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Vasculitic Neurologic Injury

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Abstract

Vasculitic diseases can affect any organ system including the peripheral nervous system and the central nervous system. Neurologic injury is characterized by the presence of inflammatory cells in and around the blood vessels resulting in narrowing or blockage of the blood vessels that supply the nervous system. Neurologic manifestations of vasculitis can range from headaches and visual disturbances to numbness and paralysis. Diagnosis of vasculitic neuropathy or central nervous system vasculitis will require a thorough history and physical and carefully selected laboratory and radiological tests. Corticosteroids and immunosuppressive medications have helped improve neurological recovery. Although significant progress has been made, there are still no controlled therapeutic trials for the treatment of vasculitic neuropathy or central nervous system vasculitis.

Keywords: Vasculitis; Neuropathy; Angiitis; Central nervous system; Peripheral nervous system; Rehabilitation

Vasculitic Neurologic Injury

- Vasculitis can cause injury to the peripheral nervous system and the central nervous system
- Neurological injury is due to inflammatory cells in and around blood vessels results in narrowing and blockage of the blood vessels that supply the nervous system
- The gold standard for the diagnosis of vasculitis of the nervous system is biopsy
- The mainstay of treatment is with high dose corticosteroids and immunosuppressive medications

Introduction

Vasculitis can cause injury to any organ system including the central nervous system (CNS) and peripheral nervous system (PNS). The damage is characterized by the presence of inflammatory cells in and around blood vessels resulting in narrowing or blockage of the blood vessels that supply the nervous system. Neurologic manifestations of vasculitis can begin suddenly or develop slowly over time. Symptoms can range from headaches and visual disturbances to numbness and paralysis.

Vasculitis of the Peripheral Nervous System

Peripheral neuropathy is a common clinical feature of systemic necrotizing vasculitis (SNV) and may be the only manifestation of the underlying vasculitic process. This type of neuropathy is the result of ischemic damage from the occlusion of blood vessels associated with an inflammatory process in the walls of the small blood vessels that supply the nerves called the vasa nervorum. Vasculitic neuropathy can occur with multisystem involvement or as an independent process called nonsystemic vasculitic neuropathy (NSVN). Peripheral neuropathy secondary to vasculitis without disorders in other systems was first described by Kernohan and Woltman in 1938 [1]. Recognizing vasculitis as a cause of neuropathy is critical as it is potentially treatable.

Anatomy of the Nerve

Nerves have a three layer fascial structure. Axons are covered by endoneurium which does not offer much mechanical support. Groups of endoneurium which are covered axons are bundled by the perineurium. The perineurium is thin but dense offering some support and also helps maintain the blood-nerve barrier. The perineurium is covered by the thicker epineurium which is highly vascular making it difficult to cause ischemia to the nerve. The blood vessels are also slightly coiled to allow for movement with the nerve. Feeder vessels from the epineurial blood vessels course to all the inner portions of the nerve. Most of the transperineurial arterioles connect with capillaries and they gradually lose their continuous muscle coat and become post-arteriolar capillaries [2].

Vulnerability of Peripheral Nerves to Vasculitic Neuropathy

Systemic necrotizing vasculitis (SNV) is characterized by inflammation and necrosis of the blood vessel walls usually involving the medium to small-sized arteries. The vasa nervorum that supply the nerves are usually small-sized arterioles. Therefore, it is common for peripheral neuropathy to occur in SNV. The main vessels responsible for vasculitic neuropathy are the arterioles of the epineurium with a typical diameter of 30-300 micrometers [3]. The blood supply to the peripheral nerves involves two different systems. The extrinsic system is composed of the epineurial vessels which become smaller arterioles and capillaries. There is also an intrinsic system of longitudinal vessels within the fascicles themselves. These two systems are linked by interconnecting vessels which provide a high flow rate. With this dual system of vascularization, there is a rich blood supply to the nerve [4]. In addition, the nerves tend to function well within an anaerobic environment making them somewhat resistant to ischemia. Extensive damage to the vasa nervorum is needed before damage to the nerves occurs.

The nerves within the endoneurial compartment may be more susceptible to injury as these endoneurial capillaries are more widely

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spaced especially in the central fascicular regions [5]. The endoneurial vessels also have a poorly developed smooth muscle layer. This makes them unable to auto regulate blood flow and makes them susceptible to small changes in perfusion. Therefore a typical feature of ischemic vasculitic neuropathy is associated with loss of central fascicular fibers [6]. Most vulnerable areas of the major nerves seem to be in a watershed zone of poor perfusion such as in the mid-upper arm or the mid-thigh.

