[Frontiers in Bioscience 9, 946-955, January 1, 2004]

CNS VASCULITIS

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1. ABSTRACT

Vasculitis of the central nervous system can be of several varieties depending upon the vessel(s) involved and type of disorder. One can see primary CNS vasculitis as a distinct entity which is primarily manifested as central nervous system injury in a vascular distribution or the vasculitic process can be secondary to a systemic disorder such as systemic lupus erythematosus (SLE) or polyarteritis nodosa (PAN). The inflammation of the CNS vessels can be immune mediated or infectious in nature and a number of "triggers" have been identified including hypersensitivity states. It is quite probable that there is a genetic predisposition in certain individuals and this can lead to an enhanced risk of a vasculitic process when there is exposure to a particular antigen that "sets off" the immune system. The potential for response of the process to antimicrobials and/or immunosuppressants, and the potential for devastating consequences if the process is left untreated, has heightened the urgency in recognizing CNS vasculitis. Key to the recognition and treatment of CNS vasculitis is the evolution of newer insights into the pathogenesis. For example, it is evident that most vasculitides are cell-mediated. Antigen stimulation of CD4+T cells is believed to play a crucial role in giant cell (temporal) arteritis which is the most common type of CNS vasculitis. Identification of genetic susceptibility has also contributed to our understanding of the cascade of events that leads to vascular injury on an inflammatory basis.

2. INTRODUCTION

CNS vasculitis includes giant cell arteritis, Takayasu's arteritis, primary angiitis of the CNS, Wegner's granulomatosis, Churg-Strauss Syndrome, Kawasaki's Disease, vasculitis associated with connective tissue disorders, vasculitis associated with Behcet's disease and sarcoidosis, as well as infectious and neoplastic processes associated with cerebrovascular inflammation (1,2). Vasculitis which affects the CNS, but not in association with a systemic process, has been termed primary angiitis of the CNS (PACNS) (3). Secondary vasculitis refers to vasculitis associated with systemic disorders including collagen vascular disease, infections, and malignancies. Table 1 provides an outline of this classification schema. However, this might well be an oversimplification. Giant cell arteritis, for example, can be a systemic process seen in association with polymyalgia rheumatica or presenting as an FUO. Thus, it can be restricted to the CNS, qualifying as a form of PACNS, or it can represent secondary CNS involvement.

CNS vasculitis is viewed as uncommon in the general population (4). However, the frequency is reflective of the population being studied and whether one is talking about primary or secondary disease. Infectious etiologies, for example, are more common in endemic areas. Coccidiomycosis, seen most commonly in southwestern United States and northern Mexico, where it resides in the topsoil, can promote a granulomatous meningitis and meningeal endarteritis (5). Herpesviruses, such as human cytomegalovirus can be associated with CNS vascular inflammation, as can infections with Hepatitis C (6), and the bacteria *Chlamydia pneumoniae*. Heubner's arteriitis was a well recognized complication of neurosyphilis (7) and cases are still being reported in susceptible populations such as those infected with Human Immunodeficiency Virus (HIV) (8). The patient population most commonly

Table 1. Classification of CNS Vasculitis

1. Primary Central Nervous System Vasculitis
a. Granulomatous versus Non-Granulomatous
b. Benign form
2. Giant Cell Arteritis
a. Temporal arteritis
b. Takayasu's arteritis
c. Overlap with Wegener's granulomatosis
3. Necrotizing Forms of Vasculitis
a. Wegener's granulomatosis
b. Churg-Strauss syndrome
c. Polyarteritis nodosa
4. Hypersensitivity Forms of Vasculitis
a. Drug-induced
b. Toxin-induced
5. Vasculitis Associated with Collagen Vascular Disorders
a. Systemic lupus erythematosus
b. Polyarteritis nodosa
c. Sjogren's syndrome
d. Rheumatoid arthritis
6. Infectious Vasculitis
a. Syphilitic
b. Bacterial
c. Fungal
d. Viral
7. Vasculitis Associated with Lymphoma
8. Vasculitis Associated with Systemic Disease
a. Sarcoidosis
b. Behcet's disease

affected by giant cell arteriitis is Caucasians over the age of 50 and most patients are at least 60 years of age.

