VASCULITIC NEUROPATHY

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Abstract

Vasculitic neuropathy corresponds to the occurrence of vasculitis at the level of *vasa nervorum*, resulting in ischemic damage of the peripheral nerve and axonal degeneration.

Vasculitic neuropathy commonly occurs in association with systemic diseases and may be the initial manifestation or arise in the course of established disease. Although rare, vasculitis can be confined to the peripheral nervous system – non--systemic vasculitic neuropathy.

This paper aims to review the classification, diagnosis and treatment of vasculitic neuropathy.

Keywords: Vasculitic Neuropathy; Vasculitis; Peripheral Nervous System.

Introduction

Vasculitis is defined as vascular wall inflammation and may occur as a primary phenomenon or secondary to an established disease. It can involve vessels of different diameters and different organs, affecting the peripheral nervous system in 60-70% of patients with some systemic vasculitic syndromes[1]. Systemic vasculitides are divided into two categories: primary systemic vasculitis, where there is no identified etiology, and secondary systemic vasculitis, which occurs in the context of other pathologies such as connective tissue diseases, infectious diseases, neoplastic or induced by drugs.

Primary systemic vasculitides are classified based on the diameter of the vessels involved. Vasculitis most associated with vasculitic neuropathy are those involving the pre capillary arteries in the nerves, ie, Polyarteritis *Nodosa*, Wegener's Granulomatosis, Microscopic Polyangiitis and Churg--Strauss syndrome[2,3].

Secondary systemic vasculitides associated with neuropathy can occur in the context of:

a) Connective tissue disorders as Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE) or Sjögren Syndrome,
b) Infections such as Hepatitis C, Human immunodeficiency virus (HIV), Cytomegalovirus (CMV) and Parvovirus B19,
c) Neoplasms as non-Hodgkin lymphoma, small cell carcinoma and gastrointestinal tumors,
d) Drugs[3].

In a minority of cases the vasculitis is confined to the nerve, denominated non-systemic vasculitic neuropathy[4,5] (Figure 1 and Table I).

Physiopathology

Vasculitis is defined as inflammation of a blood vessel, with consequent destruction of the vascular wall and tissue ischemia. Histologically, it is characterized by fibrinoid necrosis of the vascular wall.

In vasculitic neuropathy, there are two mechanisms of induction of vasculitis in the *vasa nervorum*: 1) deposition of immune complexes and 2)

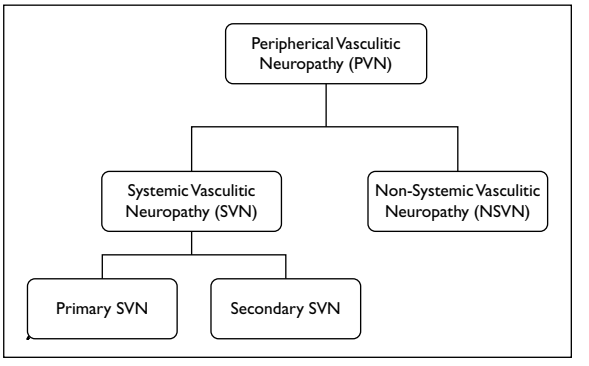

Figure 1. Classification of peripheral vasculitic neuropathy

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Table I. Classification of Systemic Vasculitic Neuropathy

Primary Systemic Vasculitis (60%):
- Churg-Strauss syndrome (20%)
- Polyarteritis Nodosa (18%)
- Wegener's granulomatosis (12%)
- Microscopic polyangiitis (7%)
- Cryoglobulinaemia (2%)
- Henoch-Schönlein purpura (1%)

Secondary Systemic Vasculitis (25%):
- Connective tissue disease (17%):
  Rheumatoid arthritis, Systemic Lupus Erythematosus, Sjögren syndrome
- Infection (4%):
  Hepatitis C and B, HIV, CMV, Parvovirus B19
- Malignancy (3%):
  Non-Hodgkin lymphoma, small cell carcinoma of the lung and digestive cancers.
  Others (1%):
  Sarcoidosis, drugs, Diabetes Mellitus

cell-mediated immunity[6].

1) Deposition of immune complexes (IC): circulating antibodies bind to endogenous or exogenous antigens forming IC, these will be deposited in the vascular wall and activate the complement, forming factors C3a and C5a, which are chemotactic for neutrophils.

Neutrophils infiltrate the vascular wall, phagocyte the IC and release proteolytic enzymes and oxygen free radicals that will destroy the vascular wall.