Wallerian degeneration of the nerves results from ischemia caused by inflammatory occlusion of the blood vessels with fibrinoid necrosis of the vessel wall and transmural inflammatory cell infiltration. There may be a leukocytoclastic mechanism versus a cellular-mediated process. Immune complexes are formed when antibodies attach to antigens found in the blood vessel walls which then activate a complement cascade which attracts polymorphonuclear leukocytes to release proteolytic enzymes and free radicals which may destroy cell membranes and damage blood vessel walls [7]. T cell mediated processes against the epineurial and endoneurial vessels seem to be an important mechanism in vasculitic neuropathies.

In vasculitic neuropathies, axonal degeneration is the main finding whereas in inflammatory neuropathies, segmental demyelination and endoneurial inflammatory cells area usually found [8]. In order to definitively diagnose vasculitic neuropathy there must be histological features of inflammation of the vessels. There may be active, inactive, or healed changes.

Active vasculitis is characterized by transmural inflammatory cell infiltration of at least one blood vessel with signs of vascular injury which may include fibrinoid necrosis, endothelial damage, or hemorrhage into the blood vessels [9]. Polymorphonuclear leukocytes, lymphocytes, or eosinophils are usually seen as intramural and perivascular infiltrates.

Inactive vasculitis is marked by more chronic changes such as concentric fibrous scarring and thickening of the tunica intima and tunica media with significantly less intramural or perivascular inflammatory cells [9]. Splitting and actual overgrowth of the internal elastic membrane can accompany inactive vasculitis [9]. During inflammation, activated vascular endothelial cells and other cell types can express adhesion molecules which help facilitate the binding of circulating leukocytes and extravasation of leukocytes into surrounding tissues. The serum concentration of these adhesion molecules can reflect the degree of activation [10].

Healed vasculitic lesions usually have signs of previous severe injury to the arterial wall. There may be perivascular and intramural fibrosis and narrowing or calcification of the lumen. There should be no perivascular or intramural inflammatory cells so these lesions sometimes are consistent with atherosclerotic changes [11]. Using special stains such as Verhoeff-van Gieson's stain can help see elastin and connective tissue and thus separate atherosclerotic changes from healed vasculitic lesions. Fragmentation of the internal elastic membrane is also consistent with healed vasculitis.

Demographics and Mortality/Morbidity

Peripheral neuropathy occurs in approximately 60-70% of patients with some systemic vasculitis [11]. One third of patients with vasculitis have disease contained within the peripheral nervous system, also known as nonsystemic vasculitic neuropathy (NSVN). The average age of presentation is 62 years old. There is no predilection for sex or a racial predominance for vasculitic neuropathy. Recovery is significantly better in NSVN patients. The one year survival rate was greater than 90% with death usually linked to older patients or patients with more severe multisystem disease [12]. Generally death is secondary to systemic complications of vasculitis.

Clinical Diagnosis

Patients with vasculitic neuropathy may present with either mononeuropathy multiplex or asymmetric sensorimotor neuropathy. Symmetric neuropathy is not as common occurring in less than one third of patients. Mononeuropathy multiplex implies the sequential involvement of individual nerves or trunks usually in a distal to proximal pattern in an asymmetric pattern. The neuropathy is often abrupt which can be preceded by pain in the affected nerve as often times there is involvement of both the motor and sensory fibers. History is important as patients may have a more subtle course similar to a distal, symmetric neuropathy from the summation of discrete nerve injuries. It can occur as an acute or subacute relapsing pattern or as a progressive pattern. Asymmetric or multifocal painful sensorimotor neuropathy is the most common presentation in more than 60% of the patients. The peroneal nerve is the most commonly affected, followed by the sural, tibial, ulnar, and then the median nerves.

Relapse rates range from 11-60% in patients with systemic or nonsystemic vasculitis. Relapse usually occurred in patients that did not get optimum treatment with immunosuppressive medications [13]. Remission is a term used to indicate there is no longer any detectable inflammatory disease activity. Once a state of remission has been achieved, the intensity of immunosuppressive therapy is usually reduced. Corticosteroids are usually replaced by better-tolerated, milder forms of immunosuppression that are used long term to keep the patient in remission (methotrexate or azathioprine).

There is a large differential diagnosis of patients with a mononeuropathy multiplex. Patients usually complain of burning or tingling pain in the distribution of nerve injury. Usually weakness is evident as motor function is the most prominent manifestations of peripheral nerve vasculitis. In addition, severe neuropathic pain is frequently seen in vasculitic neuropathy which can limit normal motor function.

