such agents have yet to be shown to have convincing clinical effect.[46]

KEY CONCEPTS

- Diabetic neuropathy is a diagnosis of exclusion because no definitive diagnostic testing is available.
- Both ischemic and hemorrhagic brainstem lesions must be ruled out in the case of an acute ophthalmoplegia.
- Extraocular mononeuropathy is sufficiently common in patients with diabetes mellitus that its occurrence in isolation warrants evaluation of the patient for previously undiagnosed diabetes.

CEREBRAL VENOUS THROMBOSIS

Perspective

No precise studies of the epidemiology of cerebral venous thrombosis (CVT) have been performed. In case series, the median patient age is approximately 37 years, with a female-to-male ratio of 3:1.[47]

Principles of Disease

Cerebral blood is drained by several major veins that lead into the dural sinuses. The major dural sinuses are the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the lateral sinuses, and the sigmoid sinuses. The variability in symptoms and signs in patients who present with CVT stems from differences in thrombus location and acuity of thrombus formation. Symptoms of intracranial hypertension are present in most patients with sinus thrombosis, whereas those with thrombosis of the cerebral veins are thought to be more prone to hemorrhagic infarction and localizing neurologic deficits.[48] As with venous thrombosis in other locations, multiple causes and predisposing factors for CVT are recognized. Underlying causes often are divided into infectious and noninfectious categories. Infectious causes include local infections, such as sinusitis, otitis media, cellulitis on the face, and systemic infections. Noninfectious causes include direct injury to the cerebral venous system from trauma, surgery, tumor, dehydration, or any other condition that may predispose the patient to development of a hypercoagulable state.[49]

Clinical Features

The symptoms and signs associated with CVT are quite varied. Headache is the primary feature of CVT in 74 to 92% of affected patients.[49,50] Papilledema is noted in 28 to 45% of cases.[47,50,51] Lethargy, decreased level of consciousness, or mental status changes may be noted. Seizures occur in 35 to 50% of patients in the acute phase.[47,49,51] In addition to the location and acuity of thrombosis formation, a patient's symptom onset will vary in accordance with the extent of collateral vessel growth in the venous territory. Early thrombotic changes may be well compensated for by the collateral venous drainage. Symptoms will appear only when the compensation for venous thrombosis is no longer sufficient. Variability in collateralization between patients also adds to the variability and time course of symptomatology. Two national and international observational studies document an average time from symptom onset to diagnosis of 7 days, reflecting the difficulty in diagnosing this rare disease entity.[47,51,52] The reported incidence of focal neurologic signs, including seizures, on clinical examination varies between series, ranging from 25 to 71%.[49,50] Because of the broad spectrum of possible clinical features, the diagnosis of CVT may be difficult but should be a consideration in any patient with unexplained headache, especially in combination with focal neurologic deficit, papilledema, or seizures.

Diagnostic Strategies

The gold standard modality for the diagnosis of CVT has shifted in recent years from cerebral angiography to magnetic resonance venography (MRV). CT scanning is useful in the initial workup of the patient with possible CVT, but noncontrast CT is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis. Findings on CT that are consistent with CVT include hyperdensity of a thrombosed sinus, brain edema, and hemorrhage secondary to venous congestion. CT venography is both more sensitive and more specific in diagnosing CVT.

Similar to CT scanning, MRI also can demonstrate local changes secondary to venous congestion, such as brain edema or hemorrhage. In addition, MRI can demonstrate the possibility of CVT based on the lack of a "flow void." On conventional MRI, a flow void indicates the presence of blood flow within the sinus, whereas the absence of a flow void indicates a possible thrombus. Diagnostic accuracy, however, is greatly improved through use of MRV. This technique takes advantage of the MRI signal characteristics of flowing blood to create images of venous structures. Combining these imaging techniques further enhances diagnostic accuracy. For imaging a particular dural sinus, presence of the sinus on conventional MRI and lack of flow on MRV are diagnostic of a sinus thrombosis. This combined approach has diagnostic sensitivity similar to that of conventional angiography.[49,53]

Two small studies show similar sensitivity between MRV and CT venography for the diagnosis of CVT when the CT study is performed on a multidetector row CT scanner. Both studies, involving a total of 69 patients, showed 100% sensitivity of CT venography for CVT in comparison with MRV.[54,55] The sensitivity of CT venography performed by scanners that do not use multidetector row technology is unknown.