Reports of the frequency of various types of CNS vasculitides vary considerably. According to one report, the annual incidence of systemic vasculitides affecting the CNS ranges from <1 to 42 per million (9). Up until 1988, there were only 46 cases of primary CNS vasculitis reported in the world's literature (10). Takayasu's arteritis, most commonly seen in younger women in the Orient, India and Mexico, has an annual estimated incidence of 2.6 per million people (11). For giant cell arteritis, the incidence in subjects greater than 50 years of age is reported to be 20 per 100,000 (12). There is usually a routine evaluation for CNS vasculitis in patients $\leq$ 50 years of age with unexplained stroke. It has been reported that this mechanism is found in roughly 3 to 5% of patients (13). However, it is possible that the potential for vascular inflammation causing stroke has been underrecognized in light of recent reports of drug-induced cerebral vasculitis related to ingestion of sympathomimetic amine-type agents (14).

3. PATHOGENESIS OF CNS VASCULITIS

3.1. Giant Cell Arteritis

Vasculitis can affect small, medium, and large arteries of the CNS. Medium- and large-vessel vasculitis has been most extensively studied (15). Giant cell arteritis is characterized by mononuclear infiltrates of all layers of the arterial wall (16). This panarteritis has granulomatous collections of activated T cells and macrophages. This inflammatory process is T-cell dependent and the CD4+ T cells serve to mediate the cell injury process (17). This T-cell activation requires the activation of dendritic cells which serve as specialized antigen-presenting cells (18). The end result is a combined monocyte and macrophage activation reflective of a systemic inflammatory process in both giant cell arteritis and polymyalgia rheumatica. Another important mediator of this vascular inflammatory process is the presence of resident arterial wall cells which respond to the infiltration of monocytes and macrophages in a specific fashion (19).

There appears to be a genetic predisposition to the development of giant cell arteritis. It has been reported that some allelic variants of class II HLA molecules are a genetic risk factor for this disorder (20). Thus, antigenic stimulation may produce the disorder in susceptible individuals and it is possible that toxins, certain bacterial and viral infections, pharmaceutical agents, and arterial autoantigens may serve as triggers. Infectious agents which have been identified as possible antigen stimulators have included influenza virus, parvovirus, varicella virus, and *Chlamydia pneumoniae* (21-24).

The vessel inflammation in giant cell arteritis includes the production of a variety of adhesion molecules and these serve to regulate leukocytic infiltration (25,26). The leukocyte-endothelial cell interactions occur in association with dendritic cell and endothelial cell activation and this is regulated by chemokines (27). The ongoing inflammatory process involves the release of interferon-? which promotes granuloma formation (28) through its induction of macrophages (29). Macrophages within the medial layer of the vessel wall promote oxidative stress with the production of oxygen-derived free radicals and their metabolites (30). The resultant oxidation of membrane lipids destroys the cellular membrane and results in cell death. During this lipid peroxidation, toxic aldehydes are produced, such as keto-aldose reductase (31), and such a process contributes to apoptosis of smooth muscle cells (15).

This inflammatory process results in intimal hyperplasia with the proliferation of myofibroblasts and extracellular matrix deposition (15). It is reported that platelet-derived growth factor plays a key role in the accelerated luminal narrowing of the affected vessel wall in giant cell arteritis (32). This intimal hyperplasia, which is the primary mechanism of resultant ischemia, rather than thrombosis, is facilitated by angiogenesis with proliferation of microvessels within the intima and media (33). The immunological reaction in giant cell arteritis usually involves the elastin component of the vessel and tumor necrosis factor, expressed by macrophages, appears to play an important role in this process (34). Since elastin is not found in intracranial arteries, this helps to explain why intracranial vessel involvement is uncommon. On temporal artery biopsy, the finding of fragmented elastic fibers, adventitial infiltration with macrophages, CD4 and CD8 T cells, as well as giant cells, and granulomatous inflammation within the media are diagnostic. A schema of

