Chapter 10
Inflammatory and Infectious Lesions of the Brainstem

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Abbreviations

ADEM	Acute disseminated encephalomyelitis
AQ4	Aquaporin 4
BBE	Bickerstaff's brainstem encephalitis
BS	Brainstem
CIS	Clinically isolated syndrome
CLIPPERS	Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CN	Cranial nerve
CNS	Central nervous system
CSF	Cerebrospinal fluid
CTDs	Connective tissue diseases
DIS	Dissemination in space
DIT	Dissemination in time
DWI	Diffusion-weighted imaging
ELISA	Enzyme-linked immunosorbent assay
EV	Enterovirus
FLAIR	Fluid-attenuated inversion recovery
HIV	Human Immunodeficiency virus
HSV	Herpes Simplex virus
Ig	Immunoglobulin
IIDB	Idiopathic inflammatory demyelinating diseases of the brain

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INO	Internuclear ophthalmoplegia
IVIg	Intravenous immunoglobulins
JC	John Cunningham
LETM	Longitudinally extensive transverse myelitis
MOG	Myelin oligodendrocyte glycoprotein
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorder
OCB	Oligoclonal bands
OMM	Oculomasticatory myorhythmia
OpM	Opsoclonus-myoclonus
PACNS	Primary angiitis of the central nervous system
PAN	Polyarteritis nodosa
PCR	Polymerase chain reaction
REM	Rapid eye movement
RRMS	Relapsing-remitting multiple sclerosis
SLE	Systemic lupus erythematosus
SN	Substantia nigra
SS	Sjögren's syndrome
T. pallidum	Treponema pallidum
TB	Tuberculosis
VZV	Varicella zoster virus
WD	Whipple's disease

10.1 Introduction

The brainstem (BS) is unique among other central nervous system (CNS) structures in that it holds in a very narrow space a number of critical neural elements such as the long tracts of the CNS, the cranial nerve (CN) nuclei and respective nerves, the reticular system, and various reflex centers, including the cardiorespiratory centers. Consequently, localizing a disease process to the brainstem is often an easy task given the abundance of objective physical findings. Conversely, determining the exact nature of the disease can prove very challenging. BS lesions span a wide range of pathologies including tumors, infections, and various inflammatory/autoimmune disorders. The main concern is often the distinction between an inflammatory/infectious disorder and a BS tumor in order to avoid unnecessary surgical intervention.

It is usually easy to exclude a BS tumor based on imaging findings, but this is not always the case. Many non-neoplastic diseases of the BS can present as a space-occupying lesion [1]. Conversely, diffuse BS tumors such as lymphomas are known to masquerade as inflammatory or infectious lesions [2]. In difficult cases, additional tests are often needed, including cerebrospinal fluid (CSF) analysis, serum testing, and advanced imaging techniques such as magnetic resonance (MR) spec-

troscopy and MR perfusion. Once a BS tumor is excluded with a reasonable degree of certainty, the next logical question becomes: is this an infectious process? The distinction between infectious and noninfectious etiologies is important in order to select the best initial therapy. BS abscesses need to be differentiated from tumefactive inflammatory lesions, and the origin of more diffuse encephalitic lesions should be rapidly determined. When faced with a case of BS encephalitis, the diagnostic approach is somewhat different from that of encephalitis in general. Unlike classical encephalitis, which is mostly infectious [3], BS encephalitis is typically an autoimmune disorder. The outcome of BS encephalitis is intimately linked to the underlying etiology. Generally speaking, the outcome is good with full or near full recovery in most patients. Nevertheless, some etiologies are potentially severe and life-threatening. As such, prompt identification of the most plausible etiology and early initiation of the most appropriate empiric treatment is often necessary.

This chapter will address the various infectious and inflammatory disorders of the brainstem with emphasis on their clinical presentation, key radiological and laboratory findings, and general principles of management. Our current understanding of many of these entities is based on case reports and small case series. Consequently, evidence-based guidelines for managing such entities are inexistent to date, as described in this chapter. In such cases, expert opinions and the limited evidence found in the literature will be provided for guidance.

10.2 Clinical Presentation

BS involvement in inflammatory and infectious disorders is often suspected on clinical grounds. Lesions of the BS may manifest as cerebellar, somatosensory, motor symptoms, as well as CN dysfunction. The clinical finding of ipsilateral CN dysfunction and contralateral hemiparesis and/or sensory loss (the so-called crossed symptoms) is the hallmark of BS injury. The involved CN(s) help(s) in determining the approximate rostro-caudal level of a lesion. A disease process affecting the midbrain manifests clinically as diplopia, ptosis, and a dilated pupil (CN III, IV). Lesions lying in the pons present with facial weakness (CN VII), horizontal diplopia (CN VI), vertigo, nystagmus and hearing loss (CN VIII), jaw weakness (CN V), and facial anesthesia to light touch (principle sensory nucleus of the trigeminal nerve). Dysphonia, dysarthria, dysphagia, and facial anesthesia to pain and temperature are suggestive of a medullary lesion.

Broadly speaking, motor deficits (affecting the limbs, ocular muscles, and tongue), sensory loss to light touch, vibration and joint position (medial lemniscus), and internuclear ophthalmoplegia (INO) tend to occur with more medial lesions. INO occurs with lesions disrupting the median longitudinal fasciculus. In this condition, the affected eye fails to adduct, whereas the contralateral eye abducts with a nystagmus. Lateral lesions are more likely to cause loss of thermal and pain sensations (spinothalamic pathways and CN V), ataxia (spinocerebellar pathways), and a Horner sign (sympathetic pathways). Cerebellar signs and symptoms ipsilateral to

CN involvement are commonly encountered with pontine lesions causing injury to the cortico-ponto-cerebellar pathways. Horizontal gaze palsy is commonly seen with pontine lesions and vertical gaze palsy with midbrain lesions. Palatal tremor is indicative of a lesion affecting the Guillain-Mollaret triangle, which includes the red nucleus, the dentate nucleus and the inferior olive [4]. Choreoathetosis and tremor may be seen with midbrain lesions involving the red nucleus.

Although strongly suggestive of BS involvement, symptoms and signs are rarely disease-specific. Nevertheless, some disease states have a distinctive tropism to certain BS structures and tend to spare others. This concerns, for example, viral infections and paraneoplastic syndromes, which almost invariably cause ataxia and often spare the motor and sensory tracts [5]. On the other hand, some forms of vasculitis, such as Behçet disease, have a tendency to cause motor and sensory symptoms with minimal ataxia [5]. Altered level of consciousness is suggestive of an infectious etiology, especially when it is associated with fever and meningismus [5]. In some cases, symptoms and signs of BS dysfunction can be fairly characteristic of a disease process. Opsoclonus-myoclonus (OpM), for instance, is often indicative of an infectious or paraneoplastic origin [6]. OpM is the combination of involuntary, arrhythmic and multi-directional saccades with myoclonic jerks in the limbs [6]. It is commonly accompanied by ataxia, tremor, and encephalopathy. Similarly, oculomasticatory myorhythmia (OMM) is pathognomonic of Whipple's disease (WD) of the CNS. It consists of a continuous pendular convergent-divergent nystagmus with concurrent contractions of the masticatory muscles and occasional rhythmic movements of the limbs [7]. OMM is often associated with supranuclear vertical gaze palsy. Deficient upward gaze is a typical feature of anti-Ma2 paraneoplastic encephalitis [29], whereas bilateral and symmetrical ophthalmoplegia is typical of Bickerstaff's brainstem encephalitis (BBE) [8].

Some disease states will produce lesions outside the BS. The occurrence of such lesions and their clinical features often provide valuable guidance as to the underlying origin of the BS lesion. Other disorders produce symptoms outside the CNS. This concerns, for example, CTDs, vasculitis, and paraneoplastic syndromes. Such symptoms can be present at the time of diagnosis or may develop later, occasionally several years after presentation. Their occurrence is also very helpful in securing a specific diagnosis.

10.3 Diagnostic Approach

The diagnostic approach to BS encephalitis involves a detailed history, a thorough physical examination, and an array of ancillary tests such as brain imaging, and serum and CSF analysis. In more difficult cases where the etiology remains unknown, a BS biopsy may be indicated.

