Selected Disorders of the Nervous System

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Meningitis

Background

Meningitis is defined as an acute inflammation of the meninges, which may result in significant morbidity and mortality. Meningitis may be caused by infectious agents (bacteria, viruses, parasites, and fungi) or may arise from a noninfectious etiology (cancer, systemic lupus erythematosus, certain medications, head injury, and brain surgery). When caused by an infectious agent, approximately one in four cases of meningitis is bacterial, with an additional 10 % due to fungus and other non-viral agents. The remainder is due to viruses. In the United States, bacterial meningitis occurs at a rate of 1.38 cases per 100,000 population per year, with a case fatality of approximately 15 %. The causative bacterial agent varies with age. Under 2 months of age, group B streptococcus is the most common bacterial agent, and in those 11–17 years of age, *Neisseria meningitides* is the most common bacterial agent. In all other pediatric age groups and in adults, *Streptococcus pneumonia* is the most common bacterial agent. Viral meningitis is most commonly caused by enteroviruses followed by herpes simplex virus type 2 and varicella zoster virus. The most common causes of fungal meningitis are *Cryptococcus neoformans* and *Cryptococcus gattii* [1].

Presentation

About half (44 %) of adults will have a "textbook" presentation of meningitis, the triad of fever, neck stiffness, and change in mental status. However, the most frequent symptom in adults subsequently found to have meningitis is headache, followed by neck stiffness, fever, and change in mental status. Using a dyad (two of four of the following: headache, fever, neck stiffness, or a change in mental status) increased the positive predictive value to 95 %. Only 4 % of patients subsequently diagnosed with meningitis had one symptom, with 1 % having none of the four symptoms. The clinical presentation of meningitis for children under the age of three is usually more subtle and atypical, may not have any of the four cardinal symptoms, and may present only with irritability and lethargy.

Diagnosis

History

Aside from making the diagnosis, a carefully taken history is important to determine if there are any predisposing or complicating factors. These include infectious illness, immunocompromised state, previous neurosurgical procedure, and immunization status. However, clinical history alone is not sufficient to diagnose meningitis.

Physical Examination

The physical exam for meningitis is focused on finding and documenting neurologic deficits on presentation. In addition to documenting meningeal signs (jolt accentuation of headache, Kernig's and Brudzinski's signs), the physical exam should include an assessment of the rest of the neurologic system including the Glasgow Coma Score. The presence of meningeal irritation is assessed by laying the patient supine and gently flexing the neck forward while examining the neck for rigidity. Kernig's sign is performed with the patient supine and the hip flexed to 90 °. A positive sign is present when extension of the knee from this position elicits resistance or pain in the lower back or posterior thigh. Brudzinski's sign is present with passive neck flexion in a supine position results in flexion of knees and hips. The jolt accentuation of headache is positive if the patient's headache worsens when turning his or her head horizontally 2–3 rotations per second. The sensitivity and specificity for neck stiffness for meningitis are 30 % and 68 %, for Kernig's sign are 5 % and 95 %, and for Brudzinski's sign are 5 % and 95 %, respectively. Since these bedside diagnostic tools have poor sensitivity, further diagnostic testing should not be precluded by the absence of these clinical signs [2].

Cerebrospinal Fluid Examination

Prompt examination of the cerebrospinal fluid (CSF) is required for diagnostic confirmation of meningitis. Imaging for intracranial lesions should be performed prior to lumbar puncture (LP) in patients with altered mentation, focal neurological findings, and papilledema or if there is clinical suspicion of increased cranial pressure. Other relative contraindications to performing a lumbar puncture include local infection at the puncture site, recent administration of anticoagulation within the past hour, and platelet count less than $20 \times 10^3/\mu L$. Videos of how to perform a LP are readily available online.

When possible, opening pressure of the CSF within the spinal canal should be documented. Normal opening CSF pressure is 10–100 mm H_2O in young children, 60–200 mm of H_2O after 8 years of age, and up to 250 mm of H_2O in obese patients. 1–5 ml samples of CSF are normally placed into four tubes, numbered in the order in which they were collected. Tube 1 is used for cell count, tube 2 for protein and glucose, tube 3 for specific tests as indicated (e.g., latex agglutination for bacterial and viral antigens, polymerase chain reaction), and tube 4 for cultures. Normal values are easily obtained from multiple references and may vary with the patient's underlying condition [3].