Table 2. Schema of the Pathogenesis of Vasculitis with Giant

Cell Arteritis as a Model
1. Inciting Inflammatory Factor
2. Activation and Infiltration by CD4 and CD8 T cells
3. Activation of Dendritic Cells which serve as Specialized Antigen-presenting Cells
4. Response of Resident Arterial Wall Cells to Inflammatory Cellular Infiltration in a Specific Fashion
5. Infiltration by Giant Cells with Disruption of the Elastic Fibers
6. Infiltration of the Adventitia by Macrophages with Expression of Tumor Necrosis Factor and other Cytokines including Interferon-gamma
7. Promotion of Oxidative Stress with the Production of Oxygen-derived Free Radicals and their Metabolites
8. Membrane Destruction through Lipid Peroxidation with the Production of Toxic Aldehydes
9. Apoptosis of Smooth Muscle Cells
10. Activation of the Nuclear Factor-?ß Pathway which mediates various Inflammatory Signals
11. Granulomatous Inflammation within the Media
12. Role of Platelet-derived Growth Factor in Accelerated Luminal Narrowing
13. Proliferation of Myofibroblasts and Extracellular Matrix Deposition within the Intima
14. Proliferation of Microvessels within the Intima and Media through Angiogenesis
15. Progressive Intimal Hyperplasia

the pathological cascade in giant cell arteritis is provided in Table 2.

3.2. Takayasu's Arteritis

This disorder is also known as pulseless disease. It represents an idiopathic granulomatous giant cell arteritis (35). It primarily involves the large elastic arteries, specifically the aorta and its major branches. The inflammatory infiltrates promote marked thickening of the involved vessels with secondary stenosis or occlusion. Involvement of the renal arteries can result in secondary hypertensive vascular injury. Unlike giant cell arteritis, diffuse dilatation, aneurysm formation, and thrombosis are not uncommon (15).

3.3. Wegener's Granulomatosis

This is a systemic disorder with necrotizing vasculitis of small and medium sized arteries. It is associated with necrotizing granulomas in the upper and lower respiratory tract. This disorder can also be seen in association with focal segmental glomerulonephritis. Unlike giant cell arteritis, Wegener's granulomatosis is associated with tissue necrosis and this is related to the release of lytic enzymes (36). Anti-neutrophil-cytoplasmic antibody (ANCA) has been associated with certain forms of vasculitis including Wegener's granulomatosis (37). Two types of ANCA have been identified: cytoplasmic (c-ANCA) and perinuclear (n-ANCA). These antibodies have been associated with oxidative stress and neutrophil degranulation and they appear to be primed by inflammatory cytokines such as tumor necrosis factor (38). They appear to contribute to endothelial injury in certain forms of vasculitis such as Wegener's granulomatosis where up to 50% of patients are c-ANCA positive (12). ANCA-related vasculitis is associated with antibodies specific for either myeloperoxidase or proteinase 3. T cell activation is involved in Wegener's granulomatosis and correlates with disease activity (39).

3.4. Churg-Strauss Vasculitis

This disorder is characterized by eosinophilic and granulomatous inflammation of the respiratory tract along with necrotizing small- and medium-sized arteritis. Like Wegener's granulomatosis, Churg Strauss is characterized by tissue necrosis resulting from lytic enzymes (15). Up to 60% of patients have positive c-ANCA associated with T cells that respond to the myeloid protein myeloperoxidase (12).

3.5. Primary Angiitis of the CNS (PACNS)

This is a T cell mediated inflammatory process which may well be set off by triggers mentioned above. The typical pathological pattern is one of segmental granulomatous angiitis confined to the CNS. Typically, small and medium sized arteries are involved, although the veins of the brain and meninges can be affected in rare circumstances (40). Not all cases are characterized by granulomatous inflammation (41). However, many clinicians use the term "granulomatous angiitis of the CNS" interchangeably with PACNS for this relatively rare disorder.