Epidemiological data often offer a first clue as to the underlying etiology. While viral infections and demyelinating diseases are more frequent in the young, paraneoplastic diseases tend to affect older age groups [5]. Autoimmune diseases are more likely to affect women, but some exceptions exist. The immune status is also a key element to consider, since immunodeficiency increases the likelihood of an

infectious disorder. The presence of an antecedent febrile illness in the preceding weeks is supportive of an autoimmune disorder.

Although the history and physical findings provide some insight as to the underlying etiology, a specific diagnosis is rarely secured at this stage and various ancillary tests are usually ordered. Magnetic resonance imaging (MRI) is often the single most useful test to advance in the diagnostic process. Imaging abnormalities involving the BS are found in most patients but are rarely disease-specific. On the other hand, when supratentorial or spinal cord lesions are present, their radiological features could be fairly characteristic of a disease process; this is particularly true in demyelinating diseases. The absence of MRI abnormalities reliably excludes some entities such as demyelinating disorders. In other conditions such as paraneoplastic syndromes and BBE, MRI is frequently unremarkable [5]. Rarely, MRI characteristics of BS lesions are virtually diagnostic; chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is one such example [9].

Lumbar puncture is often recommended if not contraindicated by the presence of an intracranial mass effect. Most patients will have CSF abnormalities including pleocytosis, high protein levels, or low glucose. CSF analysis is pivotal when an infectious origin is suspected [5]. A white cell count exceeding 100 cells/μl is usually indicative of bacterial infection or certain forms of vasculitis such as Behçet disease [5]. Neutrophil predominance is often seen in Listeriosis and Behçet disease, whereas lymphocyte predominance is found in viral infections, tuberculosis (TB), and autoimmune diseases. Low glucose in usually indicative of an infectious etiology, such as Listeria and TB. The demonstration of intrathecal production of immunoglobulin G (IgG) and the presence of oligoclonal bands (OCB) are characteristic of demyelinating disorders and some CTDs.

Serum testing often adds little to the clinical, imaging, and CSF findings. However, in rare clinical settings, these can prove extremely helpful by detecting specific antibodies such as aquaporin 4 (AQ4), myelin oligodendrocyte glycoprotein (MOG), and GQ1b antibodies. When a specific diagnosis cannot be reached or a certain degree of uncertainty remains, stereotactic BS biopsy should be considered. When performed with appropriate MRI guidance and by experienced staff, this procedure is both safe and accurate [10]. However, obtaining tissue does not guarantee that a final diagnosis will be reached, because sampling errors and misinterpretation of histological findings can occur [11]. Despite all efforts, the etiology will remain unknown in up to 30% of cases [5]. Most cases of undefined BS encephalitis will eventually turn out to be immune-mediated, and it seems justifiable to offer such patients a trial of immunosuppressants under close clinical and radiological monitoring.

10.4 Etiologies

10.4.1 Brainstem Infections

Infectious lesions of the BS are collectively rare and include BS abscess and encephalitis. Infectious diseases can be further subdivided by etiology: bacterial, viral, fungal, and parasitic. Before these pathogens can infect the BS, they first need

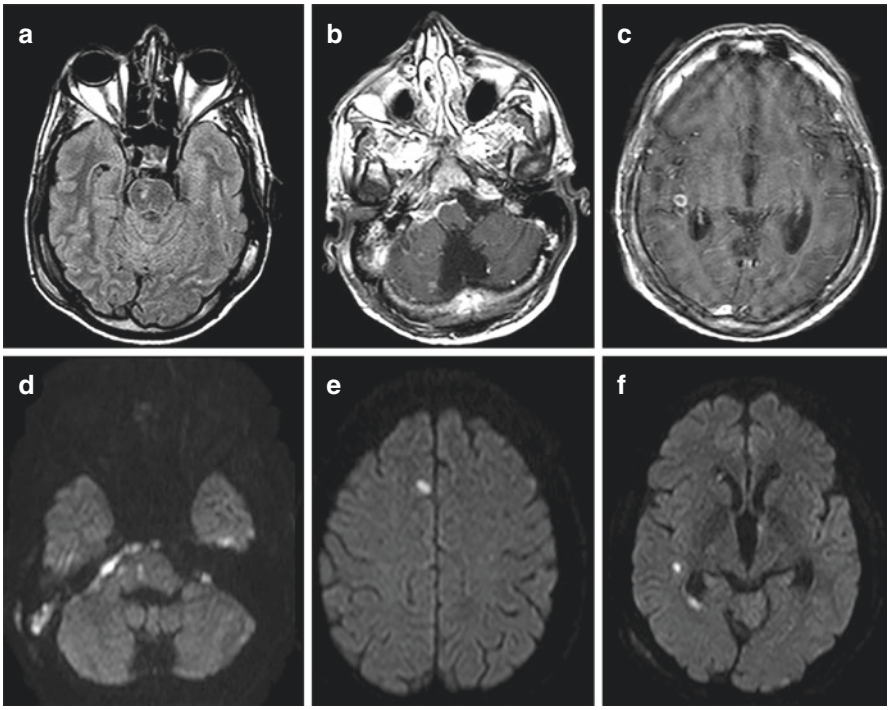

Fig. 10.1 Patient with right-sided mastoiditis and multiple brain micro-abscesses. (**a**) Axial FLAIR image showing a right paramedian pontine abscess. (**b**) Post-contrast axial T1-weighted image showing right-sided mastoiditis and leptomeningeal enhancement. (**c**) Postcontrast axial T1-weighted image showing a ring-enhancing lesion at the supratentorial level. (**d**) Empyema in the right prepontine cistern showing restricted diffusion. (**e**, **f**) DWI showing central restricted diffusion within the supratentorial lesions

to travel and gain access to the CNS. The most common portal of entry is the hematogenous route. Alternatively, some pathogens, such as bacteria, can also gain access to the brain by direct extension from a contiguous focus, such as sinusitis, otitis media, and mastoiditis (Fig. 10.1). Neurosurgical procedures and trauma, by breaching the integrity of the skull and meninges, also allow easy access to the CNS. The last portal of entry is nerves, whereby the pathogen travels along the peripheral nerve and bypasses the defense mechanisms of the CNS. One classical example is the varicella zoster virus (VZV). Regardless of the route, once the pathogen enters the brain, it sets off an inflammatory reaction; many of the manifestations and complications of CNS infections are attributed to the immune response mounted against the pathogen rather than its direct effect on brain tissue. Occasionally, infectious agents trigger an immune reaction directed against the CNS itself, a condition known as postinfectious encephalitis. In this condition, no evidence of direct invasion of the pathogen can be found. In rare cases, the infectious agent invades the brain's vasculature, a condition known as infectious vasculopathy.

10.4.1.1 Brainstem Abscess

Clinically, BS abscesses behave like a brainstem mass with focal neurological symptoms and signs, with or without signs of increased intracranial pressure. The onset is typically subacute. The most frequent presenting symptoms in decreasing order are headache, diplopia, hemiparesis, and nausea/vomiting [12, 13]. Although the presence of fever should alert to the infectious nature of the underlying lesion, it is present in fewer than a third of the cases [13]. In an afebrile patient, the clinical presentation is no different from other space-occupying lesions, and the distinction between an abscess and a tumor can be difficult. This is compounded by the fact that white blood cell count can be normal in roughly 50% of patients with BS abscesses [13]. Brain MRI plays a pivotal role in the diagnosis and management of BS abscesses; these are recognizable by their round shape, ring-enhancement, and varying amount of perilesional edema (see Fig. 10.1). MRI is usually able to distinguish abscesses from other ring-enhancing lesions such as tumors and tumefactive inflammatory lesions. Brain abscesses are characterized by central restricted diffusion indicating the presence of a fluid with high protein content (pus), lack of restricted diffusion of the enhancing part, and a T2-hypointense capsule [11]. MRI findings may differ depending on the patient's immune status [14]; this concerns contrast enhancement and the degree of edema, which seem to parallel the white cell count. With less severe immunosuppression, the host's defense system is able to mount an immune response and isolate the agent. This results in nodular or ring-enhancement of the lesion [14]. Lumbar puncture is not recommended and may even be contraindicated because of the risk of herniation [15].