Laboratory Findings

Most patients have elevated acute phase reactants such as erythrocyte sedimentation rate (ESR). Diagnostic laboratory tests should be selected that support or help eliminate systemic conditions. Some vasculitic processes are associated with antineutrophil cytoplasmic antibodies (ANCAs), antinuclear antibodies (ANA), antibodies to double stranded DNA (dsDNA), rheumatoid factor, cryoglobulins, C-reactive protein, antibodies to extractable nuclear antigens (anti-Sm, anti-Ro, anti-La, and anti-RNP), and complement components.

Electrodiagnostic testing in patients with vasculitic neuropathy is usually characterized by axonal damage of multiple individual nerves

in an asymmetric pattern. In axonal injury, motor and sensory nerve conduction studies show reduced amplitude or even an unobtainable potential. It is very important to assess side to side differences in amplitude which will reflect a multifocal axonal process. As the injury is usually axonal, evidence of significant demyelination would suggest an alternative neuropathic process. Conduction velocities should be normal or slightly reduced whereas distal latencies are normal or slightly prolonged [8]. Electromyographic examination of the affected muscles may show diffuse signs of denervation with fibrillation potentials or positive sharp waves which are indicative of axonal nerve injury. Direct imaging of the nerve is not usually performed, however ultrasound of the affected nerves may appear enlarged and hypoechoic.

If the clinical presentation and diagnostic tests are consistent with a vasculitic neuropathy and if there is histopathologic or angiographic evidence of vasculitis in other organs, then biopsy may not be necessary to confirm the diagnosis. Biopsy is usually done to confirm the clinical diagnosis when patients lack more definitive features. The most common nerves used for biopsy are the sural nerve, sensory branch of the superficial peroneal nerve, and the radial sensory nerves. Vasculitic neuropathy can be demonstrated on nerve and/or muscle biopsy. Because doing simultaneous biopsies of both the nerve and muscle increases the overall diagnostic yield, many physicians will biopsy the superficial peroneal nerve as the peroneus brevis muscle can also be biopsied from the same incision. In a study by Collins in 2003, 48 patients with NSNV were studied over a median of 63 months. Diagnostic sensitivity for vasculitis was 58% for superficial peroneal nerve/peroneus brevis muscle biopsy and 47% for sural nerve biopsy alone [14]. Another common nerve/muscle biopsy combination is the sural nerve with the gastrocnemius muscle. Numbness is expected to occur in the skin along the innervation area of the sensory nerve biopsied.

Histopathology is the gold standard to diagnose a vasculitic neuropathy. In order to diagnose vasculitis definitely, there must be evidence of transmural inflammatory cell infiltration and necrosis of the vessel wall. Immunocytochemistry may show immunoglobulins, complement, and membrane attack complement deposition on blood vessels. Nerve biopsies may show immunostaining for the receptor for advanced glycation end products (RAGE) [15]. Binding of ligands to RAGE results in activation of the proinflammatory transcription factor nuclear factor-kappa B and subsequent expression of cytokines which may play a critical role in vasculitic neuropathy [4]. Matrix metalloproteinases may be upregulated as they are important inflammatory cell invasion.

Treatment

There is a lack of randomized trials in the treatment of vasculitic neuropathies as shown in the 2007 Cochrane review [16]. As there are no adequate randomized controlled clinical trials to base treatment, the therapeutic decisions are based on small trials and clinical experience. Much of the treatment protocols are based on trials of immunosuppressive medications in systemic vasculitis or connective tissue diseases. Since the use of corticosteroids to treat systemic vasculitis in the 1950s, the 5 year survival rate has increased from 10% to 55% by the late 1970s [17]. With the addition of cyclophosphamide the 5 year survival rate is now greater than 80% [17]. In a non-randomized cohort of 48 patients, combination corticosteroid and cytotoxic therapy (cyclophosphamide) was more effective than corticosteroid monotherapy in inducing remission in patients with NSVN. There was also an improvement in disability with a trend toward decreased relapses and decreased pain [14].

Initially the treatment of SVN is associated with immunosuppressive therapy directed at the underlying disease. The frontline in the treatment of most vasculitic neuropathies is corticosteroids and cyclophosphamide. There is no standard dosing for corticosteroids, but a widely used regimen begins with intravenous methylprednisolone 1gm/day for three days and then switching to oral prednisone in the range of 1 mg to 1.5 mg/kg/day with a maximum of 100 mg/day. After 2-4 weeks, the prednisone is tapered slowly over the course of several weeks to a few months.

Side effects of long term corticosteroid use should be considered and thus it would be prudent to start patients on calcium and vitamin D supplementation to prevent steroid-induced osteoporosis. Concomitant use of a proton pump inhibitor or a histamine blocker may decrease stomach irritation from long term corticosteroid use. Blood sugars should also be monitored for the possibility of steroid induced hyperglycemia. The patient should also be monitored closely during the tapering process looking for signs of recurrent nerve damage or even inflammatory disease in other organs affected by the vasculitis. Nerve ischemia can occur in an area of extensive vascular compromise even up to several weeks after an effective therapy is implemented. Therefore worsening nerve damage right after starting immunosuppressive therapy does not signify the need to immediately increase corticosteroid or immunosuppressive medication dosages.