Several small studies have attempted to evaluate the usefulness of the D-dimer assay as a screening tool to exclude CVT, particularly when MRI or CT venography is not available. Although the reported sensitivity rates are fair at 83 to 100%, larger prospective studies need to be done to further define the role of D-dimer in the evaluation of CVT, because several case reports have noted normal D-dimer levels in the setting of documented CVT.[56-59] In general, although a normal D-dimer level does not exclude the diagnosis of CVT, it does appear to make this diagnosis much less likely, particularly in a patient with symptoms of less than 2 weeks in duration.

Differential Considerations

Considerations in the differential diagnosis of CVT include the conditions that cause patients to present with the new onset of neurologic deficits, alteration in consciousness, or severe headache. A diagnosis of CVT should be considered in a patient with such symptoms when the etiology is unclear, presence of having a hypercoagulable state is likely, and the head CT scan is normal in appearance or shows subtle signs of CVT.

Management

CVT is a relatively rare disease, and controlled studies evaluating its treatment are lacking. Current therapeutic consensus

strongly recommends systemic anticoagulation with low-molecular-weight or unfractionated heparin to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging.[49,50,60,61] In one placebo-controlled randomized trial comprising 20 patients, anticoagulation with heparin to a target partial thromboplastin time (PTT) of 80 to 100 seconds demonstrated benefit, even in patients in which evidence of intracranial hemorrhage was seen on the CT scan before anticoagulation.[62] In another study of 60 patients randomized to receive placebo or low-molecular-weight heparin, no statistical benefit was shown for treatment.[63] Two large observational trials showed improvement in modified Rankin scale at follow-up in the anticoagulated groups, although the trials were not randomized.[47,51] Despite a paucity of randomized controlled trials, expert opinion favors anticoagulation in all groups unless another contraindication is present.[64]

Catheter-based intervention with thrombolysis has been attempted in multiple case series using either urokinase or tissue plasminogen activator. Thrombolysis was shown to be relatively safe and relatively successful in very small case series.[61] In one nonrandomized study of 40 patients, 20 received systemic heparin and 20 received catheter-based infusion of urokinase followed by systemic heparin. Despite initially worse neurologic function in the thrombolysis group, a significant difference in neurologic function favoring thrombolysis was observed at discharge.[65] Although this therapy is promising, it should be considered only for patients with symptoms of decreased level of consciousness, elevated ICP, or rapid deterioration on neurologic examination.

Disposition

All patients with suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Patients should be anticoagulated if no contraindication exists, and catheter-based thrombolysis should be considered in patients with depressed mental status or focal findings on neurologic exam.

KEY CONCEPTS

- CVT is a relatively rare entity, and only awareness of and familiarity with the clinical presentation will lead to the correct diagnosis.
- The onset may be insidious with a considerable delay between onset and arrival in the treatment setting.
- The differential diagnosis for CVT should consider other conditions that cause patients to present with new-onset neurologic deficits, alteration in consciousness, or severe headache. CVT is more likely to be present in such patients when the etiology is unclear, the patient is suspected of having a hypercoagulable state, and the head CT is normal in appearance or shows subtle signs of CVT.
- Noncontrast CT scanning is not adequate to rule out CVT. An MRI with MRV is recommended, although multidetector row CT venography is an acceptable alternative.
- Treatment of most patients with CVT should include systemic anticoagulation, even in the setting of hemorrhagic cerebral infarcts, unless another contraindication exists.

MULTIPLE SCLEROSIS

Perspective

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS). Although the exact etiology remains uncertain, the pathologic manifestation of this inflammatory disease is a demyelination of discrete regions (plaques) within the CNS with a relative sparing of axons. The clinical picture is highly variable but is classically characterized by episodes of neurologic dysfunction that evolve over days and resolve over weeks.