Pyogenic Brain Abscess Pyogenic brain abscesses as a whole have become less frequent since the widespread use of antibiotics. They rarely localize to the brainstem (mostly the pons) and represent fewer than 1% of brain abscesses [12]. They reach the BS by direct spread from a contiguous site or by hematogenous seeding. Spread from a contiguous site generally causes a solitary lesion, whereas hematogenous spread typically causes multiple CNS abscesses. The most common underlying infectious agents are the Streptococcus species, Staphylococcus species, and TB [13]. Immunocompromised hosts can have a vast array of pathogens, from the usual organisms to other more unusual pathogens such as Listeria [16] and Nocardia [17].

The treatment options for a solitary BS abscess include stereotactic drainage, open microsurgical excision, or antimicrobial agents alone. Microsurgery and stereotactic aspiration help in establishing a diagnosis, identifying the causative agent, and relieving the mass effect. Stereotactic drainage has a favorable safety profile and has become the surgical option of choice in many centers [18]. Hydrocephalus is treated by insertion of a temporary or permanent CSF draining shunt. For patients with a small lesion and mild neurological deficits on presentation, medical treatment alone is a valid option, especially if the abscess is deep-seated and difficult to access surgically. If the patient fails to improve or deteriorates, then drainage and identification of the underlying organism becomes essential. The outcome is variable and is dependent on several factors including the severity of the neurological

deficit on admission and the treatment regimen (medical treatment alone versus surgery) [13]. The majority of patients will eventually recover with no or mild neurological sequelae [13].

Tuberculous Brain Abscess TB should be considered in endemic regions or immigrants originating from these regions. TB brain abscess is a rare form of CNS TB and may occur in the absence of signs of active systemic infection [19]. More commonly, CNS TB manifests as a single or multiple tuberculomas. Tuberculomas are caseating granulomas rather than true abscesses. Tuberculomas may affect the BS and present as a solitary mass, especially in children [20, 21]. MRI findings characteristically show an outer hyperintense rim (representing the cellular infiltrate), a hypointense inner region (representing the central necrotic components), and perilesional edema. Contrast enhancement is rather patchy, and the margins are ill-defined [22]. The diagnosis can be challenging since more than half of the cases have no evident systemic signs of TB [23]. This is compounded by the fact that tuberculomas can develop or paradoxically grow during anti-TB treatment [24]. Treatment is based on anti-tuberculous drugs. The addition of steroids often offers symptomatic relief. There is no consensus regarding the optimal duration of treatment, which is usually dictated by the clinical and radiological responses.

Parasitic Brain Abscess Parasitic infections should be considered in endemic regions or immigrants originating from these regions. Cysticercosis, a condition caused by the larvae of Taenia solium, classically presents with multiple supra- and infratentorial abscesses [25]. Although neurocysticercosis can cause almost any neurological symptom, late-onset epilepsy and intracranial hypertension are its most common manifestations [25]. BS cysticerci most often appear as small, well-defined, round enhancing lesions [25]. These primarily localize to the midbrain and tend to have a good prognosis if promptly treated with cysticidal drugs [26]. Rare cases of isolated BS abscesses have been described in the literature [26].

In immunocompromised patients, CNS toxoplasmosis is always a consideration. Toxoplasmosis is caused by the intracellular protozoan parasite Toxoplasma gondii [27]. The clinical disease usually results from the reactivation of a latent infection during immunosuppression. The clinical manifestations are protean and most often include headaches, confusion, and focal neurological findings including hemiparesis, ataxia and CN palsies [27]. Typical MRI findings include multiple ring-enhancing lesions involving the basal ganglia and cerebral/cerebellar hemispheres with perilesional edema [27]. Solitary lesions are not uncommon and occur in roughly 20% of cases [27–30]. BS lesions are rare and tend to affect the midbrain [30, 31], and solitary BS lesions are exceptional [30, 31]. Confirming the diagnosis of CNS toxoplasmosis can be challenging. High titers of IgG anti-toxoplasma antibodies are helpful; however, the results need to be interpreted with caution given the high seroprevalence in the general population and the possibility of false-negative results [27, 32]. Some studies suggested the utility of polymerase chain reaction (PCR) on the CSF samples [33]. Occasionally, the only simple means of confirming the diagnosis is a

therapeutic trial with anti-toxoplasma medications. Treatment should be initiated early and consists of pyrimethamine and a sulfonamide. The outcome is not always favorable, especially in severe cases, where up to 50% of patients are expected to have a poor outcome (severe residual disability or death) [34]. Bad prognostic factors include profound immunosuppression and impaired consciousness [34]. Other parasitic infections of the BS are rare and include Amoebiasis [35] and Schistosomiasis [36].

Fungal Brain Abscess Fungal infections can also disseminate to the CNS, usually by the hematogenous route [37, 38]. The most frequently identified agent is the Aspergillus species followed by the Candida species [37, 39]. Fungal CNS infections are mostly seen in immunosuppressed patients but have also been described in patients with no clear defect in the immune system. BS involvement is exceedingly rare.

10.4.1.2 Brainstem Encephalitis

There is a long list of pathogens that can cause BS encephalitis, including viral, bacterial, and fungal agents. The clinical manifestations are rarely disease-specific. On the other hand, epidemiological features often help in narrowing the broad differential diagnosis. Key elements include age at onset, immune status, season during which the disease was contracted, geographic location, travel and exposure history, contact with animals, similar cases in the family or neighbors, and known cases of encephalitis in the surrounding. The patient's occupation, hobbies, and vaccination history are other important factors to consider. Physical examination can provide some insight regarding the underlying pathogen. For instance, the presence of an exanthem or enanthem are supportive of some forms of viral encephalitis. The diagnosis is often supported by an elevated white blood cell count and protein levels in the CSF, and serology helps in pinpointing the underlying pathogenic agent. Because IgM antibodies do not readily diffuse across the blood-brain barrier, the finding of IgM antibodies by enzyme-linked immunosorbent assay (ELISA) is diagnostic of CNS disease, though false-negative results are not uncommon [40]. IgM antibodies by ELISA testing are available for several pathogens including the VZV and flaviviruses. PCR assays are useful in diagnosing herpes encephalitis and have a high sensitivity and specificity (95–99%), although false-positive and false-negative tests can occur [40]. Imaging findings are often nonspecific. The outcome is dependent on the underlying infectious agent. Although most viral infections are self-limited, some have a particularly poor outcome if the treatment is delayed; this concerns, for example, the herpes simplex virus (HSV) and the VZV BS encephalitis. Bacterial and parasitic BS infections are almost uniformly fatal if untreated. Patients with BS encephalitis often require supportive care to ensure oxygenation, airway protection, and circulatory support. Close monitoring for cerebral edema, increased intracranial pressure, epileptic seizures and acute hydrocephalus is recommended.

Viral Encephalitis Virtually any viral encephalitis can spread to the BS. Host factors affecting the susceptibility to a particular pathogen include the immune status, age, and various genetic factors. When viral encephalitis is suspected, diagnostic efforts should initially focus on differentiating HSV from the other causative agents. To this end, serological tests are pivotal. These include serological testing of CSF IgM, as well as PCR and reverse-transcriptase PCR assays of a CSF sample to identify DNA and RNA viruses, respectively. It is recommended to start empirical acyclovir therapy in all patients with suspected encephalitis [40] until the underlying pathogen is identified and/or HSV encephalitis is excluded. The addition of glucocorticoids is a common practice but is of uncertain benefit [41]. MRI findings in BS encephalitis are often non-specific with patchy areas of increased T2-weighted signal and variable mass effect [42–45]. Lesions are typically non-enhancing [44, 46] or display minimal patchy enhancement [45]. Locations outside the BS such as the cortex, basal ganglia, thalamus, and cerebellum are often affected [42, 44–46]. Spinal cord lesions centered on the ventral horns have been described in West Nile virus and enterovirus (EV) encephalitis [44, 47]. Hippocampal involvement is typical of HSV encephalitis [48] but has also been described in Japanese encephalitis [49].