In addition, oral or intravenous cyclophosphamide can be started with the corticosteroid. In particular, patients with more motor nerve dysfunction should have combination therapy. The approach is to establish disease control quickly with combination therapy of corticosteroid and cyclophosphamide and then to stop the cyclophosphamide in three to six months and replace it with a lower risk medication such as azathioprine or methotrexate. Oral cyclophosphamide at the dose of 1 to 2 mg/kg is more potent than intravenous doses and usually associated with more side effects such as hemorrhagic cystitis. Some advocate treatment with monthly intravenous pulse doses of cyclophosphamide at the dose of 500-1000 mg/m2 body surface area. The patient should be premedicated with sodium 2-mercaptoethane sulfonate to reduce bladder toxicity and with anti-nausea medications. It is also important to hydrate the patient well both before and after the administration of the cyclophosphamide. If the patient does not respond to intravenous cyclophosphamide, oral dosing should be considered usually at the dose of 1-2 mg/kg/day. Daily dosing can be titrated in response to white blood cell counts to avoid leukopenia which will usually dip around 1 to 2 weeks after treatment. Blood counts should be checked periodically as well as a urinalysis. Prophylaxis for Pneumocystis carinii such as with trimethoprim/sulfamethoxazole should be implemented.

High dose corticosteroids and cyclophosphamide should be continued until the patient continues to improve or their condition at least becomes stable which is usually in the 4 to 6 month timeframe. As there is potential for toxicity with long-term cyclophosphamide

treatment, other less toxic drugs should be used for maintenance therapy after disease control has been attained by corticosteroids and cyclophosphamide. The use of methotrexate and azathioprine is mainly based on proven maintenance therapy in patients with Wegener's granulomatosis. Stopping cyclophosphamide and starting methotrexate at 7.5 to 15 mg/week may be better for long term maintenance. Doses may need to be adjusted on a weekly basis up to approximately 25 mg/week. Azathioprine is another option but patients should be screened for thiopurine methyltransferase (TPMT) deficiencies prior to initiation of therapy. Initial doses of 50 mg/day should be increased gradually over several weeks to 1.5 to 3.0 mg/kg/day with a maximum of about 200 mg/day [18].

After a disease free period of 6-12 months, these immunosuppressive medications can be discontinued. The azathioprine or methotrexate does not need to be tapered so it can be stopped abruptly. Other immunosuppressive medications that can be used for maintenance therapy include tacrolimus, cyclosporine, chlorambucil, and intravenous immunoglobulins albeit with variable success. Plasmapheresis has not been shown to be beneficial in patients with vasculitic neuropathy [19].

Therapeutic regimens are usually customized based on the specific clinical situation. For example, patients with vasculitis due to Hepatitis C are usually treated with an alpha-interferon (3 million units three times a week). Conventional treatment with corticosteroids and cyclophosphamide may allow the virus to replicate causing further liver damage [17].

Prognosis

There are a limited number of studies on the prognosis in patients with vasculitic neuropathy. The long term outcomes in patients with vasculitic neuropathy were evaluated for 106 patients with clinicopathologic vasculitic peripheral neuropathy. Of the 106 patients with vasculitis neuropathy, 95 patients had systemic vasculitis and 11 had vasculitis confined to the peripheral nervous system. Corticosteroids were used in the predominant number of patients and included cyclophosphamide in about half of these patients. Initial stabilization was achieved in all but 6 patients and the one-year survival was greater than 90% [20]. Nine patients died in the first year in which two had severe, multisystem vasculitis. The neurological relapse rate was 10%. Outcome was reported as good in 72% of the treated patients [20]. Based on this study it was concluded that death and relapse rate were infrequent in treated patients. Most of the relapses occurred in patients on monotherapy with corticosteroids. Aggressive treatment with cyclophosphamide may help prevent a relapse. The combination therapy of corticosteroids with cyclophosphamide appears largely effective.

Studies of Polyarteritis Nodosa (PAN) showed that patients with peripheral neuropathy were not associated with poorer outcome [21]. Older age has been shown to be a prognostic factor linked to poorer outcomes [8]. Vasculitic neuropathy seen in rheumatoid arthritis is linked with poorer prognosis with a survival rate of 57% in 5 years [22].