This mechanism is associated with vasculitis secondary to infection, connective tissue diseases, cancer, drugs and cryoglobulinemia[3,6].

2) Cell-mediated immunity: T cells in circulation recognize antigens associated with endothelial cells that act as antigen presenting cells. This interaction leads to increased expression of cell adhesion molecules and release of chemotactic cytokines [eg. Tumor Necrosis Factor (TNF) alpha], which in turn recruit and activate neutrophils and lymphocytes with subsequent inflammation and destruction of the vascular wall[6,7]. This mechanism occurs in vasculitis associated with anti-neutrophilic cytoplasmatic antibodies (ANCAs).

The end result of both processes is the induction of immunological inflammation and necrosis of vessel wall, compromise of the lumen and peripheral nerve ischemia. Ischemia will cause focal and asymmetric axonal degeneration, and this process is more frequent in myelinated fibers than in non-myelinated fibers.

Clinical Manifestations

Clinical manifestations of vasculitic neuropathy can be divided into neurologic and systemic manifestations.

Neurological manifestations include pain, dysesthesia, paresthesia and decreased muscle strength in the territory of a nerve, usually of acute or subacute onset. The first nerves to be affected are the longest and with progression from distal to proximal. The nerves most commonly involved are the peroneal, tibial, ulnar, median and radial[8]. It is a sensory or sensory-motor neuropathy, with pure motor neuropathy being extremely rare. In vasculitic neuropathy, there are three patterns of peripheral nerve injury: mononeuritis multiplex, asymmetric polyneuropathy and distal symmetric polyneuropathy.

Mononeuritis multiplex is characterized by injury of two or more nerves in separate areas. A common clinical presentation is the foot drop by infarction of peroneal nerve, or the hand drop by damage of radial nerve. This is the most specific form of presentation of vasculitis, occurring in approximately 10-15% of vasculitic neuropathies, however it is important the differential diagnosis with other pathologies such as leprosy, Lyme disease or diabetes[8] (Table II).

With progressive involvement of various nerves we have overlapping mononeuropathies, resulting in a pattern of asymmetric polyneuropathy. This form of presentation is more frequent in vasculitic neuropathy, accounting for three quarters of patients.

Distal symmetric polyneuropathy is the less frequent form of presentation of vasculitic neuropathy. It usually presents with sensorimotor disturbances that have a symmetrical «stocking and glove» distribution[8].

Systemic manifestations include constitutional symptoms and specific organ symptoms. Constitutional symptoms such as weight loss, fever and malaise, are more common in systemic vasculitic neuropathies, but may also be present in 15-40% of non-systemic vasculitic neuropathy[9].

Specific organ symptoms occur only in systemic vasculitic neuropathies. The most characteristic skin manifestations are purpura, ulcers or nodules. Respiratory system involvement can be translated

Table II. Differential Diagnosis of Mononeuritis Multiplex

- Acute or chronic inflammatory demyelinating polyneuropathy
- Lyme disease
- Leprosy
- Diabetes mellitus
- Neurofibromatosis
- Neoplasia with nerve invasion
- Multiple cholesterol embolism
- Vasculitic neuropathy

as rhinitis, purulent rhinorrhea, asthma and hemoptysis. Gastrointestinal involvement can present as abdominal pain and gastrointestinal bleeding, musculoskeletal involvement as arthralgia, myalgia and arthritis, and renal involvement as hematuria, proteinuria, or hypertension[2,3].

Primary Systemic Vasculitic Neuropathy

Neuropathy occurs mainly in vasculitis with involvement of arteries of medium and small size, being very rare in vasculitis with involvement of large vessels only (eg, Takayasu arteritis). Polyarteritis *nodosa* is a vasculitis of medium and small arteries. Vasculitic neuropathy is one of its classification criteria of ACR 1990 and it is present in 50-75% of patients[3,10]. Clinical features associated with this systemic vasculitis are: livedo reticularis, palpable purpura, digital ischemia, arthralgia and nephropathy. The presence of microaneurysms and occlusion of small and medium arteries are angiographic characteristics of this vasculitis.

Churg-Strauss syndrome is a primary vasculitis of small and medium sized vessels, associated with peripheral eosinophilia and ANCA with anti--mieloperoxidase (MPO) specificity. Clinical characteristics often associated are: palpable purpura, rhinitis, asthma, and arthralgia. Neuropathy appears in about 80% of patients, and is also one of the ACR 1990 classification criteria[8,10].