Laboratory Testing and Imaging

Additional testing should include a complete blood count with differential, complete metabolic panel, and blood culture. Cultures should be obtained from blood as well as other potential sources of infection. Additional imaging performed should be obtained as warranted by clinical suspicion.

Treatment

Antibiotic therapy should be initiated as soon as possible after the diagnosis of meningitis is entertained and should not be delayed to obtain a CSF sample. Antibiotic choice is dependent on age, comorbidities (e.g., immunodeficiency, prior neurosurgical procedures), and situation (e.g., head trauma). For most suspected meningitis cases, an initial broad-spectrum approach such as vancomycin and a third-generation cephalosporin is suggested as an empiric antibiotic regimen with subsequent changes based on culture results. For adults older than 50 years, the regimen should include ampicillin, as well as vancomycin and a third-generation cephalosporin. For infants younger than 1 month, the suggested empiric antibiotic regimen should include ampicillin and cefotaxime or ampicillin and an aminoglycoside. The use of dexamethasone remains controversial. If herpes simplex meningitis is clinically suspected, empiric treatment should include acyclovir. For uncomplicated cases of viral meningitis, no specific antibiotic therapy is necessary.

Course and Prognosis

Without treatment, mortality of patients with bacterial meningitis approaches 100 %. However, even with treatment, the mortality rate for children is 3 % and for adults is 21 %. Hearing loss is seen in 14 % of adult patients and hemiparesis in 7 % of adult patients. Stroke is seen in 3 % of children [4, 5].

Special Considerations

Chronic Meningitis

Chronic meningitis is defined as "irritation and inflammation of the meninges persisting for more than 4 weeks associated with pleocytosis in the cerebrospinal fluid." Chronic meningitis may be caused by persistent infection, allergic inflammatory reaction to an infection, autoimmune disease, or chemical and drug exposure. Clinical presentation is often nonspecific and only becomes similar to that of acute meningitis over time. The approach to diagnosis is necessarily broad, but an accurate and detailed history and physical exam will help to narrow the differential diagnosis. Up to one-third of patients with chronic meningitis will not have a definitive diagnosis

even after a thorough and complete investigation [6].

Noninfectious Meningitis

Medications [trimethoprim–sulfamethoxazole (Bactrim), ibuprofen (Motrin), and naproxen (Naprosyn)] and medical procedures (intrathecal injections and neurosurgical procedures) can rarely cause noninfectious meningitis. Brain tumors may cause "chemical" meningitis due to the lipid-induced chemical irritation and may require repeated LPs and careful examination of CSF for diagnosis. Connective tissue diseases and vasculitis syndromes have been reported to be associated with noninfectious meningitis, especially sarcoidosis, systemic lupus erythematosus, and Behçet's disease [7].

Prevention

Vaccines as primary prevention have been successful in greatly reducing the incidence of bacterial meningitis in children and adults – especially since their addition to the childhood vaccine schedule. Vaccines are available for *Haemophilus influenzae* type b, *Neisseria meningitis*, and *Streptococcus pneumonia*. Guideline for chemoprophylaxis for close contacts of individuals diagnosed with bacterial meningitis is available. In addition, universal screening of all pregnant women for group B streptococcal disease with subsequent treatment during labor has caused a marked decline in perinatal group B streptococcal disease [5].

Encephalitis

Background

Encephalitis is the presence of an inflammatory process of the parenchyma of the brain in association with clinical evidence of neurological dysfunction. Encephalitis can be caused by a large variety of pathogens. Of the cases where an etiology was identified, most were viral, followed by bacterial, prion-related, parasitic, and fungal etiologies. In the majority of cases, an etiology will not be identified. In the United States, the most commonly identified etiologies are herpes simplex virus (HSV), West Nile virus, and enteroviruses, followed by other herpesviruses. Exposure can be immediately proximate to the onset of symptoms or delayed such as encephalitis associated with measles, congenital rubella, or HIV. HSV encephalitis can be either acute (33 %) or the result of reactivation of latent infection (66 %).