Systemic Vasculitic Neuropathy

Polyarteritis Nodosa (PAN) is the most common of the necrotizing vasculitides which is a systemic disorder involving small and medium sized vessels. Organ systems affected include the liver, kidney, gastrointestinal tract with sparing of the lungs. Neuropathy has been recognized as one of the most frequent clinical manifestations and is often the initial presenting symptom along with weight loss, fever, and loss of appetite. Fifty to seventy percent of the diagnosed cases have neuropathy [21]. The most common pattern is multiple neuropathies where the sciatic nerve or its branches are the most frequently involved. Central nervous system or cranial nerve involvement occurs in less than 2% of these patients.

Wegener's granulomatosis is characterized by necrotizing vasculitis and granulomas involving the respiratory tract and kidneys. Of 128 patients with Wegener's granulomatosis, 56 patients had peripheral neuropathy [23]. Multiple mononeuropathies and distal symmetrical polyneuropathies were the most common. Neuropathy was also more common in patients with severe kidney involvement. Cranial neuropathies developed in 5-10% of patients most likely secondary to granulomas than actual vasculitis.

Churg-Strauss syndrome has similar clinical and neurologic manifestations to PAN except there is respiratory involvement. It is characterized by systemic small vessel vasculitis, extravascular granulomas, and eosinophilia. Peripheral nerve involvement is seen in as many as 75% of patients [17]. Mononeuropathy multiplex secondary to vasculitis in patients with rheumatoid arthritis is rare. More common are entrapment neuropathies and a chronic, distal symmetric neuropathy. Secondary vasculitis may complicate systemic lupus erythematous and Sjogren's syndrome.

Vasculitis neuropathy can occur in the setting of a variety of infections [24]. Hepatitis B and C have been associated with PAN. A mononeuropathy multiplex or symmetrical neuropathy in patients with elevated liver function test should lead to the diagnosis of Hepatitis B or Hepatitis C. Necrotizing vasculitis has also been seen in patients with HIV [4]. Multiple mononeuropathies in HIV occur in 1 to 3% of patients with AIDS. CD4 counts are usually below 600/mL. The differential diagnosis should include evaluation for other opportunistic infections such as CMV and Mycobacterium tuberculosis.

Cryoglubulins are circulating immune complexes that consist of immunoglobulins directed against polyclonal immunoglobulins [25]. These complexes precipitate out of solution when cold and dissolve back when rewarmed. Peripheral neuropathy develops in 25-90% of patients with cryoglobulinemia [5]. The neuropathy may arise from ischemia due to hyperviscosity or due to a vasculitis related immune complex deposition in small epineurial blood vessels.

Certain diabetic syndromes such as diabetic amyotrophy have been associated with inflammatory angiitis. Nerve and muscle biopsy have shown inflammatory infiltrate and sometimes necrotizing vasculitis. Immunotherapy for diabetic amyotrophy has been suggested based on these pathologic findings. Rarely, cancers have been associated with vasculitic neuropathy. Small cell lung cancer and lymphoma are the most commonly associated with malignancy-related vasculitis [26]. Hypersensitivity vasculitis can occur secondary to a drug reaction and is usually self limiting. Drugs of abuse such as cocaine and opioids have been linked to peripheral vasculitis.

Nonsystemic Vasculitis Neuropathy (NSVN)

Vasculitis is restricted to the peripheral nerves in about one third of cases. In NSVN there is no significant involvement of other organ systems or evidence of any underlying disease. The prognosis is much better than systemic vasculitic disorders and particularly good if no vasculitic involvement of other tissues appears during the year following diagnosis. Patients with vasculitis that is localized to the peripheral nervous system at presentation should be followed closely for signs of other organ involvement [27].

Vasculitis of the Central Nervous System

Vasculitis that affects the CNS is sometimes difficult to diagnose and can be a diagnostic challenge for physicians. The ischemia induced by CNS vasculitis may be similar to damage done by infection, emboli, atherosclerosis, or malignancy. There is also a lack of accurate and sensitive tests to diagnose certain vasculitis. CNS vasculitis can be classified as primary CNS vasculitis when it is confined to the CNS alone or secondary CNS vasculitis when associated with other disorders. The preferred name for vasculitis that is confined to the central nervous system is primary angiitis of the central nervous system (PACNS).

Primary Angiitis of the CNS (Primary CNS Vasculitis)

PACNS may affect small-sized and medium-sized vessels of the brain, spinal cord, or leptomeninges resulting in CNS dysfunction. It does not involve blood vessels or organs beyond the CNS. Initial reports of PACNS have described it as a fatal and progressive granulomatous vasculitis. However with the use of glucocorticoids and cyclophosphamide there has been improving success in treatment.

