effect are thought to represent indications for treatment and may warrant total or partial resection or corticosteroid therapy, which has been reported in small case series to reduce mass effect, and endocrinological function may improve as well [28, 29]. Corticosteroid therapy carries a risk of relapse, as well as significant morbidity. Other immunosuppressive agents such as methotrexate, azathioprine, rituximab, infliximab, cyclosporine, and mycophenolate mofetil have been utilized in a small number of patients with steroid-refractory or recurrent hypophysitis [26, 30–32]. Treatment with stereotactic radiosurgery and fractionated radiotherapy has been reported in a few patients, typically with refractory disease [33, 34].

Dural Meninges

Hypertrophic pachymeningitis (HPM) is characterized by chronic fibrous inflammation of the dural meninges. Although it can be seen in association with systemic fibrotic, rheumatologic, or granulomatous diseases, cases of primary and idiopathic HPM have also been reported in the literature. Symptoms may include headaches, nausea, seizure, or ataxia as a consequence of parenchymal compression, edema, or venous infarction from impaired sinus drainage or cranial neuropathy. There may be associated sinusitis or mastoiditis [35–37].

Primary HPM remains a diagnosis of exclusion, and work-up should include evaluation for IgG4-RD, granulomatosis with polyangiitis (GPA), sarcoidosis, giant cell arteritis, and other systemic inflammatory processes, as well as infections, including tuberculosis and syphilis. Biopsy remains the gold standard for diagnosis. Although the mechanism of HPM is unknown, treatment options include corticosteroids and other immunosuppressive therapies including methotrexate, cyclophosphamide, and rituximab [38–40].

Skull-Based Manifestations of Systemic Inflammatory Disorders

Systemic disorders, including rheumatologic diseases and auto-inflammatory syndromes, can commonly affect the skull base, with a diverse range of presentations. Although this review focuses primarily on inflammatory disorders, atypical infections, including mycobacterial and fungal infections, and malignancies, including lymphoma and perineural spread of cutaneous or aerodigestive malignancies, should also be considered in the differential diagnosis and evaluation.

IgG4-Related Disease

IgG4-RD is a multisystem, fibro-inflammatory disease with a predilection for the head and neck. Although fibrotic syndromes of single organ systems have been described for over a century, including Riedel's thyroiditis and submandibular gland "Küttner's tumor" these were previously believed to be rare, isolated entities, and the association with elevation of serum IgG4 levels was not identified until 2001 [41]. The unified nomenclature for IgG4-RD was described in 2012, and in recent years, awareness of the extent of possible involvement of IgG4-RD has dramatically expanded, with new presentations continuing to be described [42]. Skull-based manifestations of IgG4-RD may include orbital pseudotumor, orbital myositis, hypophysitis, hypertrophic pachymeningitis, dacryoadenitis, and vasculitis (Fig. 1e).

Approximately one-quarter of IgG4-RD patients will develop an orbitopathy, which manifests with chronic, progressive, painless periorbital, lacrimal gland, or lid swelling progressing to frank ptosis or proptosis with involvement of the extraocular muscles, most often the lateral rectus [43]. Hypertrophic pachymeningitis is also common, and most often manifests with headaches, cranial nerve palsies, and vision loss, with less common manifestations including weakness, numbness, and seizures [44]. In patients with isolated pachymeningitis, serum studies may be normal, though CSF may reveal a lymphocytic pleocytosis with an elevated CSF protein and elevated ratio of CSF to serum IgG. Contrast-enhanced MRI will reveal pachymeningeal thickening, with homogenous or nodular dural enhancement. Patients with hypertrophic pachymeningitis may also develop disease in the sinuses, orbits, or pituitary gland, or less commonly in the brain parenchyma [45, 46]. Other manifestations include hypophysitis and cranial neuropathies, with a particular predilection for the infraorbital nerve.

In addition to the neurological and general ophthalmological examination, particular attention should be paid on physical examination to palpation of the submandibular and lacrimal glands and cervical lymph nodes for evaluation of sclerosing sialadenitis, dacryoadenitis and lymphadenopathy [47]. Laboratory testing should include the calculation of a serum ratio of IgG4 to IgG1, with a cutoff of 0.114 in patients who are corticosteroid-naïve [48••]. Among untreated patients, flow cytometry to detect circulating plasmablasts has a high sensitivity, though its specificity is low and it is not yet widely available [49••]. PET imaging may be helpful in identifying biopsy sites and occult organ involvement [50]. Pathology is key in diagnosis and in ruling out mimics, including infection and neoplasm. Pathologic features include lymphoplasmacytic infiltration [51].

Most manifestations of IgG4-RD can be treated with glucocorticoids. However, responses to this therapy are often incomplete, and relapses are common, as are treatment-related toxicities [52]. Rituximab has been used with success [53••], and radiotherapy may be employed in refractory cases [52].

Sarcoidosis and Other Granulomatous Diseases

Sarcoidosis is a multisystem, granulomatous disease that most often affects the lungs, skin, and eyes. Although the minority of patients have neurological involvement, among those who do, half present with neurological symptoms before developing pulmonary manifestations [54••]. Skull-based manifestations of neurosarcoidosis include optic neuritis, cranial neuropathies, pachymeningitis, hypothalamic and pituitary dysfunction, and vasculitis.