Microscopic polyangiitis is a necrotizing vasculitis involving small vessels, associated with perinuclear pattern ANCA (p-ANCA) in approximately 60-80% of cases. The main clinical features are arthralgia, alveolar hemorrhage, and rapidly progressive glomerulonephritis[1,10]. Vasculitic neuropathy is present in 70% of patients[10].

Wegener's granulomatosis (WG) is a vasculitis of small vessels, associated with ANCA with anti-proteinase 3 specifity (PR3) in approximately 90% of cases. Neuropathy is present in 15-40% of patients and the typical clinical characteristics include destruction of the nasal sinuses, oral ulcers, arthralgias, pulmonary infiltrates and glomerulonephritis[3,11].

Cryoglobulinemia is a small vessel vasculitis associated with cryoglobulins and it presents commonly with palpable purpura, skin ulcers and arthralgia[12]. Neuropathy occurs in about two thirds of patients[12].

Henoch-Schönlein purpura is a vasculitis of small vessels which may also involve the *vasa nervorum* causing neuropathy. Clinical features associated with this vasculitis are: palpable purpura, arthritis, abdominal pain and nephropathy[1,3].

Systemic Vasculitic Neuropathy Secondary to Connective Tissue Diseases

In Rheumatoid Arthritis (RA), vasculitis involves mainly medium and small arteries. Vasculitic neuropathy occurs in about 10% of patients, presenting as mononeuritis multiplex or symmetric sensory-motor polyneuropathy[13]. It is more common in patients with severe RA (nodules, joint erosions and deformities), with long standing disease and with high rheumatoid factor (RF) titers[13]. Clinical features associated with rheumatoid vasculitis are skin ulcers, digital ischemia, pericarditis and mesenteric vasculitis[13].

In systemic lupus erythematosus (SLE), neuropathy appears in approximately 5% of patients[14]. The most common presentations are mononeuritis multiplex or symmetric sensory-motor polyneuropathy[14,15]. One large study of patients with SLE showed an association between vasculitis and Raynaud's phenomenon, serositis, myocarditis, leukopenia and antiphospholipid antibody syndrome[15]. In this study peripheral neuropathy was the most common initial presentation of vasculitis, aside from cutaneous lesions. Patients with vasculitis had longer disease duration and younger age of SLE onset[15].

Vasculitic neuropathy is reported in 10% of patients with Primary Sjögren Syndrome[16]. It commonly presents as a distal symmetric sensorimotor polyneuropathy, with predominant sensory characteristics[16].

Vasculitic neuropathy secondary to infection

Infections most often associated with vasculitic neuropathy include: Hepatitis B and C, HIV, CMV,

and parvovirus B19[17].

Hepatitis B (HBV) can be associated with Polyarteritis *Nodosa* (PAN), with the clinical picture similar to idiopathic PAN. The prevalence of HBV-related PAN has declined over the past few years to 20%[10]. Vasculitis usually appears within the first 12 months of infection. Neuropathy appears in about 83% of patients[10,17].

Hepatitis C has a strong association with Mixed Cryoglobulinemia, with 80 -90% of such patients being positive for anti-HCV antibodies. The most frequent clinical features are purpura, arthralgias, neuropathy and glomerulonephritis[17].

Vasculitis in HIV infection can be directly related to HIV or secondary to an opportunistic infection, particularly to CMV. Neuropathy occurs in less than 1% of patients, presenting mainly as a distal symmetric sensory polyneuropathy[18]. It may arise at any stage of the disease[18].

Parvovirus B19 infection can induce a vasculitis of small vessels, mimicking Henoch-Schönlein purpura, in about 1% of patients[17].

Vasculitic neuropathy secondary to malignancy

Cancers most often associated with vasculitic neuropathy are: non-Hodgkin lymphoma, small cell carcinoma of the lung and digestive cancers. The clinical picture of the neuropathy is similar to that of primary vasculitis, with the exception of neuropathy secondary to lymphoma, which commonly involves the central nervous system (CNS). Other manifestations of these neuropathies are weight loss, asthenia and anorexia[3,8].

Vasculitic neuropathy secondary to sarcoidosis

Sarcoidosis can cause granulomatous vasculitis at the level of *vasa nervorum* resulting in vasculitic neuropathy. The usual form of presentation is an acute or subacute mononeuritis multiplex, but a sensorimotor polyneuropathy can also be present[19]. The main clinical characteristics associated with this disorder are erythema nodosum, arthralgias, hilar adenopathy and CNS involvement[19].