Secondary CNS Vasculitis

Secondary CNS vasculitis has been associated with multiple conditions including systemic vasculitis, infection, and connective tissue diseases. In both primary and secondary CNS vasculitis, ischemia is the cause of neurological loss of function. Interaction between antibody-dependent and cell-mediated activities results in vascular injury with focal or multifocal infarction or diffuse injury affecting any part of the brain. Therefore, the diagnosis is often difficult as there is no specific laboratory or imaging test.

Systemic Vasculitis

Most of the systemic vasculitis can involve the CNS, but are most commonly seen in Wegener's granulomatosis, Churg-Strauss syndrome, and Behcet's disease. Wegener's granulomatosis is characterized by granulomatous inflammation of the respiratory tract and necrotizing vasculitis affecting the small-medium vessels. CNS pathology may be involved in around 2-8% of these patients evidenced by strokes, headaches, and seizures [28]. Confirmation of CNS vasculitis in Wegener's granulomatosis is rare because the small vessels are usually below the sensitivity of cerebral angiography. Churg-Strauss is a less common form of vasculitis with eosinophil-rich, granulomatous inflammation involving the respiratory tract and affecting small to medium vessels. Cranial neuropathy and stroke occurs in approximately 5% of patients. The CNS may be affected in 10-49% of patients with Behcet's disease ranging from primary CNS inflammation to vasculitis of the venous system leading to stroke [29].

Infections

Infections linked to CNS vasculitis include HIV, varicella zoster (VZV), and syphilis. Varicella associated cerebral angiitis affects older patients and is usually more localized and less severe than PACNS. A known history of herpes zoster can suggest this etiology. Cerebral angiography with findings of segmental, unilateral involvement of the vessels in the distribution of the middle cerebral artery and internal carotid artery are characteristic of varicella angiitis. Diagnosis can be confirmed with higher antibodies to VZV in the CSF than the serum or VZV PCR in the CSF [30].

HIV has also been associated with CNS vasculitis however opportunistic infections account for the majority of HIV-related brain disorders. Treponema pallidum (syphilis) can invade any vessel in the subarachnoid space and cause thrombosis and ischemia. Neurosyphilis is most commonly found in patients who are immunocompromised as in HIV patients. There is also CNS vasculitis associated with hepatitis B and C [31]. Borrelia burgdorferi, Bartonella, and Mycobacterium tuberculosis can have be associated with vasculitic syndrome.

Infection can present itself similarly to PACNS, thus it is important to search for an infectious cause.

Connective Tissue Disease

CNS involvement in connective tissue diseases is not uncommon especially in patients with SLE. The most common disorder affecting the CNS in SLE is a bland vasculopathy with small-vessel hyalinization, thickening, and intramural thrombus formation with micro-infarcts [32]. When dealing with connective tissue disorders, it is important to assess if the CNS dysfunction is actually related to vessel injury, infection, medication side-effects, or metabolic disturbances.

Other connective tissue diseases that can involve the CNS include Sjogren's syndrome, rheumatoid arthritis, and mixed connective tissue diseases. In Sjogren's syndrome, CNS manifestations may be caused by a mononuclear inflammatory vasculopathy involving the small vessels of the cortex and meninges [33]. Vasculitis from rheumatoid arthritis only occasionally involves the CNS whereas vasculitic neuropathy is much more common. Approximately 5% of patients with sarcoidosis will develop neurological involvement with associated granulomatous brain masses and encephalopathy.

Miscellaneous Disorders

A variety of drugs, particularly those with sympathomimetic properties have been associated with CNS vasculitis. CNS vasculitis has been reportedly linked with intravascular lymphoma which leads to widespread occlusion of small vessels [34].

Pathology

Pathologic exam of the brain in PACNS reveal granulomatous inflammation within the small arteries. Inflammatory cells such as Langerhan's cells, multinucleated giant cells, macrophages, and lymphocytes are often present. These pathologic findings in PACNS are similar to those in the aorta and large-sized and medium-sized

arteries of patients with giant cell arteritis and Takayasu arteritis. It is more likely to affect blood vessels in the cerebral cortex and the leptomeninges than the subcortical regions. Blood vessels supplying the cranial nerves may also be involved. Disruption of blood flow or occlusion of blood vessels may cause ischemia to brain parenchyma whereas rupture of dilated arteries can result in intracerebral hemorrhage.

The cause of PACNS is still unknown. It has been speculated that an altered host immune system may play a significant role. Most likely the cause of PACNS is multifactorial. Pathologic confirmation is difficult as the condition is rare and it is hard to obtain adequate amounts of diseased tissue. There may be an infectious trigger in developing PACNS.