MS has an overall prevalence in the United States of 0.1%. The peak age at onset is 25 to 30 years, with women being slightly younger at onset than men. The incidence in women exceeds that of men by a ratio of 1.8 : 1. The worldwide prevalence is greatest in the United Kingdom, Scandinavia, and North America. Epidemiologic studies indicate that both genetic and environmental factors are associated with an increased incidence of this disease. MS has a 30% concordance rate between monozygotic twins, and 20% of patients with MS have at least one affected relative. MS is more common in temperate climates. It is rare between 23 degrees north and south latitudes but has a rising incidence above and below 50 degrees north and south latitudes, respectively. Although no exact environmental factor has been identified, if a person emigrates from an area of high prevalence to an area of low prevalence before the age of 20, the risk is diminished. MS is rare in Africans and Asians, but African Americans have a higher incidence than their relatives who remain in Africa.[66] In addition, reports of clusters or miniepidemics support environmental factors. Thus, an environmental cause superimposed on genetic susceptibility appears to be a likely etiologic scenario.[67,68]

Principles of Disease

MS is considered to be an organ-specific autoimmune disease. One theory proposes that genetic factors interact with an environmental trigger or infection to establish pathologically autoreactive T cells in the CNS. After a long and variable latency period (typically 10 to 20 years), a systemic trigger, such as a viral infection or superantigen, activates these T cells. The activated T cells, on reexposure to the autoantigen, initiate the inflammatory response. This sets off a complex immunologic cascade that leads to the demyelination characteristic of MS. This demyelination process releases CNS antigens that are hypothesized to initiate further episodes of autoimmune-induced inflammation. The mechanisms underlying this autoimmunity in MS are unknown.[69]

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and the degree and time course of progression.

The clinical features of MS can be divided into areas of specific CNS impairment: cognition, cranial nerves, motor pathways, sensory pathways, cerebellar pathways, and bowel, bladder, and sexual dysfunction.[66]

Patients with MS have frequent complaints of poor memory, distractibility, and a decreased capacity for sustained mental effort. Formal neuropsychological testing suggests that cognitive involvement is common and underreported. Specifically,

neuropsychological testing has shown that 43 to 65% of patients with MS have some degree of cognitive impairment.[70,71] Of note, a correlation has been found between the MRI-based total lesion load and presence of cognitive impairment.[72]

Cranial nerve dysfunction is common in MS. The most common associated cranial nerve abnormality is *optic neuritis*, a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss affecting primarily central vision. Within 2 years of an attack of optic neuritis, the risk of MS is approximately 20%, and within 15 years, it is approximately 45 to 80%.[73,74] Optic neuritis often is the first symptom of MS.[75,76]

As a result of lesions in the vestibulo-ocular connections, the oculomotor pathways also may be affected. The deficit may manifest as diplopia or nystagmus. The nystagmus may be severe enough that the patient may complain of oscillopsia (a subjective oscillation of objects in the visual field). Cranial nerve impairment also may include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways also are commonly involved. Specifically, corticospinal tract dysfunction is common in patients with MS. Paraparesis or paraplegia is all too common and occurs with greater frequency than upper extremity lesions, owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with significant motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that typically is worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms frequently are bilateral, they generally are asymmetrical.[66]

Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.[66]

Impairment of the cerebellar pathway results in significant gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), a breakdown in the ability to perform complex movements, an intention tremor in the limbs and head, truncal ataxia, and dysarthria.[66]

Impairment of bowel, bladder, and sexual function also is common. The extent of sphincter and sexual dysfunction usually parallels the motor impairment in the lower extremities. Urinary frequency may progress to urinary incontinence with progression of the disease. An atonic bladder may develop, which empties by simple overflow and often is associated with the loss of perception of bladder fullness and with anal and genital hypoesthesia. Constipation becomes common over time, and almost all patients with paraplegia require special measures to maintain effective bowel habits. Sexual dysfunction, although frequently overlooked, is very common in MS. Approximately 50% of patients become completely sexually inactive as a result of this disease.[66]