3.6. CNS Vasculitis Related to Infection

The pathology is usually reflective of the type of infection. Typically, there is a panarteritis with predilection for the media in viral infection (42). Interferon-? is an important mediator of viral-induced vasculitis and both B and T cells are involved (43). Heubner's arteritis is characterized by medium or large vessel involvement in syphilis (44). The focal narrowing results in ischemic stroke when vascular perfusion is impaired by the degree of stenosis or vessel occlusion. Small artery involvement can also be seen. Despite the fact that positive syphilis serology remains relatively frequent in susceptible populations, the risk of stroke, overall, is quite low (45) and this reflects the fact that syphilitic infection now rarely progresses to the meningovascular phase.

3.7. CNS Vasculitis Related to Collagen Vascular Disease

An inflammatory CNS vasculitis can be seen with systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), rheumatoid arthritis, and Sjogren's syndrome (12). CNS vasculitis with SLE tends to involve the small arteries that are less than 2 mm in diameter (46). It is considered to be relatively uncommon with a reported frequency of 6 to 13% (46). More likely mechanisms for ischemic stroke in SLE include the presence of antiphospholipid antibody syndrome, hypertensive small vessel disease, and cardiac involvement with secondary cardio-embolism (47). CNS vasculitis in SLE is associated with elevated levels of interleukin-2 receptor in the cerebrospinal fluid (48). Lupus-related cerebral transmural angiitis can also affect larger vessels leading to either ischemic or hemorrhagic stroke and the latter can include

Table 3. Manifestations of Primary Angiitis of the

Central Nervous System
1. Headache
2. Encephalopathy
3. Stroke
4. Seizures
5. Visual disturbances
6. Myelopathy
7. Neurobehavioral changes
8. Ataxia
9. Cranial neuropathies

rupture of vasculitic aneurysm (49). PAN can also produce aneurysms. The hallmark of PAN-related vasculitis is fibrinoid necrosis with destruction of the vessel wall (50).

3.8. CNS Vasculitis Associated with Drug Abuse

It is now well recognized that certain illicit drugs can be associated with necrotizing arteritis with sacculation and aneurysm formation (51). The pathological findings resemble PAN with fibrinoid necrosis. Agents implicated have included those with sympathomimetic amine-type activity including methamphetamine, ephedrine, cocaine and its derivatives, heroin and the agents phenylpropranolamine (PPA) and ephedrine (52, 53).

3.9. CNS Vasculitis Associated with Malignancy

Certain malignancies, such as Hodgkin's and non-Hodgkin's lymphoma, can be associated with vasculitis of the CNS (12). The presentation can be very similar to PACNS, but lymphoproliferative disease is more likely to be associated with CNS hemorrhage, mass lesions or spinal cord involvement. Of note, the biopsy of lesions associated with lymphoproliferative disease may be misleading as there may be only angiitis with no evidence of the malignant process (54).

4. MANIFESTATIONS OF CNS VASCULITIS

The manifestations of CNS vasculitis range from relatively minor to severe and life threatening. Headache is a common initial symptom and is the hallmark feature of temporal (giant cell) arteritis. Stroke-like symptoms are a major concern as they tend to progress in a step-wise fashion without effective interventional therapy. As mentioned previously, stroke is uncommon with giant cell arteritis and, when intracranial arteries are involved, there is a predilection for the vertebrobasilar distribution (55). The risk of larger artery involvement in giant cell arteritis is reported to be up to 10% according to one report (56). On the other hand, a stroke-like picture is generally considered the primary manifestation of PACNS.