Diagnosis

Criteria for primary CNS vasculitis is usually defined as an acquired and otherwise unexplained neurologic deficit with the presence of either classic angiographic or histopathologic features of vasculitis within the CNS and no evidence of systemic vasculitis or any condition that could cause this angiographic or pathologic feature [35].

Primary CNS vasculitis appears to be male-predominant in a 2:1 ratio and can occur at any age [34]. It is usually characterized by a long prodromal period with the mean time from symptom onset to diagnosis of 170 days. Because the vasculitis can affect any area of the CNS, there is a varied presentation and no specific clinical sign is specific for diagnosis. Some patients may develop headaches, seizures, cognitive changes, motor and sensory changes, and balance issues. In a series of 116 patients with histopathological confirmation, almost 70 percent of the patients presented with diffuse neurologic dysfunction with the most common symptom in 83% of patients as decreased cognition [33].

The reversible cerebral vasoconstriction syndromes (RCVS) are a group of disorders that sometimes mimic the appearance of PACNS. RCVS are characterized by a reversible multifocal narrowing of the cerebral arteries usually accompanied by severe "thunderclap" headaches. Neurologic deficits may or may not occur. Other distinguishing characteristics include a female predominance, acute presentation, and most notably reversible angiographic findings. There is a lack of evidence of blood vessel inflammation as would be seen in PACNS. Hajj-Ali described the improvement of patients with RCVS in a series of 16 patients who had resolution of angiographic findings within 4-12 weeks without immune treatment. RCVS can also occur in certain defined clinical settings such as after taking vasoconstrictive medications, during a migraine headache attack, or after the postpartum period. It is absolutely essential to differentiate between RCVS and PACNS as the treatment and prognosis are different. The mechanism for alteration in vascular tone in RCVS is unclear and may be related to adrenergic or serotonergic drugs, trauma, or hypertension [36].

Diagnostic Tests

Laboratory tests are somewhat similar to patients with peripheral nerve vasculitis. There are no laboratory tests that are diagnostic for CNS vasculitis. Acute phase reactants such as ESR and C-reactive protein are usually normal. Serum markers for inflammation usually indicate a secondary form of CNS vasculitis. Testing for infection is critical as the treatment for infectious causes of CNS dysfunction is very different from the therapy for immune-mediated disorders. Therefore cultures of blood, CSF, and other bodily fluids should be collected. Certain organisms such as mycobacteria, fungi, syphilis, Hepatitis B and C viruses, and HIV should be assayed [33]. Evaluation should also rule out hypercoagulable states and drug exposure.

Lumbar puncture and then the analysis of CSF should be part of the evaluation of patients with potential PACNS. CSF findings are abnormal in almost 90% of patients with pathologically documented cases of primary CNS vasculitis. Usually CSF findings associated with vasculitis are consistent with aseptic meningitis with lymphocytic pleocytosis, elevated protein levels, elevated opening pressures, normal glucose, and the occasional presence of oligoclonal bands [37]. CSF cultures should be negative as a positive culture would imply an infectious etiology.

Neuroimaging such as MRI and CT scans are not specific for the diagnosis of CNS vasculitis. MRI findings may include multiple infarcts with or without contrast enhancement. Small studies have shown that the combination of a normal CSF and MRI has a high negative predictive factor for PACNS and therefore does not need further workup as with a cerebral angiography [38]. Magnetic resonance angiography does not have the resolution to evaluate the small vessels that are usually affected and are generally not useful in evaluating patients for suspected PACNS. Cerebral angiography is critical in evaluating patients with CNS vasculitis. The sensitivity of cerebral angiography decreases with the caliber of the vessel as it is more sensitive for the larger vessels. Although non-specific, vasculitic changes on angiography show alternating areas of vascular constriction and ectasia or beading. The presence of abnormalities in more than one vascular territory including circumferential or eccentric vascular irregularities and multiple occlusions with sharp cutoffs are also consistent with vasculitis.

In pathologically proven cases of PACNS, the sensitivity of cerebral angiography can be as low as 20% [39]. Significant resolution of angiographic abnormalities may occur in a short interval of time with the diagnosis of RCVS. Although it is not common to perform serial angiograms, repeat angiography may be useful if the diagnosis remains unclear days to weeks after the initial study. In patients with RCVS, resolution of abnormal findings would verify the diagnosis. Histological confirmation is not needed if RCVS is suspected.

Histological confirmation remains the gold standard for the diagnosis of CNS vasculitis. Biopsy of the CNS is important in ruling out other mimicking conditions such as infection, lymphoma, and sarcoids. Directing the biopsy to an area of leptomeningeal enhancement may improve sensitivity. Brain biopsy is limited by its low sensitivity and false negatives are common in up to one-fourth of samples. An open wedge biopsy of the tip of the non-dominant temporal lobe has also been suggested as an area of sampling [33].