Diagnostic Strategies

Although no laboratory tests are diagnostic for MS, one clinical feature remains relatively unique to this disease: *Uhthoff's phenomenon*, temporary worsening of current or preexisting signs or symptoms of MS secondary to small increases in the patient's body temperature. Accordingly, exercise, a hot bath, exposure to a warm environment, or fever can bring about Uhthoff's phenomenon. This phenomenon reflects subclinical demyelination or preexisting injury to nerves without obvious significant clinical involvement before heat exposure or temperature elevation.[66]

The clinical diagnosis rests on occurrence of at least two clinical episodes with different neurologic symptoms at different times. Thus, MS commonly has been characterized as a disorder with lesions that differ in time and space. It also has been described as a relapsing-remitting disorder with symptoms that fluctuate over time.

Findings on cerebrospinal fluid (CSF) analysis are abnormal in 90% of the cases. Fifty percent of patients will have pleocytosis, with more than 5 lymphocytes per high-power field in the CSF. Approximately 70% of patients will have an elevated gamma globulin level, with immunoglobulin G (IgG) ranging from 10 to 30% of the CSF total protein. Electrophoresis of the CSF demonstrates oligoclonal bands of IgG in 85 to 95% of patients who carry a diagnosis of MS; however, oligoclonal bands of IgG also are seen with neurosyphilis, fungal meningitis, and other CNS infections. Lumbar puncture should be considered for all patients with suspected MS, but mass lesions and elevated ICP should be ruled out before lumbar puncture.[77]

The initial imaging test to aid in the diagnosis of multiple sclerosis is MRI. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity.[78] The lesions of MS typically appear hyperintense, or bright white, on T_2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI studies. Lesions usually are multiple and commonly are found in the periventricular white matter.[79] In patients with an initial neurologic event consistent with CNS demyelination and an MRI cranial study showing multiple white matter lesions, the 5-year risk of developing MS is 60%. Patients with similar clinical syndromes and a normal MRI appearance have less than a 5% 5-year risk.[80]

Differential Considerations

Other diseases that affect the CNS white matter may be clinically and radiographically similar to MS. Considerable care must be taken to exclude these disease processes before making a diagnosis. These include CNS tumors (especially lymphomas and gliomas), spinal cord compression, vasculitides, Behçet's disease, neurosarcoidosis, postinfectious and postvaccinal encephalomyelitis, human immunodeficiency virus (HIV) encephalopathy, Lyme disease, and vitamin B_{12} deficiency.

Management

Management of patients with MS has essentially three aspects: (1) therapies aimed at halting the progression of the disease, (2) treatment for acute exacerbations, and (3) therapies designed to modify complications.

Therapies aimed at halting disease progress are based primarily on the use of either β-interferon or glatiramer acetate. The interferons are a group of natural compounds with antiviral and immunomodulatory actions, which are retained by the recombinant preparations used in therapy for MS, interferon beta-1a and interferon beta-1b. Side effects include flulike symptoms, depression, anxiety, and confusion. In one study, 560 patients with MS were randomly assigned to receive subcutaneous interferon beta-1a or placebo ($n = 187$) three times a week for 2 years. The relapse rate was significantly lower at 1 and 2 years with interferon beta-1a than with placebo. The time to first relapse was prolonged significantly and the accu-

mulation of brain lesions on MRI was lower in the treatment group than in the placebo group. The investigators concluded that subcutaneous interferon beta-1a is a well-tolerated and effective treatment for relapsing-remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures.[81] β-Interferon also has been shown to retard progression to clinically definite MS and to decrease the total number of brain lesions seen on subsequent MRI studies in patients who have their first demyelinating episode with MRI abnormalities at initial presentation.[82-85] This finding highlights the importance of early evaluation and treatment.