Presentation

The presentation of encephalitis is very similar to that of meningitis and includes fever, headache, nausea and vomiting, and altered level of consciousness often associated with seizures and focal neurological findings. Other common findings include disorientation, speech disturbances, and behavioral changes. Alterations in mental functions may cause lethargy, drowsiness, confusion, disorientation, and coma.

Diagnosis

History and Physical Exam

As the differential diagnosis of encephalitis is broad, a thorough history and physical exam are necessary to narrow the differential diagnosis list. Helpful questions to ask during history taking to determine the etiology include age, animal contact, immunocompromised states, ingested items, insect contact, occupation, recent sick contacts, recent vaccinations, recreational activities, season, transfusion and transplantation, travel history, and vaccination status. A detailed physical exam with careful attention paid to a careful neurological exam may be helpful in narrowing the differential diagnosis list as certain physical exam findings are associated with specific etiologies (see Table 1).

Laboratory Testing

Cerebrospinal fluid (CSF) analysis is essential to diagnosis in all patients with encephalitis (unless contraindicated) and will typically demonstrate lymphocytic pleocytosis with normal glucose and a modest elevation of protein. CSF should

Table 1 Findings associated with specific etiologies

Etiology	Findings
Herpes simplex virus	Frontotemporal signs Mucous membrane lesions
Rabies	Psychomotor excitation Bulbar dysfunction and spasm
Creutzfeldt–Jakob disease	Subacute personality changes Dementia with myoclonus

Adapted from Refs [9, 10]

be analyzed for virus-specific IgM antibodies and nucleic acid amplification – especially herpes simplex polymerase chain reaction (PCR). Other studies should include complete blood count; tests of renal and hepatic function; coagulation studies and chest radiography; cultures of body fluid specimens; biopsy of specific tissue for cultures, antigen detection, nucleic acid amplification tests, and histopathology examination; serological testing of IgM antibodies; acute- and convalescent-phase serum samples for retrospective diagnosis of an infectious agent; nucleic acid amplification of body fluids outside of the CNS; and peripheral blood smear. Additional diagnostic studies should be performed on the basis of specific epidemiological and clinical clues.

Imaging

Magnetic resonance imaging (MRI) of the brain is the most sensitive neuroimaging test to evaluate patients with encephalitis, although computerized tomography (CT), with and without contrast, should be used in patients if MRI is unavailable, impractical, or cannot be performed. MRI may show characteristic patterns seen with specific agents in patients with encephalitis.

Treatment

All patients with encephalitis should empirically be started on acyclovir (Zovirax) 10 mg/kg (500 mg/m^2 for children <12 years) IV infused over 1 h every 8 h for 14–21 days pending results of diagnostic tests and elimination of the possibility of HSV as a causative agent. Other antimicrobial agents should be started on the basis of specific epidemiological or clinical factors, including appropriate therapy for bacterial meningitis. In patients with clinical and epidemiological clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline (Vibramycin) 100 mg twice daily for 10–14 days should be added to the empirical regimen. Specific therapy should be tailored based on the results of diagnostic testing.

Course and Prognosis

Morbidity and mortality remain high with encephalitis. Poor prognostic factors include age above 60, reduced Glasgow Coma Score on admission, and, for HSV encephalitis, delay between hospitalization and starting treatment with acyclovir. The mortality rate for encephalitis is dependent on the causative organism ranging from less than 5 % with ehrlichiosis to 33 % with Eastern equine encephalitis virus to 100 % with rabies. In addition, approximately two-thirds of survivors will have significant neuropsychiatric sequelae including memory impairment, personality and behavioral change, dysphagia, and seizures [8–10].

Brain Abscess

Background

Brain abscesses, or focal intracerebral infections consisting of an encapsulated collection of pus caused by bacteria, mycobacteria, fungi, protozoa, or helminths, are most commonly caused by bacteria. *Streptococcus* species is the most common causative agent, followed by *Staphylococcus* species, then gram-negative enteric species. Brain abscesses are rare, with the incidence estimated to be 0.3–1.3 per 100,000 people per year. The incidence is significantly higher in developing countries and in patients who are alcoholic, are immunosuppressed (e.g., acquired immune deficiency syndrome, chemotherapy, biologic drugs), have cyanotic heart conditions, or are severely debilitated by neurological conditions. Brain

abscesses most often arise from direct invasion from a contiguous focus of infection (i.e., otitis, mastoiditis, sinusitis, meningitis, and odontogenic). They can also be secondary to blood-borne pathogens (i.e., pulmonary focus or heart disease) or arise in areas of previous head trauma.