In addition to headache, other manifestations of giant cell arteritis include unilateral visual loss for which there is an early risk of up to 15% (12). Up 60% of patients have warning symptoms of visual loss in the week preceding the irreversible loss of vision. Untreated, the risk of visual loss in the other eye is up to 75% within two weeks of the initial insult. Other symptoms of giant cell arteritis can include jaw claudication, malaise, fever of unknown origin and up to 30 to 40% of patients have polymyalgia rheumatica in association with temporal arteritis (15).

Takayasu's arteritis typically affects the CNS through large vessel occlusive disease. One can see hemodynamically significant carotid stenosis or vertebrobasilar occlusive disease as well as subclavian steal. The involvement of these vessels can result in transient ischemic attack (TIA) or stroke. Syncope and visual obscuration are two of the more common neurological manifestations (12). One can also see hypertensive-related small vessel occlusive disease, resulting in lacunar-type stroke, in patients who develop hypertension secondary to renal artery involvement.

Wegener's granulomatosis can result in cerebral arterial or venous thrombosis as well as intracerebral hemorrhage when there is CNS involvement. However, this is seen in less than 10% of patients affected by this disorder (57, 58). Not all CNS involvement is directly related to inflammatory vasculitis as one can see vascular compression secondary to granulomatous tissue at the base of the skull, cardio-embolism from cardiac involvement, and CNS vascular disease related to Wegener's associated hypertension (12). Churg-Strauss syndrome can produce cranial neuropathy, ischemic and hemorrhagic stroke, as well as encephalopathy (59, 60). One can also see cardio-embolic disease related to cardiac involvement which is the most common cause of death in this disorder (12).

PACNS can be idiopathic or can be seen related to herpes zoster viral infection, lymphoma, sarcoid, Behcet's disease, or certain drugs (61, 62). It most commonly presents with severe, atypical headache and/or focal neurological deficit (63). Despite such a presentation, the disease course can be self-limited and monophasic, with good recovery, and this has been termed "benign angiopathy of the central nervous system" (BACNS) (64). However, more aggressive disease is more typical and the manifestations reflect the underlying pathology. For example, infectious mechanisms generally promote a panarteritis with the inflammatory cells promoting vascular occlusion or rupture. HIV infection can promote lymphomatous infiltration of the vessel wall or can predispose to meningovascular syphilis. Drug-induced cerebral vasculitis is probably impacted by the degree of exposure, the presence of contaminants within the particular agent, the route of administration, and whether or not the immune system has been primed by previous exposure. Evolution of an autoimmune process will presumably translate into a more aggressive necrotizing arteritis with a worse prognosis. Manifestations of PACNS are summarized in Table 3.

SLE can produce ischemic stroke, hemorrhagic stroke, cerebritis, aseptic meningitis, ischemic optic neuropathy, hypercoagulable state, and non-infective endocarditis (65, 66). As mentioned previously, the more common causes of stroke are not related to CNS vasculitis. These can include stroke associated with lupus-related hypertension. PAN can cause both ischemic and hemorrhagic stroke and this affects up to 12% of patients (67, 68). Stroke can also be seen secondary to CNS vasculitis in association with rheumatoid arthritis and Sjogren's syndrome (69, 70).

CNS vasculitis associated with a lymphoproliferative disorder tends to present with headache and seizures (12). Typically, neurological involvement, which is seen in up to 25% of patients, occurs later on in the course of the disease.

5. DIAGNOSIS OF CNS VASCULITIS

Other than characteristic clinical features, the diagnosis of giant cell arteritis is usually presumptively arrived at with significant elevation of the ESR. An ESR $\geq$ 47 mm per hour is reported to be 92% sensitive for temporal arteritis (71). Obviously, the specificity is lower than this as an elevated ESR can be reflective of a number of different processes. Furthermore, a normal ESR does not exclude the diagnosis (72). It has been reported that the combination of a significantly elevated ESR and C-reactive protein has a sensitivity approaching 100% in temporal arteritis and a specificity of 97% (73). A positive temporal artery biopsy is the definitive diagnostic procedure, but the presence of "skip" lesions can lead to false negative results. This has led to the recommendation that the specimen should consist of 3 to 5 cm length of vessel to enhance the diagnostic yield (12).