HSV is the most common cause of viral encephalitis in general and accounts for 50–75% of the identified viral cases [41]. Infection is non-seasonal, affects both sexes equally, and can occur at any age. HSV characteristically involves the temporal/cingulate cortices but only rarely the infratentorial compartment [43, 50]. BS involvement in HSV is typically associated with evidence of supratentorial involvement [51], but restricted BS infection has also been reported [52]. Although HSV encephalitis is predominantly caused by HSV-1, it has also been described with HSV-2, usually as a complication of genital herpes [53]. BS involvement without any evidence of genital herpes infection has also been described [54].

EV71 is another cause of BS encephalitis [47, 55]. EV71 is largely restricted to infants and classically presents as hand-foot-mouth disease or herpangina [56]. EV71 can also cause epidemics of aseptic meningitis, BS encephalitis, encephalomyelitis, and acute flaccid paralysis. BS encephalitis is the most common neurological manifestation. Children usually present with ataxia, myoclonic jerks, nystagmus, CN dysfunction, and tremor [57]. MRI shows abnormal areas of T2-hyperintense signal in the BS in most patients. These findings characteristically involve the dorsal pons and medulla oblongata [58]. The outcome is generally good and most patient fully recover in a few days [57]. Severe cases are usually treated with intravenous immunoglobulins (IVIg) and corticosteroids despite the lack of evidence to support this approach [59]. EV68 is another EV linked to BS involvement. This virus has a distinctive tropism to the anterior horn cells and BS motor nuclei leading to flaccid paralysis and CN dysfunction [60]. Most children who develop neurological complications are left with some degree of motor weakness and CN dysfunction including permanent dysphagia [60].

Epidemics of BS encephalitis have been described with Japanese and St. Louis encephalitis viruses [61]. These infections preferentially affect the midbrain and more particularly the substantia nigra (SN), with parkinsonism as a classical sequela

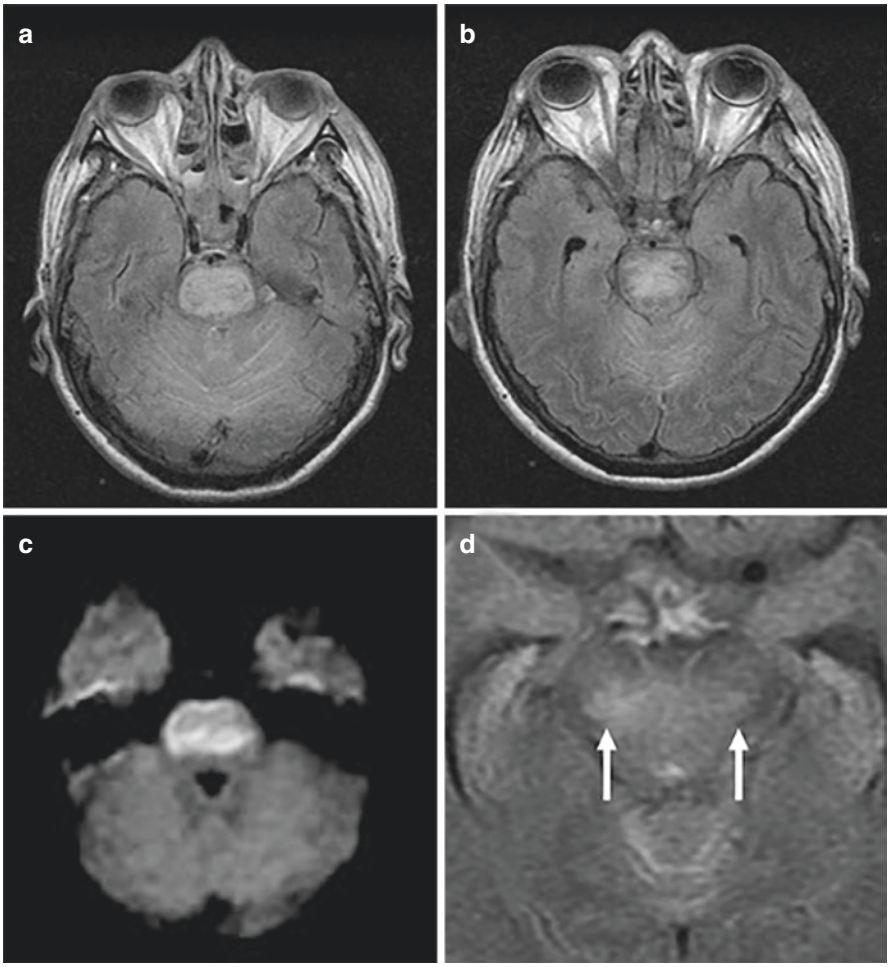

Fig. 10.2 Brainstem encephalitis caused by West Nile virus. (**a**, **b**) Axial FLAIR images of the brainstem, showing diffuse central spread at the midbrain-pons region. (**c**) Axial DWI, at the same level, demonstrating avid restricted diffusion. (**d**) Axial FLAIR image showing bilateral involvement of the substantia nigra, more pronounced on the right (arrows)

[62, 63]. Sporadic cases of SN involvement have been reported with Epstein-Barr virus (EBV) and West Nile virus infections [64, 65] (Fig. 10.2). BS encephalitis has been rarely reported with other viral infections such as adenovirus [45], Nipah virus [66], influenza A virus [67], and VZV [68].

As opposed to classical viral encephalitis, which has an acute onset and a rapid clinical course, some viral infections follow a slower clinical course. Progressive multifocal leukoencephalopathy (PML) is a subacute encephalitis caused by the John Cunningham (JC) polyomavirus, occuring almost exclusively in immunocompromised patients [69]. This includes patients with hematological malignancies, those

infected with the human immunodeficiency virus (HIV), or those treated with various immunosuppressant drugs such as natalizumab for multiple sclerosis (MS) [70]. Clinically, the disease manifests as cognitive decline with cortical symptoms and signs. MRI typically displays multiple subcortical areas of high signal on fluid-attenuated inversion recovery (FLAIR) images in both hemispheres. Isolated BS PML is very rare and poses a serious diagnostic challenge [69, 71]. The challenge is even greater when BS PML occurs in the setting of MS, where it can masquerade as an MS relapse [72]. Early marked T1 hypointensity, diffusion-weighted imaging (DWI) hyperintensity, and close MRI follow-up may distinguish new MS activity from PML [72]. Treatment is based on reversal of immunosuppression whenever possible and initiation of highly active antiretroviral therapy in HIV-infected patients. Prognosis is often poor.

Bacterial Brainstem Encephalitis Bacterial infections rarely localize to the BS with the exception of Listeria monocytogenes, which affects the BS in 9% of cases of CNS infections [73]. Predisposing factors for listeriosis are age >50 and immunosuppression. Neurological manifestations usually follow a prodrome of fever, headache, nausea, and vomiting. Signs and symptoms may also include single or multiple asymmetrical CN palsies, cerebellar signs, hemiparesis, hypoesthesia, and impairment of consciousness [74, 75]. MRI displays hyperintense, patchy lesions within the BS and/or multiple microabscesses [74]. CSF findings are often nonspecific with lymphocytic pleocytosis and negative cultures in more than half of the cases [74]. Blood cultures are more likely to be positive in this setting [74]. Early empiric treatment with ampicillin is crucial in patients at risk. Prognosis is often poor with an overall mortality of 50% [74].

In rare cases, bacterial infections can follow a more subacute clinical course. WD is a systemic bacterial infection caused by Tropheryma whipplei. It classically manifests as gastrointestinal symptoms, weight loss, and arthropathy [76]. CNS manifestations occur in 10–50% of patients and can precede other manifestations of the disease [76, 77]. These include cognitive decline, cerebellar ataxia, myelopathy, hypothalamic-pituitary axis dysfunction, and various BS syndromes [77, 78]. The latter can present as the pathognomonic finding of OMM or oculofacial-skeletal myorhythmia, which generally occur in combination with supranuclear vertical gaze palsy [7]. Focal MRI abnormalities are observed in 50% of patients, ranging from focal lesions without mass effect to multiple enhancing lesions with mass effect [7] (Fig. 10.3). Neuro-WD can be diagnosed using PCR applied to a CSF sample. Neurological symptoms often respond dramatically to antibiotics; however, they may recur after discontinuation, prompting prolonged treatment periods that may extend up to 1 year [76].