Glatiramer acetate also has successfully been used in the treatment of MS. This agent is a mixture of synthetic polypeptides designed to mimic myelin basic protein. The mechanism of action by which glatiramer acetate exerts its effect is unknown, but it is thought to modify the immune processes responsible for the pathogenesis of MS. In one study, 251 patients with relapsing-remitting MS were randomized to receive daily subcutaneous injections of glatiramer acetate (previously called copolymer 1) or placebo for 24 months. Patients receiving glatiramer acetate experienced significantly fewer relapses and were more likely to demonstrate neurologic improvement, whereas those receiving placebo were more likely to worsen. This drug generally is quite well tolerated.[86]

Current recommendations for management of relapsing-remitting MS are to initiate treatment with β-interferon or glatiramer acetate. Such regimens have been demonstrated to decrease the volume of plaques seen on MRI and to diminish relapses.[69] Immunosuppressive agents, including mitoxantrone and azathioprine, also have been shown to be effective in reducing progression of disease but, in view of concerns over side effects, generally are used as second-line agents.[87,88]

Acute exacerbations of MS also should be targets for therapy. Although most such episodes will resolve without therapy, steroids have been demonstrated to diminish the duration of acute exacerbations. More than 85% of patients with relapsing-remitting MS show improvement with intravenous methylprednisolone. Intravenous steroids have been shown in controlled trials to speed the recovery from the visual loss of optic neuritis when compared with placebo. In addition, when patients with acute optic neuritis are treated with high-dose intravenous steroids, the 2-year rate of development of MS is reduced, although this effect diminishes over time.[74,89] Of interest, oral prednisone was not found to be helpful in the optic neuritis trials and was associated with a potential increase in the number of optic neuritis episodes.

The current standard therapy for an acute exacerbation in MS is intravenous methylprednisolone. A typical dose administered intravenously is 250 to 500 mg every 12 hours for 3 to 7 days. Whether this should be followed by an oral prednisolone taper remains controversial. Potential adverse effects of methylprednisolone therapy include fluid retention, gastrointestinal hemorrhage, anxiety, psychosis, infection, and osteoporosis.

Several therapies directed toward the complications of MS may be helpful. The associated spasticity generally is treated with baclofen. This is a highly effective therapy aimed at reducing the painful flexor and extensor spasms. A major side effect is drowsiness, which generally diminishes with continued use. Higher-dose therapy can cause confusion, especially in the setting of baseline cognitive impairment. For patients with intractable spasticity, baclofen is available for intrathecal administration by either bolus therapy or continuous implanted pump therapy. Additional therapeutic agents for control of spasticity include tizanidine, diazepam, and dantrolene.

The tremor and ataxia associated with MS occasionally are treated with propranolol, diazepam, or clonazepam. The results of these therapies, however, generally are unsatisfactory. Pain often is associated with MS and affects the shoulders, pelvic girdle, and face. The facial pain may be indistinguishable from that of trigeminal neuralgia. Treatment options include carbamazepine, baclofen, and tricyclic antidepressants. Fatigue, which is common, may be ameliorated with amantadine. This agent produces partial relief for a minority of patients. In controlled studies, the effect is only slightly better than placebo.[69]

Disposition

Patients with a history of MS who seek treatment for significant symptoms must first be evaluated to rule out other, non–MS-related pathology. Also, the presence of other systemic illnesses, especially infections, which can worsen the symptoms of MS, should be excluded. If the problem is thought to be an exacerbation of MS, most patients will require hospital admission for intravenous steroid therapy. An alternative to hospitalization may be to initiate intravenous steroids in the ED and to arrange for a next-day follow-up visit with the primary care physician or neurologist if outpatient intravenous steroid administration is an option.

Patients with the new onset of symptoms suggestive of MS should be admitted or referred to a neurologist, depending on the type and severity of symptoms.

KEY CONCEPTS

- Any patient with a long-term illness, such as MS, must be evaluated to rule out pathologic processes not related to that illness before an exacerbation of the illness can be assumed to be the cause of any problems experienced by the patient.
- Therapy for patients with MS will require consultation with the patient's primary care provider or neurologist to provide consistent disease management.
- Intravenous methylprednisolone effectively promotes earlier resolution of recurrences.
- Intravenous methylprednisolone has been shown to speed the recovery from vision loss from optic neuritis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.