Presentation

An area of damaged brain tissue allows a nidus of infection to occur with subsequent local areas of infarction. Cerebritis follows as the area becomes necrotic and encapsulated within a few weeks. Presentation is dependent on mechanism and pathogen, which includes focal mass expansion, increased intracranial pressure, diffuse destruction, or focal neurological deficit. Clinical signs and symptoms of brain abscesses are varied and commonly include fever, headache, hemiparesis of a cranial nerve, hemiparesis, meningism, altered level of consciousness, seizure, nausea and vomiting, and papilledema.

Diagnosis

Physical Exam

The most common symptoms of brain abscess are headache (69 %), fever (53 %), and focal neurological deficits (48 %). However, as a triad, the three together only occur in 20 % of patients with brain abscesses. A high index of suspicion is required to make the diagnosis, particularly in febrile patients with a history of central nervous system instrumentation.

Laboratory Studies

Laboratory studies, such as blood cultures, complete blood count, and chest radiograph, are commonly performed, but may not provide useful data, as only 28 % of blood cultures were positive in one study. CSF cultures are often sterile, and lumbar puncture is not recommended and may be contraindicated due to increased intracranial pressure.

Neuroimaging

Diagnosis is dependent on neuroimaging. Classically, a hypodense lesion with a contrast-enhancing ring will be seen on computed tomography (CT) of the brain or magnetic resonance imaging (MRI) of the brain. CT of the brain allows for detection, localization, characterization, and is ubiquitous in emergency departments. In addition, CT of the brain can detect hydrocephalus, increased intracranial pressure, edema, and other associated infections. However, CT of the brain has a 6 % false-negative rate. Diagnosis of brain abscess by MRI of the brain is more accurate than CT, but MRI is not as ubiquitous or available as CT and so is less commonly used.

Treatment

Treatment of brain abscess requires a combination of antibiotic treatment, surgical intervention, and eradication of the primary foci. Successful treatment of brain abscesses often requires drainage under CT guidance in addition to antibiotic therapy.

Antibiotic Therapy

Until the abscess can be drained and cultured, empiric antibiotic therapy should consist of broad-spectrum antibiotics that easily cross the blood–brain, and blood–CSF barriers should provide coverage for the most common pathogens. Acceptable antibiotic choices include a third-generation cephalosporin and metronidazole. Vancomycin should be added if there is a history of penetrating trauma or recent neurosurgical procedure. Antibiotic therapy should be tailored for patients with specific immune function defects, transplant recipients, cancer, and on chronic steroid therapy. However, as cultures are often sterile, broad-spectrum antibiotics should be continued for the entire course.

Duration of antimicrobial therapy has been suggested to be 4–6 weeks for a surgically drained abscess, 6–8 weeks for a brain abscess solely treated with antibiotics, and 3–12 months for immunocompromised patients.

Neurosurgical Intervention

Emergent drainage of brain abscesses is indicated as part of the management and to establish the causative pathogen due to the high sterile culture rate. Aspiration has become the preferred method for drainage providing relief from increased intracranial pressure and avoids the possibility of damage to the surrounding brain. However, aspiration often (70 %) requires repeat procedure and can possibly cause iatrogenic puncture of the ventricle and subarachnoid leakage of pus leading to extension of the brain abscess.

Adjunctive Therapy

Steroids are generally avoided except in the perioperative period. They are indicated for reduction of intracranial pressure and avoiding acute brain herniation in those patients that demonstrate signs of meningitis or disproportionate cytotoxic edema posing a life-threatening problem. Steroids should be tapered as rapidly as possible.