10.4.1.3 Postinfectious Brainstem Encephalitis

BBE is a rare postinfectious disorder, where the inflammatory process is typically confined to the BS. BBE is clinically characterized by progressive impairment of consciousness along with ataxia and bilateral external ophthalmoplegia [8]. Some

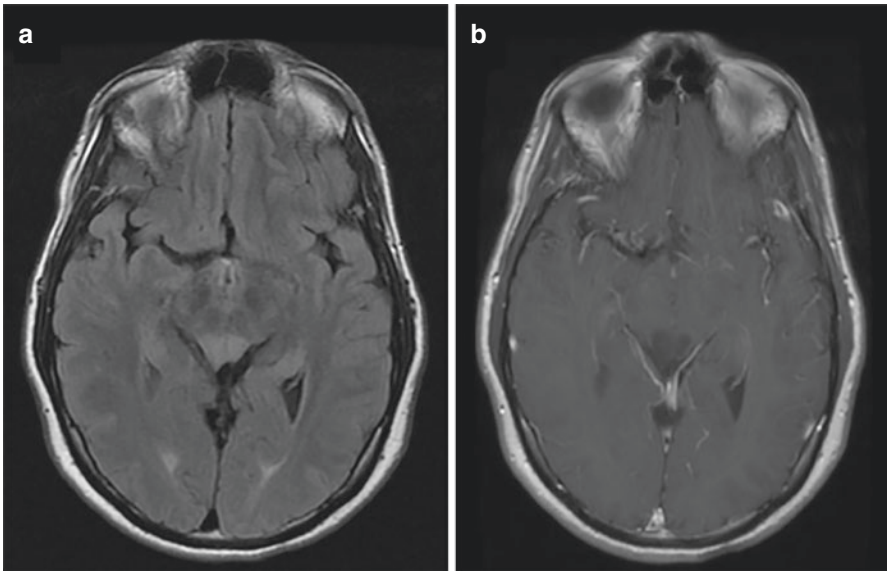

Fig. 10.3 Brainstem involvement in a patient with biopsy-proven Whipple's disease. (**a**) Tectal hyperintensity on FLAIR images. (**b**) Lack of enhancement on post-contrast T1-weighted images

additional features were occasionally described such as bilateral facial palsy, pupillary abnormalities, bulbar palsy, and generalized limb weakness [79]. The disease follows a monophasic course with a subacute onset and a favorable outcome in most cases. BBE is usually preceded by an infectious event, most often an upper respiratory tract infection [79]. CSF analysis shows pleocytosis in roughly half of the patients. Brain MRI is usually normal but may occasionally show T2-weighted BS anomalies [8]. IgG anti-GQ1b antibodies are highly specific for this disorder but can be absent in up to one-third of the cases [80]. These antibodies are also found in Miller-Fisher syndrome, a variant of Guillain-Barré syndrome characterized by ataxia, ophthalmoplegia and areflexia. Whether these two entities represent a spectrum of the same disorder remains unsettled. There are no evidence-based recommendations for the treatment of BBE. Patients are typically offered immunotherapy such as plasma exchange therapy, IVIg, or high-dose steroids [79]. The clinical outcome is usually good.

Acute disseminated encephalomyelitis (ADEM) is another disease state believed to be caused by an immune response mounted against an infectious agent. ADEM is preceded by a bacterial or viral infection in 50–75% of cases, most frequently a nonspecific upper respiratory tract infection. A long list of viral infections has been associated with ADEM, including influenza, EV, hepatitis A, HSV, EBV, measles, mumps, rubella, VZV, and cytomegalovirus [81]. It may also develop after vaccination [82]. ADEM affects children more often than adults. Onset is acute with rapid clinical progression, often with fever and occasionally meningismus [1]. The inflammatory process is usually multifocal and primarily affects the white matter of

the brain and spinal cord. The clinical manifestations include altered mental status and multifocal neurological symptoms or signs. The infratentorial compartment is frequently affected in ADEM, especially in children who often present with signs and symptoms attributable to BS/cerebellar dysfunction (ataxia, oculomotor disturbance, and dysarthria) [83]. Typical MRI findings include patchy, asymmetrical, bilateral subcortical white matter confluences seen on the T2/FLAIR-weighted images, with ill-defined margins, limited mass effect, and variable contrast enhancement [1]. CSF findings include normal glucose, increased protein level, and lymphocytic pleocytosis. Serum testing is positive for MOG antibodies in up to 59% of cases [84]. The presence of these antibodies seems to portend a better clinical and radiological outcome. Currently, high-dose intravenous corticosteroids are the mainstay of treatment. Plasma exchange therapy and IVIg can be used in non-responders [1]. The disease usually follows a monophasic course and most patients achieve a good recovery with no or little residual disability [1].

10.4.1.4 Infectious Brainstem Vasculitis

Some infectious agents have a tropism for vessels. Among the various bacterial agents, Treponema pallidum (T. pallidum) and Borrelia burgdorferi are known to affect CNS vessels. T. pallidum vasculopathy (meningovascular syphilis) usually presents during the secondary stage of syphilis and manifests as encephalopathy, cognitive decline, focal neurological findings, and CN abnormalities [85]. The most frequently involved arteries are the middle cerebral artery and branches of the basilar artery [86]. BS infarcts are found in 14% of patients with neurosyphilis [85]. When the diagnosis is suspected on clinical grounds, serological testing helps in confirming the diagnosis. Treatment consists of intravenous penicillin G for 10–14 days.

Cerebral vasculitis is also a complication of Lyme neuroborreliosis, a multisystem infection caused by Borrelia burgdorferi. The disease tends to affect large and medium-sized vessels including the vertebral and basilar arteries and their branches [87]. This results in single or multiple areas of stenosis and dilatation, leading to ischemic stroke. There is a strong predilection towards the posterior cerebral circulation, especially in children [88]. Appropriate antibiotic treatment often results in a favorable clinical outcome.

Viral agents can also cause CNS vasculitis. VZV vasculopathy is a rare complication of chickenpox in children and herpes zoster in adults [89]. This condition leads to ischemic and hemorrhagic strokes that classically occur 7 weeks after herpes reactivation, but longer intervals have been described. Although VZV vasculopathy is classically a complication of herpes zoster ophthalmicus and involves the anterior circulation, it has been described in the posterior circulation following reactivation of VZV in the cervical region [90]. Treatment of VZV vasculopathy is with anti-viral agents.

10.4.2 Brainstem Inflammatory Lesions

Brainstem inflammatory lesions fall into one of two broad categories: (1) primary inflammatory diseases of the CNS and (2) systemic diseases, where CNS involvement is only one of many manifestations of the disease. In the latter case, CNS manifestations often occur in the setting of a known disorder, and the diagnosis is usually straightforward. Alternatively, neurological symptoms can precede other manifestations of the disease, and establishing the correct diagnosis becomes significantly more challenging. In this setting, the demonstration of subclinical symptoms/signs or specific biological markers can be valuable clues as to the underlying etiology.

10.4.2.1 Idiopathic Inflammatory Demyelinating Diseases of the Brainstem

This group represents a broad spectrum of disorders with variable severity, disease course, lesion distribution, and outcome. MS is the most representative form of idiopathic inflammatory demyelinating diseases of the brain (IIDB). Other entities include neuromyelitis optica (NMO), ADEM, and rare MS variants, such as Marburg disease, Balo concentric sclerosis, and Schilder disease [1]. Although the BS is a frequent target for demyelination, lesions in other parts of the CNS are usually present at the time of presentation. In such cases, the diagnosis of IIDB is relatively straightforward. Rarely, BS lesions occur in isolation, and establishing the correct diagnosis becomes much more challenging. In these cases, more advanced imaging techniques, serum testing, and, in more difficult cases, brain biopsy may be necessary.