Vasculitic neuropathy secondary to diabetes *mellitus*

Vasculitic neuropathy secondary to diabetes *mellitus*, also known as lumbosacral radiculo plexopathy, occurs in a small percentage of patients, especially in those over 50 years old [20]. It is characterized by acute or subacute pain and muscle weakness at lower limb, proximal and unilateral, progressing to bilateral[20].

Vasculitis neuropathy secondary to drugs

Several drugs can induce vasculitis, involving more commonly the small vessels of the skin, and less frequently the peripheral nerves. The drugs most commonly associated with the induction of vasculitis are hydralazine, propylthiouracil and leucotriene antagonists[21].

Non-systemic vasculitic neuropathy

Non-systemic vasculitic neuropathy comprises approximately 15% of the cases of vasculitic neuropathies[7]. It was first described in 1938 by Kernohan and Woltman, but only in 1987 was introduced the term of non-systemic vasculitic neuropathy by Dyck and colleagues[4].

In 2004 Collins proposed the following diagnostic criteria: (1) clinical evidence of neuropathy, (2) electrodiagnostic changes consistent with axonal neuropathy, (3) nerve or nerve/muscle biopsy diagnostic of vasculitis, (4) without clinical, laboratory or radiological evidence of non-neuromuscular involvement, (5) non-identified etiology, and (6) no systemic disease predisposing to vasculitis (e.g, connective tissue disease, malignancy, cryoglobulinemia)[7].

As with systemic vasculitic neuropathy, non-systemic vasculitic neuropathy most commonly presents as mononeuropathy multiplex. The evolution is slower than in systemic vasculitic neuropathy, with better prognosis[7].

General symptoms, such as weight loss and fever, can be present in approximately 15-40% of patients. Sixty percent have mild to moderate increase in sedimentation rate. Thirty percent have anemia and 15% leukocytosis. Approximately 30% have positive ANA, 13% are RF positive and 11% have positive ANCA[22,23].

Several studies have shown that 6-37% of patients develop systemic vasculitis[22,24].

Diagnosis

The diagnosis must be based on clinical history and physical examination, including neurological examination, laboratory studies, nerve conduction and electromyography studies, and nerve biopsy[2,7]. In the clinical history it is important to search for peripheral neurologic symptoms, such as dysesthesia, paresthesia and muscle weakness. A careful history of organ/system symptoms should be taken, in order to rule out respiratory, cardiovascular,

musculoskeletal, genitourinary, gastrointestinal or cutaneous involvement.

On physical examination is important to perform general and neurological examination with identification of territories involved, evaluating sensitivity, muscle strength and tendon reflexes. Laboratory tests can exclude or confirm the presence of systemic disease and should always be guided by clinical history and physical examination. The initial analytical study should include complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine, transaminases, urinary sediment study, and in selected cases, antibodies to hepatitis B, C and HIV, CMV and Parvovirus B19 serology, angiotensin converting enzyme, antinuclear antibodies, anti-ds DNA, ANCA, RF, anticyclic citrullinated protein antibodies (anti-CCP), anti SSa and SSb, cryoglobulins and complement.

Electrophysiological studies reveal axonal injury involving multiple individual nerves. Nerve conduction studies show low amplitude muscle action potentials, with normal or slightly decreased conduction velocity. Electromyographic evaluation of the affected muscles reveals fibrillation potencials and decreased recruitment of motor unit potencials[8].

Nerve biopsy can provide a definitive diagnosis when it shows infiltration of inflammatory cells in the vascular wall associated with necrosis of the wall of *vasa nervorum*. However, this technique has a sensitivity of only 60% because the vasculitis lesions are focal. The combination of nerve and muscle biopsy increases the sensitivity of the nerve biopsy alone, being the most frequent combinations the sural nerve and gastrocnemius muscle, or peroneal nerve and peroneal muscle[4,6].

However, nerve biopsy is not always necessary for the diagnosis of vasculitic neuropathy, ie. in cases where the clinical presentation is compatible with vasculitic neuropathy and there is histological or angiographic evidence of vasculitis in another organ[2].

Treatment

Treatment of vasculitic neuropathy is initiated by the removal of precipitating factors in cases related to drugs, infection or malignancy, followed by immunosuppressive therapy, analgesics and physical rehabilitation.

Immunosuppressive treatment

NON-SYSTEMIC VASCULITIC NEUROPATHY

Given the paucity of randomized controlled trials for the treatment of non-systemic vasculitic neuropathies, the therapeutic decision is based upon the physician's clinical experience, on data from observational studies and extrapolation of results obtained in the treatment of systemic vasculitides.