Anticonvulsants are commonly used to control seizures and are used as prophylaxis for subsequent seizures after resolution of brain abscesses. Anticonvulsants are recommended to be continued for 5 years after resolution of the brain abscess. However, discontinuing anticonvulsants may be considered if the patient has been seizure-free for 2 years after surgery and no epileptic activity is seen on electroencephalography (EEG). The law regarding driving with a diagnosis of seizure is dependent on the state, but usually requires being seizure-free for 6–12 months prior to resumption of driving.

Course and Prognosis

The mortality rate of brain abscesses has declined by 50 %, from 20 % to 10 % in recent years. Approximately half of patients will have a good outcome, but the other half will either die or have neurological sequelae. Poor prognostic indicators include delayed diagnosis, rapidly progressing disease, coma, multiple lesions, intraventricular rupture, and fungal etiology. Outcomes are worse in the elderly and newborn. Neurological sequelae include focal neurologic deficits, intellectual disability, and postoperative seizures [11–13].

Neurosyphilis

Background

Syphilis is a sexually acquired condition caused by infection with *Treponema pallidum* and is known as the "great imitator" due to its varied presentation. Although syphilis was close to eradication in 2000, in the years between 2005 and 2013, syphilis has increased in annual rate from 2.9 to 5.3 cases per 100,000 population [14].

Presentation

Syphilis is divided into primary infection (ulcer or chancre), secondary infection (skin rash, mucocutaneous lesions, lymphadenopathy), neurologic infection (cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities), and tertiary infection (cardiac or gummatous lesions). However, neurosyphilis can occur at any stage of infection and has three distinct patterns of occurrence. Asymptomatic neurosyphilis is defined as the presence of cerebrospinal fluid (CSF) abnormalities consistent with neurosyphilis in persons with serological evidence of syphilis and no neurological signs or symptoms. Early symptomatic neurosyphilis involves diffuse inflammation of the meninges and presents similarly to meningitis – headache, photophobia, nausea, vomiting, cranial nerve palsies, and occasionally seizures. Lastly, meningovascular syphilis consists of endarteritis of vessels anywhere in the central nervous system resulting in thrombosis and infarction.

Headache, vertigo, and insomnia often occur early in the course of infection. Dramatic symptoms such as the sudden onset of contralateral hemiparesis, hemianesthesia, homonymous hemianopsia, and aphasia lead to a more rapid

diagnosis. Symptoms of syphilis involving the spinal cord include spastic weakness of the legs, sphincter disturbances, sensory loss, and muscle atrophy. Parenchymatous syphilis may manifest as either paretic neurosyphilis ("general paralysis of the insane") or tabetic neurosyphilis ("tabes dorsalis"). Early symptoms of paretic neurosyphilis include irritability, forgetfulness, personality changes, headaches, and changes to sleep habits, while late symptoms include emotional liability, impaired memory and judgment, disorientation, confusion, delusions, seizures, and other psychiatric symptoms. Tabetic neurosyphilis presents classically as ataxic gait, lightening pains, paresthesias, bladder dysfunction, and failing vision.

Diagnosis

Physical Exam

Depending on the stage and presentation of neurosyphilis, the physical exam may be unremarkable or may be similar to other disease processes. Physical exam findings may include papillary abnormalities (Argyll Robertson pupils), diminished reflexes, impaired vibratory sense and proprioception, ocular palsies, and Charcot joints (progressive degeneration of weight-bearing joints) [15, 16].

Laboratory Studies

The diagnosis of syphilis is made using a combination of serological tests [Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR)], treponemal tests [fluorescent treponemal antibody absorbed (FTA-ABS) or *T. pallidum* passive particle agglutination (TP-PA)], or dark-field examination. Laboratory testing can only be used to support the diagnosis of neurosyphilis, but no single test can be used to diagnose neurosyphilis in all circumstances. The identification of serologic changes in the cerebrospinal fluid (CSF-VDRL) has a high specificity, but low sensitivity. CSF-VDRL can be positive in early syphilis, but is a finding of uncertain significance. CSF can be tested for treponemal antibodies using FTA-ABS. This is more sensitive than CSF-VDRL, but less specific. Therefore, diagnosis of neurosyphilis is a combination of reactive serological test results and a reactive CSF-VDRL, in the presence of signs of CSF inflammation (elevated cell count and protein), with or without clinical manifestations.