Multiple Sclerosis MS is a chronic demyelinating CNS disease, characterized pathologically by areas of inflammation, demyelination, axonal loss, and gliosis scattered throughout the CNS [91]. The clinical course of MS can follow several patterns. A relapsing-remitting course (RRMS) accounts for 85% of cases and is characterized by recurrent clinical events that recover to a varying degree [92]. Evidence of dissemination in space (DIS) and dissemination in time (DIT) of the disease process is a prerequisite for diagnosis. Accordingly, the diagnosis of MS can be secured clinically by two clinical relapses occurring at least 30 days apart (i.e., DIT) and affecting separate sites within the CNS (i.e., DIS). A first clinical event consistent with demyelination is called a clinically isolated syndrome (CIS) [93]. Short of a second event, the diagnosis of MS cannot be secured on clinical grounds at this stage. In this case, MRI and CSF findings can replace some clinical criteria. MRI showing subclinical areas of demyelination that fulfill the criteria for DIS ($\geq$1 lesion in $\geq$2 areas typical for MS) and DIT (simultaneous presence of enhancing and non-enhancing lesions) can substitute for a second clinical event [94]. For patients with CIS who meet the criteria of DIS, the presence of CSF-specific OCB can substitute for the demonstration of DIT by MRI [94].

Demyelinating lesions frequently involve the BS in MS. Relapses typically present sub-acutely, with progressive worsening over hours or days, a plateau lasting for days or weeks, followed by gradual improvement. Symptoms are those of nonspecific BS dysfunction, such as diplopia, facial sensory symptoms, and gait disturbance [95]. Other more characteristic symptoms include bilateral INO, continuous facial myokemias, and Uhthoff phenomenon (transient worsening of symptoms and signs when core body temperature increases, such as after exercise or a hot bath). The occurrence of trigeminal neuralgia in a young patient, especially when bilateral, is also suggestive of MS [96].

When a BS syndrome occurs in the setting of established MS, the diagnosis is usually straightforward. On the other hand, when BS dysfunction is the first manifestation of MS, further testing is usually needed to secure the diagnosis. MRI is the single most useful test in this setting by demonstrating that the BS lesion is consistent with a demyelinating event (Fig. 10.4). Of equal importance, MRI can confirm the diagnosis if it demonstrates the presence of subclinical lesions that meet the criteria for DIT and DIS. Supratentorial lesions have a predilection to localize to the periventricular white matter and tend to have an ovoid configuration, with the major axis perpendicular to the ventricular surface (see Fig. 10.4d). Cortical/juxtacortical and callosal lesions are also typically seen in MS. Acute lesions enhance with contrast administration. When no additional lesions outside the BS can be demonstrated, a yearly follow-up study is recommended. Occasional patients show no subsequent evidence of clinical activity and follow a monophasic course [95].

In the BS, MS lesions have the propensity to affect the peripheral aspect of the pons and the middle cerebellar peduncle while sparing the central white matter [97] (see Fig. 10.4). Compared to MS lesions in other locations, BS lesions tend to be less bright on T2-weighted images and more diffuse. MS can rarely present as a solitary, tumor-like mass. These so-called tumefactive MS lesions often display mass effect, perilesional edema, and/or ring-enhancement with gadolinium contrast and can be easily mistaken for a glioma or a cerebral abscess. MRI findings that favor a demyelinating lesion include open ring-enhancement directed towards the cortical surface, relatively little mass effect relative to size, ring-shaped diffusion restriction on DWI, and a T2-hypointense rim [1, 98]. The changes on DWI tend to evolve rapidly as opposed to tumors and abscesses [1]. Tumefactive MS lesions mostly occur in the supratentorial regions but involves the BS in up to 24% of cases [99]. Recognition of this MS variant is important to avoid unnecessary surgical intervention.

The importance of early diagnosis of MS cannot be overemphasized since early initiation of immunotherapy is an important determinant of long-term outcome [100]. Relapses are treated with high-dose intravenous steroids.

Neuromyelitis Optica Spectrum Disorder NMO is a more anatomically restricted form of IIDB characterized by severe unilateral or bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM). The term NMO spectrum disorder (NMOSD) is currently favored to avoid the distinction between phenotypes not completely expressed at presentation (restricted forms of the disorder such as recurrent optic neuritis, relapsing transverse myelitis) and classical NMO. NMOSD also includes some BS and encephalitic presentations. The disease course is characterized

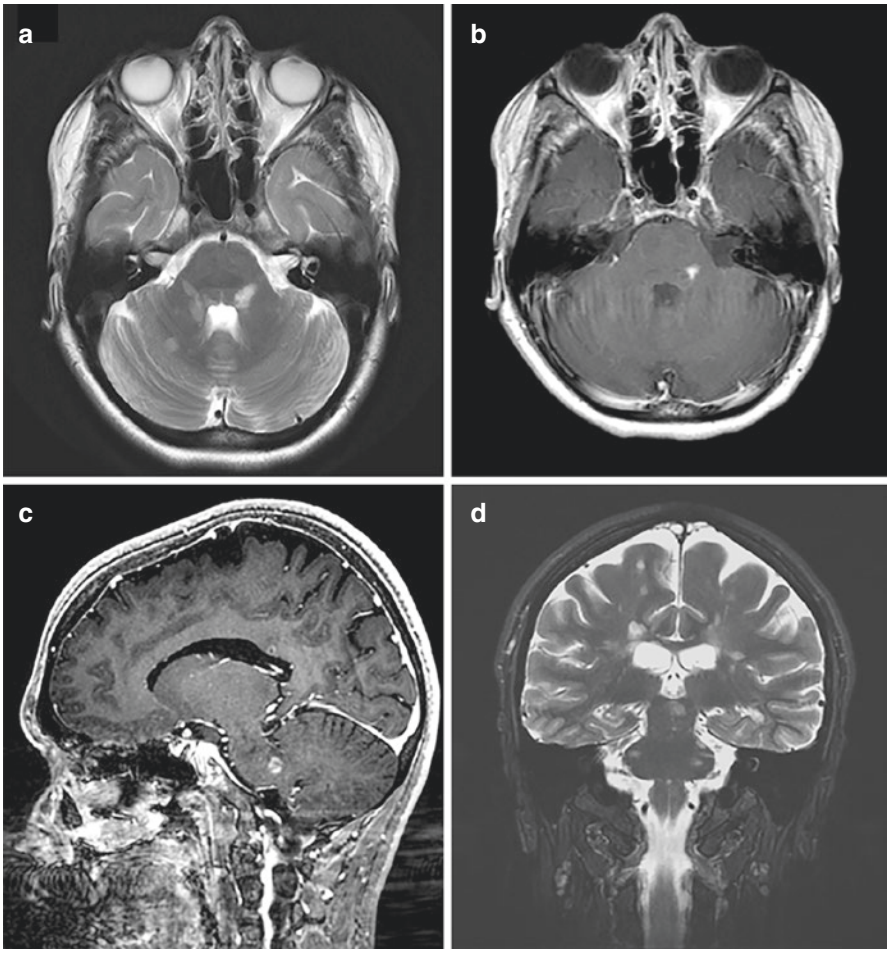

Fig. 10.4 Left brainstem lesion in a patient with multiple sclerosis. (**a**) Axial T2-weighted image. (**b**, **c**) Same lesion showing abnormal enhancement on post-contrast T1-weighted images, indicating an active lesion. (**d**) Multiple associated lesions with typical distribution in the subcortical, periventricular and ponto-medullary white matter on coronal T2-weighted images

by relapses of variable frequency. MRI characteristically shows LETM (involving more than 3 vertebral levels) and/or large areas of hyperintense signals of the optic nerve/chiasma. MRI changes outside of these disease-defining regions are common [101] (Fig. 10.5). These changes have the tendency to distribute near the ventricular system, an area rich in AQP4, which is the target antigen in NMO. Common locations include the thalamus, hypothalamus, and BS around the cerebral aqueduct [1]. CSF analysis shows high protein levels and pleocytosis. As opposed to MS, OCB are only seen in 30% of patients [102]. Serum is positive for AQP4 antibodies in 70–80% of cases [103]. AQP4 is a cell membrane water channel that is highly expressed on astrocytic foot processes. Up to one third of AQP4-seronegative NMOSD patients have MOG antibodies [104]. These patients have less acute