The criteria of the American College of Rheumatology (ACR) for Wegener's granulomatosus include at least two of the following four (74): (1) oral ulcers and/or purulent or blood nasal discharge, (2) abnormal, characteristic chest x-ray, (3) microhematuria and (4) presence of granulomatous inflammation within the wall or perivascular space of an artery or arteriole on biopsy. This disorder can occur at any age, but it is most common in the fourth and fifth decades with no sex predilection reported. The diagnosis is supported by the presence of a positive c-ANCA test, specific for proteinase 3, with a negative antinuclear antibody test (75). Of note, there can be an overlap between features of Wegener's granulomotosis and giant cell arteritis (76).

Churg-Strauss syndrome is a combination of pulmonary infiltrates, seen in up to 90% of patients, cutaneous rash in up to 70% of patients, gastrointestinal involvement in up to 50% of patients, along peripheral and central nervous system involvement, as well as allergic manifestations (77). Allergic manifestations can include asthma, allergic rhinitis and nasal polyps in association with eosinophilia. Biopsy of affected tissue reveals granulomatous inflammation along with necrotizing vasculitis of medium and small vessels. CNS involvement is seen in up to 25% of patients (12). The diagnosis is supported by the presence of c-ANCA specific for myeloperoxidase and this is seen in up to 60% of patients.

The diagnostic criteria for Takayasu's arteritis, based upon ACR recommendations (78), include at least three of the following: (1) onset before 40 years of age, (2) claudication of an extremity, (3) > 10 mm Hg systolic blood pressure difference between the arms, (4) decreased brachial artery pulse, (5) bruit over the subclavian arteries and the aorta and (6) stenosis/occlusion of the aorta or its major branches in the proximal upper or lower extremities. Active disease is defined by the presence of at least two of the following features: (1) new onset or worsening of extremity claudication, decreased or absent peripheral pulses, difference in blood pressure measurement between the arms, development of bruit or aggravation of vascular pain, (2) documentation of new arteriographic changes, (3) systemic manifestations such as fever or (4) significant elevation of the ESR.

Diagnostic criteria for PACNS are as follows (10): 1. Definite disease: leptomenigneal, cerebral cortex, or spinal biopsy demonstrating primary angiitis with or without granulomatous features. 2. Possible disease: cerebral arteriogram which demonstrates typical findings of arteritis including beading, ectasia, or segmental narrowing as well as headache or multifocal neurological dysfunction for at least 3 months and CSF exam demonstration of elevated cell and protein levels as well as exclusion of other etiologies.

BACNS is based upon typical cerebral arteriographic findings of arteritis in a patient with relatively mild focal or multifocal neurological deficit along with normal or near normal CSF and the exclusion of other etiologies.

The use of MRI and MRA as well as CT scan of brain can be helpful in the diagnostic assessment of CNS vasculitis. Obviously, an infarction pattern or hemorrhage helps to characterize the type of tissue injury and the area(s) of involvement. In Wegener's granulomatosis, the MRI can reveals not only a hemorrhage or infarction pattern, but also contrast-enhancing inflamed tissue contiguous with orbital, nasal or paranasal sinuses, nonspecific white matter abnormalities, cortical atrophy, granulomatosis lesions within the brain parenchyma, and pituitary gland enlargement with infundibular thickening and enhancement (79, 80). In PACNS, MRI brain scan with and without contrast can demonstrate parenchymal signal intensity changes with variable degrees of enhancement. The level of involvement on MRI tends to correlate with disease activity clinically (81). Patterns of involvement, by MRI, can include: irregular subcortical streaks, leptomeningeal enhancement with relatively spared brain parenchyma, focal cortical ribbon-like appearance, or diffuse parenchymal parenchymal enhancement (81-83). The sensitivity of MRI brain scan has been reported to be of the order of 75% while it is 65% for CT brain scan (84). However, the combination of lumbar puncture with CT scan improves the sensitivity to 92% and the sensitivity approaches 100% when combining lumbar puncture with MRI brain scan. It is important to recognize that the findings on MRI or CT brain scan can be quite nonspecific (85). PACNS can produce lesions on MRI that mimic demyelinating disease (86) or glioma (87).