Treatment

Antimicrobial Treatment

Penicillin is the preferred drug for treating all stages of syphilis – including in pregnancy. Those with a penicillin allergy should undergo desensitization and be treated with penicillin.

A frequent reaction to the administration of penicillin G at any stage of syphilis is the Jarisch–Herxheimer reaction, which is an acute febrile reaction frequently accompanied by headache, myalgia, and fever. Although this may induce early labor or fetal distress in pregnant women, this should not delay or prevent therapy.

Penicillin G 18–24 million units per day is the preferred dosage and should be administered as 3–4 million units by IV every 4 h or as a continuous infusion for 10–14 days. If compliance is an issue, an alternative regimen is procaine penicillin 2.4 million units once daily and probenecid 500 mg orally four times daily for 10–14 days.

If CSF pleocytosis was present initially on examination, repeat CSF examination should occur every 6 months until the cell count is normal. If cell count or protein is not normal after 2 years, retreatment should be considered.

Special Considerations

Persons who are exposed to syphilis via intimate contact at any stage should be evaluated clinically and serologically. If the exposure was within 90 days preceding the diagnosis of any stage of syphilis – even if the exposed person is seronegative – he or she should be treated presumptively. Persons who are exposed 90 days or more prior to diagnosis of any stage of syphilis in a sex partner should have serologic testing prior to treatment. However, the exposed person should be treated

presumptively if serological testing is not available immediately and follow-up is uncertain. In addition, intimate partners of infected patients should be provided presumptive treatment if they have had sexual contact with the patient within 3 months plus the duration of symptoms for primary syphilis, within 6 months plus duration of symptoms for secondary syphilis, and within 1 year for patients with early latent syphilis [17].

Brain Tumors

Background

Primary brain tumors are rare, accounting for 1.4 % of all new cancer cases with an incidence of 5.42 per 100,000 children aged 0–19 years and 27.9 per 100,000 adults aged 20 years and older. Approximately 34 % of all primary brain tumors are malignant. The most common types of primary brain tumor are malignant glioblastoma and meningioma. In adults, the most common types of primary brain tumor are glioblastoma, meningioma, astrocytoma, and pituitary adenoma, while in children, the most common types of primary brain tumors are tumors of pilocytic astrocytoma, embryonal tumors, and malignant glioma (see Table 2) [18].

Metastatic disease to the CNS is much more common than primary brain tumors occurring up to ten times as often as primary brain tumors.

Table 2 Distribution of primary brain tumors by histology

Histology	Percentage of total
Meningioma	36.1 %
Glioblastoma	15.4 %
Tumors of the pituitary	15.1 %
Nerve sheath tumors	8.0 %
All other astrocytomas	6.0 %
Lymphomas	2.1 %
Ependymal tumors	1.9 %
Oligodendrogliomas	1.6 %
Embryonal tumors	1.1 %
Oligoastrocytic tumors	0.9 %
All other	11.8 %

Adapted from Ref [18]

Although primary lung cancers are the most common source of metastatic lesions, melanoma and breast cancer are becoming more frequent. Approximately 80 % of brain metastases occur in the cerebral hemispheres, followed by 15 % in the cerebellum, and 5 % in the brainstem.

Presentation

The presenting signs and symptoms of metastatic brain lesions are similar to other mass lesions and can be separated into focal or generalized symptoms. Focal symptoms are dependent on tumor location. For example, focal symptoms of brain tumors in the frontal lobe include dementia, personality changes, gait disturbance, expressive aphasia, and seizures; in the parietal lobe include receptive aphasia, sensory loss, hemianopia, and spatial disorientation; in the temporal lobe include complex partial or generalized seizure, behavior change, including symptoms of autism, and quadrantanopia; in the occipital lobe include contralateral hemianopia; in the thalamus include contralateral sensory loss, behavior change, and language disorder; in the cerebellum include ataxia, dysmetria, and nystagmus; and in the brainstem include cranial nerve dysfunction, ataxia, papillary abnormalities, nystagmus, hemiparesis, and autonomic dysfunction. Generalized symptoms include headache, memory loss, cognitive changes, motor deficit, language deficit, seizures, personality change, visual problems, changes in consciousness, nausea or vomiting, sensory deficit, and papilledema [19].