Facial nerve palsy was first described in 1909, in a case series of 3 patients with sarcoidosis and uveitis, of which 2 had facial nerve palsies [55], and remains the most common neurological syndrome seen in sarcoidosis [54••]. These

palsies often remit, with a favorable prognosis. Bilateral facial nerve palsies or other cranial polyneuropathy should raise particular concern for neurosarcoidosis. Patients with cranial neuropathies often have concomitant basilar meningitis. In cases with hypothalamic and pituitary dysfunction, onset is typically insidious [56]. Patients may present with bitemporal vision loss as a result of compression of the optic chiasm or with endocrinopathies such as diabetes insipidus. Rarely, sarcoidosis can cause an extraocular myopathy [57].

In two-thirds of patients with cranial neuropathies related to neurosarcoidosis, CSF reveals a mild or moderate lymphocytosis, increased protein, or hypoglycorrhachia. MRI may reveal pachymeningeal thickening or enhancement, enhancement of the hypothalamus or pituitary, or cranial nerve enhancement on high-resolution, heavily T2-weighted, skull-based images (Fig. 1f). FDG-PET has utility in determining sites for biopsy, which typically discloses non-caseating granulomas.

Corticosteroids are the treatment of choice for neurosarcoidosis with involvement of the skull base. In cases with cranial nerve involvement, daily prednisone 20–40 mg with a subsequent taper over 1–6 months is recommended. If prednisone cannot be tapered below 10 mg/day, consideration of steroid-sparing agents, including methotrexate, azathioprine, or mycophenolate mofetil are recommended. In steroid-refractory cases, tumor necrosis factor alpha (TNF-a) inhibitors are recommended. In cases where sarcoid lesions cause mass effect or secondary hydrocephalus, neurosurgical intervention may be required.

In the differential diagnosis for sarcoidosis with involvement of the skull base are related granulomatous diseases, including infectious pathogens such as mycobacteria, syphilis, and cat-scratch disease (bartonellosis) that can incite granuloma formation, as well as other autoimmune granulomatous diseases, including granulomatous polyangiitis (GPA), Churg-Strauss syndrome, and Behçet's disease [58–60]. Like sarcoidosis, GPA commonly affects the orbit and can cause enlarged lacrimal glands or present as an orbital mass [61]. GPA can also present with cranial neuropathies or with pituitary or hypothalamic involvement. GPA, Churg-Strauss, and Behçet's disease also characteristically cause vasculitis, most often of the small vessels and not always readily visible on imaging. Lesions that cause skull base erosion can also lead to inflammatory stenosis or occlusion of major intracranial vessels [62–64].

Sjögren's Syndrome and Other Rheumatologic Diseases

Sjögren's syndrome (SS) is characterized by chronic inflammation of exocrine glands, including the lachrymal and salivary glands. Neurologic manifestations are common in SS as a result of a host of different mechanisms, including a small vessel vasculitis with resultant ischemia, direct effects of anti-neuronal and anti-Ro antibodies, and direct infiltration of nervous tissue by lymphocytic cells [65]. Within the skull base, SS has a predilection for the cranial nerves and is a notable cause of trigeminal sensory neuropathy, as are systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, and scleroderma [66–68]. Rarely, SS has been described in association with hypertrophic pachymeningitis, most often presenting with headache, cranial neuropathies, and ataxia, as well as pituitary or hypothalamic involvement [69, 70]. Hypertrophic pachymeningitis has also been described in association with mixed connective tissue disorder and rheumatoid arthritis [71]. Treatment primarily focuses on symptoms, including neuropathic pain medications in the setting of trigeminal nerve involvement, and on targeting the underlying rheumatologic disorder, including corticosteroids and steroid-sparing anti-inflammatory medications [67].

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a proliferative disorder of pathologic dendritic cells that may present with localized or multifocal lesions. Within the skull base, multifocal LCH has a particular predilection for the hypothalamus and pituitary gland, where it most often manifests with diabetes insipidus. The hypothalamic/pituitary region is occasionally the primary site of LCH in patients without multifocal disease [72]. MRI most often reveals thickening and enhancement of the pituitary stalk with loss of the posterior pituitary bright spot, and evaluation should include testing for endocrinopathy [73]. Craniofacial lesions involving the orbit, mastoid, sphenoid, or temporal bones have also been described, and patients with these lesions have a higher risk of developing pituitary or other central nervous system involvement [74••]. Treatment of LCH involving the skull base is similar to that of non-neurologic LCH, with systemic chemotherapy and surveillance body imaging.

Conclusions

As the current understanding of inflammatory disorders continues to expand, a number of skull-based syndromes previously thought to be idiopathic have been described in association with IgG4-RD and other systemic inflammatory conditions. Diagnosis of skull-based syndromes can be complex and challenging, and the differential remains broad. However, familiarity with this diverse set of diseases is essential to early diagnosis and treatment initiation, as skull-based symptoms may represent the initial manifestations of a severe, systemic illness.

Compliance with Ethical Standards

Conflict of Interest Pria Anand and Bart K. Chwalisz each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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