Magnetic resonance angiography (MRA) and spiral CT angiography hold some promise for the noninvasive detection of CNS vasculitis, but the diagnostic yield has not been convincingly determined to date. MRI is considered to be a more sensitive indicator of CNS vasculitis, but the sensitivity has been called into question.

In a study which compared MRI with cerebral arteriography (88), of 50 arterial territories with vasculitic changes by arteriography, one third had normal MR.

The cerebral arteriogram is generally considered to be the most sensitive test for CNS vasculitis, but a normal study does not completely exclude this process, especially if there is primarily small vessel involvement. In one study (89), only 56% of 31 patients with biopsy-proven CNS vasculitis had an abnormal angiogram and half of these abnormalities were nonspecific. Others have reported a sensitivity of 70 to 90% (90, 91). Chu et al (62) reported on the limitations of cerebral arteriography, and MRI, in PACNS when compared to brain biopsy. They found a positive predictive value of 90 to 100% for brain biopsy, 37 to 50% for cerebral arteriography, and 43 to 72% for MRI with the recognition that MRI often provides nonspecific findings. Clinical suspicion, even with normal arteriographic findings, warrants leptomeningeal biopsy (92). The performance of this procedure can be supported by CSF findings as the CSF is reported to be abnormal in up to 80 to 90% of pathologically confirmed cases of PACNS (12). The mean CSF protein level is 177 mg% with a mean lymphocytic pleocystosis of 77/mm3 (10, 93).

In terms of other etiologies of CNS vasculitis, clinical features and serological findings can support particular collagen vascular disorders. CSF cytology can be helpful in the assessment of carcinomatous meningeal involvement associated with vascular infiltration. CSF exam is also the definitive study in meningovascular syphilis where there is expected to be lymphocytic pleocytosis, elevated CSF IgG, and a positive VDRL. Viral titers and PCR may be useful for possible viral-mediated CNS vasculitis. Sarcoid is supported by the presence of characteristic hilar lymphadenopathy, cranial neuropathy, elevated angiotensin converting enzyme level, and characteristic findings on tissue biopsy. Behcet's disease is characterized by the triad of oral apthous ulcers, genital ulcers, and uveitis (94).

6. TREATMENT OF CNS VASCULITIS

It is now fairly standard to use immunosuppressive therapy for CNS vasculitis. Giant cell arteritis tends to respond readily to corticosteroid therapy in most instances. However, there have been reports of actual worsening of this disorder with steroid therapy (95). Up until recently, a presumptive diagnosis of giant cell arteritis led to immediate initiation of oral prednisone, usually at an initial dose of 60 to 80 mg a day and careful follow-up monitoring of the ESR to determine how effectively the dose could be tapered over time. More recently, it has been recognized that intravenous methylprednisolone might well be a superior choice for initial therapy in an effort to more rapidly protect against the risk of ischemic optic neuropathy (96). Corticosteroid therapy serves to suppress production of inflammatory cytokines and also inhibits the nuclear factor-?? pathway which mediates a number of inflammatory signals (97).

Corticosteroids have limited efficacy in suppressing vascular inflammation and their established benefit in preventing blindness, in temporal arteritis, could well be related to their effect on vascular edema or suppression of the triggering mechanism of dendritic cells within the arterial adventitia (15). Theoretically, combination therapy should be more effective and this might include corticosteroids in addition to agents that either protect against oxidative stress, down-regulate proliferation of myofibroblasts, or suppress angiogenesis within the vessel wall. Low dose aspirin has been reported to be of some benefit in temporal arteritis through its antiplatelet effect as well as an anti-inflammatory effect (98). For example, the ability of aspirin to inhibit the transcriptional activation of the interferon-? gene may serve to interfere with granuloma formation by blocking T-cell function. Patients who are intolerant of steroids must be treated with alternative immunosuppressants such as cyclophosphamide or methotrexate (99).