Diagnosis

Diagnosis is dependent on appropriate brain imaging followed by histopathology to confirm diagnosis. Acute headaches with red flag symptoms should prompt immediate imaging (See Table 3) [20]. The imaging modality of choice is gadolinium-enhanced magnetic resonance imaging (MRI). For those who cannot have a MRI performed, computed tomography (CT) of the head and spine is acceptable; however, CT does not have as high of a resolution as MRI and is

Table 3 Red flag symptoms that should prompt immediate imaging

Red flag	Differential diagnosis
Headache beginning after 50 years of age	Temporal arteritis, mass lesion
Sudden onset of headache	Subarachnoid hemorrhage, pituitary apoplexy, hemorrhage into a mass lesion or vascular malformation, mass lesion
Headaches increasing in frequency and severity	Mass lesion, subdural hematoma, medication overuse
New-onset headache in a patient with risk factors for HIV infection or cancer	Meningitis (chronic or carcinomatous), brain abscess (including toxoplasmosis), metastasis
Headache with signs of systemic illness (fever, stiff neck, rash)	Meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease
Focal neurological signs or symptoms of disease (other than typical aura)	Mass lesion, vascular malformation, stroke, collagen vascular disease
Papilledema	Mass lesion, pseudotumor cerebri, meningitis
Headache subsequent to head trauma	Intracranial hemorrhage, subdural hematoma, epidural hematoma, posttraumatic headache

Adapted from Ref [20]

unable to adequately assess lesions in the posterior fossa and spine.

Treatment

Due to the varied course and symptoms of primary and metastatic brain tumors, prognosis and treatment are highly individualized and are dependent on age and performance status of the patient, proximity to "eloquent" areas of the brain, feasibility of decreasing the mass effect, resectability of the tumor, and time since last surgery for those with recurrent disease. In general, regardless of tumor histology, the best outcome is through a combination of maximal safe resection (stereotactic biopsy, open biopsy, subtotal resection, or complete resection) and radiation therapy (brachytherapy, fractionated external beam radiotherapy, or fractionated stereotactic radiotherapy). Whole brain radiotherapy and stereotactic radiosurgery is often reserved for metastatic disease.

Symptom Treatment

Corticosteroids may be necessary to treat vasogenic edema. Often, corticosteroids need to be tapered slowly, although side effects of long-term use of corticosteroids include cognitive impairment, hypoglycemia, gastrointestinal problems, myopathy, and opportunistic infections. Seizures are common with brain tumors, including after surgery. However, prophylactic use of antiseizure medications is not indicated [21].

Course and Prognosis

Prognosis is dependent on histopathology (oligodendrogliomas have a better prognosis than mixed gliomas, which have a better prognosis than astrocytomas) and tumor grade. Younger age, good initial performance score, and O6-methylguanine methyltransferase (MGMT) gene promoter hypermethylation are associated with a more favorable prognosis [22].

Multiple Sclerosis

Background

Multiple sclerosis (MS) is a disabling demyelinating immune-mediated disease of the central nervous system (CNS) that disproportionately affects women, smokers, persons living at higher latitudes, and persons with a family history of MS. Increased exposure to sunlight and higher 25-hydroxyvitamin D levels confer lower risk. The incidence of MS ranges from 47.2 to 109.5 per 100,000 persons in the United States [23].

Presentation

The clinical presentation of MS is varied and can include symptoms such as depressed mood, dizziness or vertigo, fatigue, hearing loss and tinnitus, loss of coordination and gait disturbance,