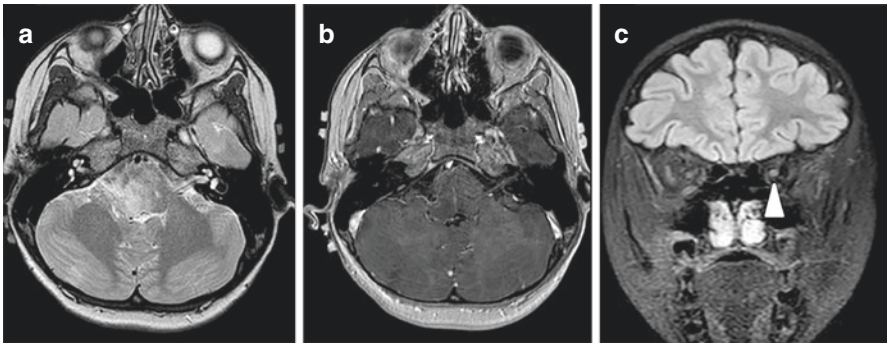

Fig. 10.5 Brainstem involvement in aquaporin 4-positive neuromyelitis optica. (**a**) Signal abnormality within the pons on axial FLAIR images. (**b**) Absence of enhancement on axial post-contrast T1-weighted images. (**c**) Left-sided optic neuritis on coronal T2-weighted images

attack-related disability and relatively less relapses than those who are AQP4-positive [1].

Symptoms related to BS involvement occur in around 40% of cases, especially in children who are AQP4-positive [105]. Common BS manifestations include diplopia, dysarthria, dysphagia, facial weakness, and ataxia [106]. NMOSD has a propensity to affect the area postrema leading to intractable hiccough, nausea and vomiting [107, 108]. These symptoms may herald the onset of NMO and pose a diagnostic challenge. Lesions involving the medullary respiratory center occasionally lead to a life-threatening respiratory compromise [109].

Management of relapses is with high-dose intravenous cortisone. Patients who fail to improve on steroids might benefit from plasma exchange. Given the high morbidity of relapses in NMOSD, early initiation of immunosuppressants is recommended as a preventive measure. These include azathioprine, methotrexate, mycophenolate mofetil, and rituximab. Disease-modifying treatments for MS seem to be poorly effective in NMOSD.

10.4.2.2 Connective Tissue Diseases (CTDs) and Vasculitis

Many CTDs have CNS manifestations, including BS dysfunction [110]. In most cases, however, there is no particular tropism for the BS. Sjögren's syndrome (SS) causes a broad spectrum of neurological manifestations, including focal BS lesions or BS encephalitis. Occasionally, these can be the first manifestation of the disease and precede the diagnosis of SS by up to 2 years [60, 111–113]. In this setting, the clinical and imaging features can mimic MS and cause significant diagnostic and therapeutic dilemmas. This is compounded by the fact that CSF often shows OCB in SS patients with MS-like lesions [114]. Systemic lupus erythematosus (SLE) can also manifest as focal or diffuse CNS lesions, including the BS [115–117]. Rarely, BS involvement can occur in isolation and precede other manifestations of the disease [117]. It is also important to mention that CTDs such as SLE and SS can coex-

ist with NMO [118]. This case scenario should be considered when LETM or optic neuritis occur in the setting of a known systemic inflammatory disease.

Similarly, most systemic vasculitis can involve the CNS, including Behçet disease, granulomatosis with polyangiitis (Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and polyarteritis nodosa (PAN) [110]. These entities have no predilection for the BS, except for Behçet disease (Fig. 10.6). Behçet disease is recognizable by its hallmark clinical

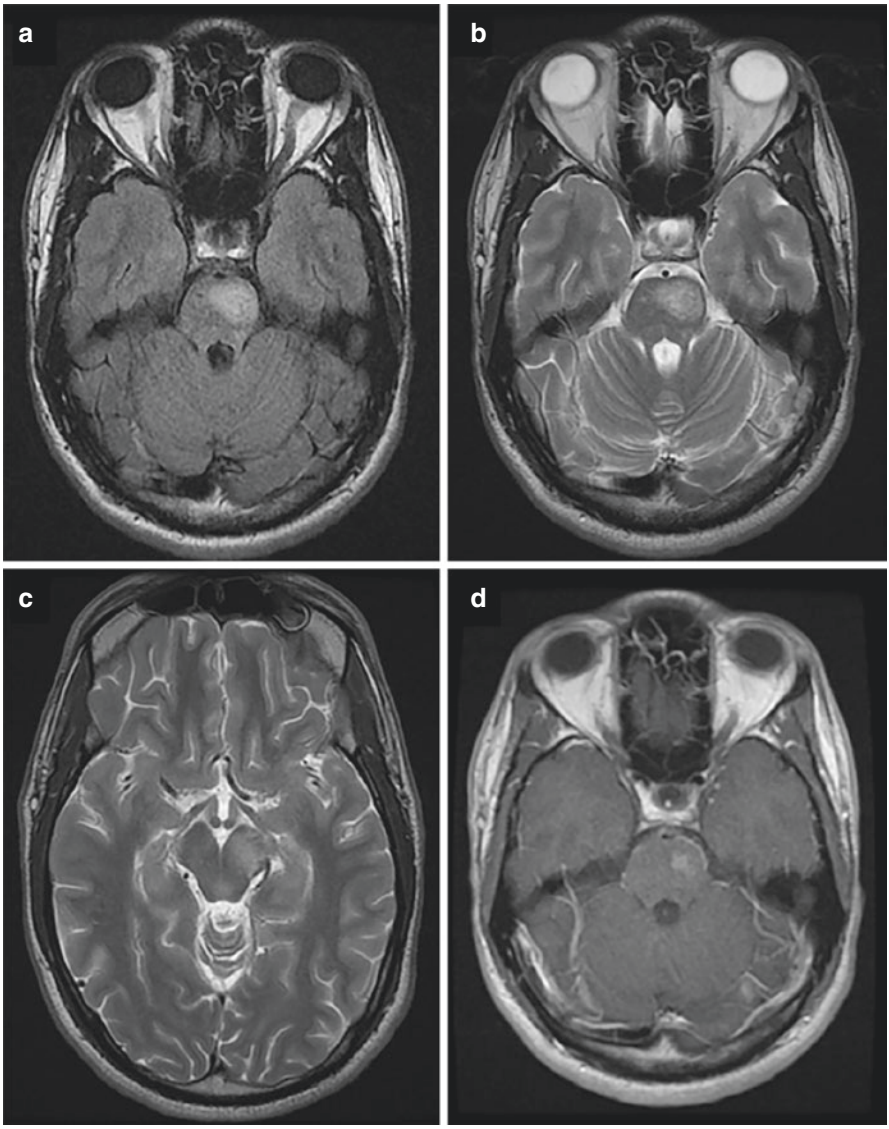

Fig. 10.6 Brainstem involvement in a patient with Behçet disease. (**a**, **b**) Axial FLAIR and T2-weighted images showing left pons involvement with surrounding edema. (**c**) Axial T2-weighted image showing spread of the disease to the left midbrain. (**d**) Central nodular enhancement of the lesion is seen on post-contrast axial T1-weighted images

signs that include uveitis, and oral-aphthous and genital ulcers. While this triad is virtually diagnostic, it is not always present at presentation. Behçet disease affects young adults, predominantly men, in their 3rd to 4th decade. Neurological complications occur in 5–14% of patients and usually occur a few years into the illness [119]. However, these may precede other manifestations of the disease in 6% of cases [120]. BS lesions most commonly affect the posterior aspect of the midbrain-diencephalic junction, characteristically sparing the red nucleus [121]. CSF typically shows slightly increased protein levels, no OCB, and mononuclear or polynuclear pleocytosis. Patients tend to respond favorably to steroids. Approximately 30–50% of patients with neuro-Behçet disease have a relapsing course [122]. Relapses or progressive disease are treated with immunosuppressant drugs.