Corticosteroids continue to be the mainstay of therapy for PACNS. However, persistent clinical disease activity warrants the use of additional immunosuppressive therapy with either cyclophosphamide, methotrexate, or azathioprine. The choice of initial dose of prednisone is debatable, but 60 to 80 mg a day for at least a month, followed by a very slow taper, is reasonable. Many choose to add intravenous followed by oral cyclophosphamide at the same time. In Takayasu's arteritis, patients are generally treated with 40 to 60 mg of prednisone per day and there is about a 40% remission rate with this approach (100). However, roughly 40% relapse with steroid therapy and will require either ongoing higher dose steroid therapy or the addition of cyclophosphamide or methotrexate (101). Of particular note, approximately 20% of patients have monophasic, self-limited disease with no clear need for a protracted course of steroid therapy. Wegener's granulomatosis is usually treated with a combination of steroid and cyclophosphamide or methotrexate (102). One recommended approach is to use glucocorticoid plus cyclophosphamide to induce remission and methotrexate to maintain remission (103). Another approach is to use azathioprine instead of methotrexate (104). However, broad suppression of the immune response is not ideal, because of the complications of long-term therapy, and it is advantageous to promote more specific immunosuppression (105). In Wegener's granulomatosis, the recent reported prominence of the type 1 (Th1) cytokine response (106, 107), associated with enhanced levels of interferon-gamma and tumor necrosis factor, suggests that specific inhibition of these pro-inflammatory cytokines may be a fruitful avenue of therapy. One newer approach is the use of high-dose immunoglobulin (108). Churg Strauss syndrome is generally responsive to corticosteroid therapy, but cyclophosphamide may need to be added (109).

Meningovascular syphilis is arrested with the use of intravenous penicillin G, 12 to 24 million units a day, for 10 to 14 days. However, there have been recent reports of relapse following this regimen especially in patients who are immunocompromised with HIV infection (110). Antiviral therapy may be of benefit in certain patients with viral induced CNS vasculitis. Lymphoproliferative disorders can be responsive to chemotherapy and/or

radiation therapy. Drug-induced CNS vasculitis is often treated with a limited course of steroid therapy (111) and some authors advocate the addition of calcium channel blocking agents to protect against vasoconstriction. The treatment of specific collagen vascular disorders generally involves immunosuppression with steroids with additional immunosuppressant therapy for ongoing disease. Steroids are also a mainstay of treatment for neurosarcoidosis as well as Behcet's disease affecting the central nervous system.

7. PROGNOSIS IN CNS VASCULITIS

The prognosis for CNS vasculitis depends upon the neurological picture at the time of presentation along with the underlying etiology. For example, lymphoproliferative mediated CNS vasculitis has a 90% three-year mortality rate (54). PACNS and Takayasu's Arteritis can both be relatively benign and self-limited. Up to 90% of patients with Takayasu's Arteritis survive for at least 10 years (12). Both Wegener's granulomatosis and Churg Strauss syndrome tend to respond to immunosuppressive therapy and can be placed in remission. However, the prognosis is impacted by the severity of the organ systems involved and the dosing and duration of immunosuppressive therapy over time. Drug-induced CNS vasculitis will probably have an outcome similar to age-matched patients presenting with a stroke-like picture. The overall 30-day case fatality rate for stroke is roughly 20% and one might be able to extrapolate this percentage to CNS vasculitis, but one must also factor in coexistent factors, deficit at time of presentation, age, and whether or not the agents ingested resulted in significant impairment of other organs.

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Key Words: Vessel, Artery, Primary Angiitis, Wegener's Granulomatosis, Churg-Strauss Syndrome, Takayasu's Arteritis, Arteritis, Review

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