Table 4 Diagnostic criteria for multiple sclerosis

Clinical presentation	Additional data needed for MS diagnosis
≥2 attacks; objective clinical evidence of ≥2 lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack	None
≥2 attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS Awaiting another clinical attack implicating a different CNS site
One attack; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time A new T2 and/or gadolinium-enhancing lesion (s) on follow-up MRI, irrespective of its timing with reference to a baseline scan Await a second clinical attack
One attack; objective clinical evidence of one lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS Await a further clinical attack implicating a different CNS site For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan Await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively determined) plus two of three of the following criteria: 1. Evidence for DIS in the brain based on ≥1 T2 lesion in at least two of four MS-typical regions of the CNS 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Adapted from Ref [26]
MS-typical regions of the CNS include periventricular, juxtacortical, infratentorial, or spinal cord

pain, sensory disturbances (dysesthesias, numbness, paresthesias), urinary symptoms, visual disturbances (diplopia and oscillopsia), and weakness and can include signs such as ataxia, decreased sensation (pain, vibration, position), decreased strength, hyperreflexia, spasticity, nystagmus, and visual defects (internuclear ophthalmoplegia, optic disk pallor, red color desaturation, or reduced visual acuity) [24, 25].

Diagnosis

History, Physical Exam, and Diagnostic Imaging

The current guideline for diagnosis of multiple sclerosis (MS), the 2010 revisions to the McDonald Criteria, requires a combination of history, physical exam, and diagnostic imaging. An attack is defined as "patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS), current or historical, with duration of at least 24 h, in the absence of fever or infection." The diagnostic criteria for MS based on clinical presentation are listed in Table 4 [26].

Differential Diagnosis

MS has a broad differential diagnosis, and consideration should be given to testing angiotensin-converting enzyme levels, autoantibody titers, *Borrelia* titers, human immunodeficiency virus (HIV) screening, rapid plasma reagin (RPR) or

Venereal Disease Research Laboratory (VDRL), thyroid-stimulating hormone, and vitamin B12 level.

Treatment

Disease-Modifying Agents

The mainstay of treatment of MS is disease-modifying agents, which slow disease progression, preserve function, and sustain the immune system while suppressing the T-cell autoimmune cascade. Approved disease-modifying agents, which include interferon beta, glatiramer, fingolimod, teriflunomide, dimethyl fumarate, natalizumab, and mitoxantrone, are usually managed by an experienced neurologist.

Exacerbations

Exacerbations are common, affecting over 85 % of patients with MS, and are often caused by infection or stress. Oral corticosteroids are the mainstay of the treatment of exacerbations. However, if there is no response to corticosteroids, plasmapheresis or plasma exchange may be performed.

Symptom-Specific Management

Neurogenic bladder, affecting more than 70 % of patients with MS, may be alleviated with anticholinergic medications for failure-to-store symptoms; limiting evening fluid intake, desmopressin, or injections of onabotulinumtoxinA for nocturia; and clean intermittent catheterization or alpha-adrenergic blockade for failure-to-empty symptoms. Neurogenic bowel, affecting more than 75 % of patients, may present with incontinence, constipation, or both and may require a colostomy if symptoms are intolerable. Sexual dysfunction is common, but often unaddressed. Men may be treated with centrally acting phosphodiesterase-5 inhibitors, although women have no similarly approved medication. Pain will affect approximately 85 % of patients with MS (trigeminal neuralgia and neuropathic pain most commonly). Trigeminal neuralgia may be treated with carbamazepine and baclofen, while neuropathic pain may be treated with tricyclic antidepressants, anticonvulsants, or selective serotonin reuptake inhibitors. Spasticity should be treated with baclofen, although diazepam, gabapentin, or onabotulinumtoxinA may also be helpful. Treatment of fatigue, present in more than 90 % of patients with MS, is multifocal and includes environmental manipulation (controlling heat and humidity levels) and energy conservation measures (napping and use of assistive devices for mobility). Amantadine has been used off-label for the pharmacological management of fatigue, but may cause insomnia and confusion [24].

Course and Prognosis

MS has an extremely varied course, characterized by two broad pathways. Primary-progressive MS is characterized by the invariable progression despite occasional plateaus or temporary minor improvements, with an average time to disability requiring use of a cane to ambulate of 6–21 years. Those diagnosed with relapsing-remitting and secondary-progressive MS tend to have an initial relapsing-remitting disease course, progressing to less prominent relapses and ensuing relentless progression. In these patients, the relapsing-remitting phase lasts for about 20 years prior to the secondary-progressive phase. The introduction of disease-modifying agents has increased the life span of a patient with MS, but is still approximately a decade shorter than expected from an age-matched general population [25].

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