Treatment

There are no controlled trials to help direct treatment. Therapeutic guidelines are based on experience from other systemic vasculitides and consensus opinions. Initial reports from PACNS showed a grave

prognosis. However, immunosuppressive therapy has been associated with some improvement in CNS vasculitis with a favorable outcome in patients with small vessel involvement.

PACNS are treated with a combination of glucocorticoids and cyclophosphamide for a period of 3-6 months until remission. It is reasonable to begin empiric therapy with prednisone at 1 mg/kg per day (maximum of 100 mg) until the diagnostic evaluation is complete. Once the diagnosis is confirmed, addition of oral cyclophosphamide at a dose of 1 to 2 mg/kg/day is started. The white blood cells must be monitored to avoid leukopenia. Another alternative would be to give intravenous cyclophosphamide at a dose of 600 to 750 mg/m2 once a month for approximately 6 months. Renal function must be monitored while on cyclophosphamide. Adjunctive therapies, such as prophylaxis for Pneumocystis carinii infection and prophylaxis for osteoporosis should be implemented while on treatment.

Treatment of CNS pathology in systemic vasculitis is directed by treating the underlying systemic vasculitis. As a general rule, high-dose glucocorticosteroids are essential in all patients in addition to a second immunomodulating agent. In infection-associated CNS vasculitis, appropriate antimicrobial drugs are used. Adjunctive immunosuppressive medications may be required in patients who do not respond to antimicrobials alone.

Pain Management

Medications can help ease pain symptoms as some patients will experience neuropathic pain. Neuropathic pain can be seen in both patients with PNS or CNS vasculitis. It is often characterized by a deep aching pain that is burning or tingling in the affected nerve distribution. Symptomatic treatment of neuropathic pain can be treated with amitriptyline, nortriptyline, carbamazepine, or gabapentin. Tricyclic antidepressants are usually the first line in managing neuropathic pain but their anticholinergic side effects must be monitored. If the nerve pain is more focal in location, topical medications such as a lidocaine patch may be enough to blunt the pain. Other medications, including opioid analgesics, mexiletine, or topical capsaicin may help ease the pain. Most of these medications, especially the antiseizure medications will need slow titration to find the lowest effective dosage that provides symptomatic relief.

Several complementary or alternative therapies and techniques may also help with pain relief. Acupuncture, hypnosis, and biofeedback may help to limit pain. Relaxation techniques, deep-breathing exercises, visualization techniques, and meditation may also help. Transcutaneous electrical nerve stimulation (TENS) is a painless therapy using electrical impulses to help block the slower conducting pain signals.

Rehabilitation

Patients with nerve damage from vasculitis may develop atrophy and weakness. Overtime, the lack of movement may progress to restricted range of motion. One of the objectives of physical therapy is to maintain range of motion by progressive passive stretching of affected joints. Strengthening of the muscles is also important by using increasing resistance and isometric exercises.

Patients with upper motor neuron involvement may develop weakness as in stroke patients. Physical therapy may help with neuroplasticity by a central remodeling process. Central nervous system damage may also lead to spasticity and increased tone. Medications to help treat hypertonia include baclofen, benzodiazepines, and alpha-agonists. Focal tone can be treated with injections of botulinum toxin. Control of synergy patterns or mass movements is important to help patients regain physical independence.

Occupational therapy is instrumental in helping the patient cope with functional limitations by improving sensorimotor skills. Self-care activities and safety techniques are taught to the patient. Adaptive devices such as long-handled reachers, sock-aids, dressing sticks, and leg-lifters may be needed to become independent with self care. Use of elastic shoelaces or Velcro may decrease the need for fine motor skills of the hand. Patients may need to pay more attention to issues which involve automatic function such as learning to change positions slowly to prevent sudden drops in blood pressure.

Splinting is used to position the fingers and wrist in order to prevent contractures. Use of the multipodus boots in the ankles will help prevent tightening of the Achilles tendon. Use of a lap board or arm trough in a CNS patient should help decrease shoulder subluxation. Use of electrical stimulation may help with cortical remodeling and neuroplasticity. Some braces incorporate an electrical stimulation device that will help activate muscle contraction to help with walking for patients with foot drop. The use of modalities such as moist heat, ultrasound, and paraffin may temporarily decrease pain.

Conclusion

Diagnosis of vasculitic neuropathy or CNS vasculitis requires a thorough history and physical and carefully selected laboratory and radiological tests. Although considerable progress has been made over the past two decades, there are still no controlled therapeutic trials for the treatment of vasculitic neuropathy or CNS vasculitis. There is a need for future controlled studies to help understand the disease process and define optimal treatment.

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