Primary angiitis of the CNS (PACNS) is an organ-specific vasculitis affecting small-to-medium sized vessels of the brain and spinal cord [123]. In the absence of a specific serum marker of the disease, diagnosis is based on the demonstration of vasculitic findings either on angiography or on brain biopsy. Clinical manifestations depend on the involved CNS region. Headache is the most common symptom on presentation, followed by cognitive impairment and focal neurological deficits [123]. CSF findings are nonspecific and include mild pleocytosis and elevated proteins. MRI characteristically shows small cortical/subcortical infarcts, leptomeningeal enhancement, intracranial hemorrhage, and areas of T2-hyperintense signal. Less commonly, PACNS presents as BS lesions or as a solitary pseudo-tumoral mass [124, 125]. When the BS is the seat of such pseudo-tumoral lesions, accurate and timely diagnosis can be particularly challenging [124]. Prognosis is usually favorable with early immunotherapy [126].

As the name indicates, CLIPPERS is a chronic inflammatory disorder of the CNS responsive to steroids [9]. It is characterized by episodic BS symptoms, including cranial sensory abnormalities, diplopia, ataxia, and dysarthria [9]. The MRI signature of this condition is a punctate pattern of patchy gadolinium enhancement centered on the pons (Fig. 10.7). These lesions can also be seen in other parts of the BS, spinal cord, and cerebellum [9]. Although these findings are highly suggestive of the disease, they are not absolutely specific. Similar abnormalities have been described in other disorders such as BS lymphoma and gliomas [127, 128]. On the other hand, atypical cases presenting as a progressively expanding tumor-like lesion have been described [129]. BS biopsy shows prominent perivascular lymphocytic infiltrate. Most patients respond well to immunosuppressants; however, symptoms tend to recur with early tapering of steroids, and most patients require prolonged therapy [9].

10.4.2.3 Paraneoplastic Brainstem Encephalitis

Paraneoplastic diseases of the CNS are a group of immune-mediated disorders with a wide range of clinical manifestations. Although BS encephalitis is not a classical paraneoplastic syndrome, some antibodies have been clearly linked to BS dysfunc-

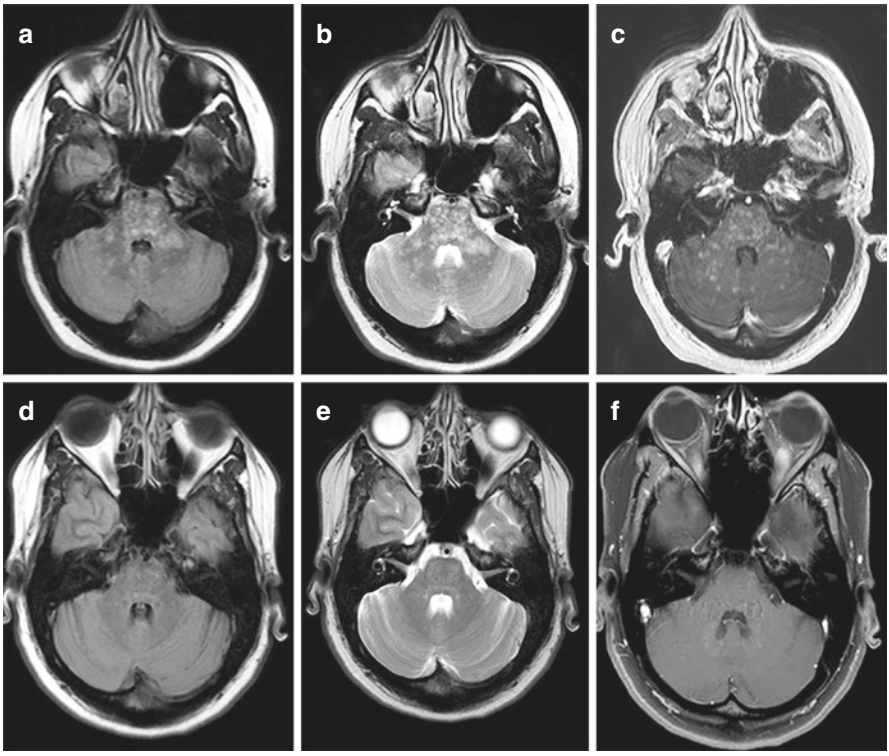

Fig. 10.7 Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Axial FLAIR (**a**), T2- (**b**) and post-contrast T1-weighted (**c**) images showing the typical multiple punctuate signal abnormalities, most prominent in the pons, but also involving the middle cerebellar peduncles and cerebellar hemispheres. After steroid administration, axial FLAIR (**d**), T2- (**e**) and post-contrast T1-weighted (**f**) images demonstrate marked resorption of the punctate signal abnormalities and enhancement pattern

tion. These include anti-Hu, anti-Ri, and anti-Ma2 antibodies, each resulting in a specific pattern of BS dysfunction. The onset is typically subacute, with rapid worsening and often devastating consequences.

Anti-Hu antibodies are classically associated with paraneoplastic encephalomyelitis, almost always in the setting of small cell lung carcinoma. The typical manifestation is extensive or multifocal encephalomyelitis. Early in the disease course, more focal syndromes can be seen, such as limbic encephalitis, cerebellar degeneration, or BS encephalitis [130, 131]. BS encephalitis is the predominant syndrome in 11% of cases [132]. This entity has a distinctive tropism for the medulla [131], and most patients present with dysphagia, dysarthria, and hypoventilation [131]. CN VI/VII palsy, vertical nystagmus, and ataxia are other possible manifestations [131]. MRI and CSF analysis are typically normal. The prognosis is usually poor despite immunotherapy and treatment of the underlying tumor.

Patients with anti-Ma2-associated BS encephalitis are clinically and radiologically distinct from those with the anti-Hu antibodies. In young men, it is almost exclusively associated with testicular germ-cell tumors, which can be microscopic and difficult to demonstrate [130]. In the older age group, the most common associated cancers are lung and breast cancers [133]. Anti-Ma2-associated encephalitis characteristically affects the limbic system, hypothalamus, and BS [130]. The presenting symptoms can result from the involvement of any of these regions and can progress to involve the others. BS encephalitis predominantly affects the midbrain and most commonly manifests as supranuclear vertical gaze palsy, followed by involvement of the oculomotor nuclei. Involvement of the other brain regions results in a variety of symptoms including excessive daytime sleepiness, narcolepsy, cataplexy, rapid eye movement (REM)-sleep abnormalities, hyperphagia, and memory impairment. Brain MRI may show T2-hyperintense lesions in the superior colliculi and periaqueductal region. Roughly one-third of patients are expected to respond to tumor resection and immunotherapy [133].

Anti-Ri antibodies also have a tropism for the BS [134]. These are the least common of the paraneoplastic auto-antibodies, mostly encountered in patients with breast and ovarian cancer. Patients typically present with signs of BS, cerebellar and spinal cord dysfunction. BS dysfunction often manifests as OpM, ophthalmoplegia, and facial sensory symptoms [134–136]. Treatment of the underlying cancer can lead to a decrease in the antibody titer and improvement of symptoms [134].

10.5 Conclusion

It is important to keep in mind that the differential diagnosis of a BS lesion is not limited to BS tumors, infections, and inflammatory/autoimmune disorders. Other disease states can also affect the BS such as hypertensive BS encephalopathy [137, 138], central pontine myelinolysis [139, 140], Wallerian degeneration [141], hepatic encephalopathy [97], and neurodegenerative diseases such as multiple system atrophy [142].

Non-neoplastic BS lesions span a wide range of pathologies, including infections, inflammatory, and autoimmune disorders. Broad and in-depth knowledge of the various disorders with possible BS manifestations is therefore essential to guide the diagnostic approach. The latter involves a detailed history, a thorough physical examination, and an array of ancillary tests such as brain imaging, and serum and CSF analysis. In more difficult cases where the etiology remains unknown, a BS biopsy may be indicated; the need for tissue diagnosis, however, has steadily dropped since the introduction and continuous optimization of imaging techniques and serum/CSF testing. This chapter addressed the various infectious and inflammatory disorders of the brainstem, with a particular emphasis on their clinical presentation, key radiological and laboratory findings, and general principles of management.

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