REMISSION INDUCTION TREATMENT

Steroids are the first line treatment in non-systemic vasculitic neuropathy. It is recommended to start with prednisolone at a dose of 1 to 1.5 mg/kg/d for two months, or in severe cases, start with pulses of methylprednisolone 1g/d for 3-5 days[25]. Subsequently, prednisolone should be gradually tapered (10mg/week) up to 40mg/d, followed by 5mg/week up to 20mg/d, and by 1mg every two weeks up to 5mg/d. It is important to carefully monitor the patient, concerning an eventual worsening of the neuropathy itself or occurrence of early systemic symptoms[5,25].

Most authors recommend the combination of cyclophosphamide in the induction treatment of non-systemic vasculitic neuropathy. It can be used the oral (2mg/kg/d) or intravenous (750mg/m^2) route. Cyclophosphamide should be continued for 3-6 months, and later replaced by a less toxic drug[5,7]. Current available data suggest that pulse-dosing cyclophosphamide results in fewer adverse effects, like haemorrhagic cystitis and transitional cell carcinoma of the bladder, but carries an increased risk for relapses compared with oral cyclophosphamide[26].

MAINTENANCE TREATMENT

After induction treatment it is recommended to replace cyclophosphamide by azathioprine or methotrexate. Azathioprine should be started at a dose of 50mg/d increased gradually to 2-3 mg/kg/d. Methotrexate should be started with 15mg/week and gradually increased up to 25mg/week[5].

The maintenance treatment should be continued for one year after remission.

PRIMARY SYSTEMIC VASCULITIC NEUROPATHY/ /SECONDARY TO CONNECTIVE TISSUE DISEASES

In systemic vasculitic neuropathy the aggressiveness of therapy will depend largely on the involvement of major organs such as kidney and/or lung, not only on the peripheral nervous system involvement.

The first line treatment recommended is the combination of cyclophosphamide with corticos-

teroids. In the remission induction phase, three pulses of 1 g/d of methylprednisolone followed by prednisolone 1mg/kg/d associated with monthly intravenous cyclophosphamide (15mg/kg, max.1g). Maintenance treatment: cyclophosphamide pulses quarterly, or azathioprine (2-3mg/kg/d)[27,28].

VASCULITIC NEUROPATHY SECONDARY TO INFECTION

Chronic immunosuppressive treatment is contraindicated in vasculitic neuropathy secondary to viral infections. Corticosteroids may be used for short periods, 1mg/kg/d in the first week with a rapid tapering and suspension after two weeks.

The anti-viral treatment should be continued for at least 6 months, in case of hepatitis C with ribavirin and interferon alpha, and in hepatitis B with lamivudine.

In resistant cases, plasmapheresis is indicated for the removal of immune complexes[17].

NEW TREATMENTS

For patients with progressive disease in spite of optimal therapy, alternative options include anti-TNF alpha agents and rituximab[29].

Aggressive forms of vasculitis have been postulated to be the result of in appropriately increased production of TNF[29]. Inhibition of TNF seems to reduce inflammation and improve endothelial dysfunction in systemic vasculitis[30]. Reports of uncontrolled trials have suggested the efficacy of TNF inhibition in patients with Wegener's granulomatosis, rheumatoid arthritis or crioglobulin associated vasculitides, refractory to standard treatment[31-33].

Rituximab, a chimeric anti-CD20 antibody, induces the death of B cells. Rituximab has shown promising results in the treatment of cryoglobulinaemic vasculitis and rheumatoid arthritis[34]. Two small studies suggest improvement in neuropathic symptoms in patients with hepatitis C associated cryoglobulinaemic vasculitis[35].

A multicenter retrospective study with 65 patients showed that rituximab was effective as a remission induction therapy for refractory ANCA-associated vasculitis. This study also found that continuing immunosuppression did not reduce relapses, but re-treatment was effective and safe[36].

However, randomized controlled trials of rituximab for vasculitis have not been done.

ANALGESIC TREATMENT

Pain is present in almost all patients with vasculitic neuropathy and can be severe. Even after appropriate immunosuppressive treatment about 44-71% of patients have chronic pain[25]. The drugs recommended for treatment of pain in vasculitic neuropathy are: amitriptyline, carbamazepine, gabapentin, pregabalin and duloxetine[25,27].

PHYSICAL REHABILITATION

Physical rehabilitation should begin as early as possible.

In the initial stage, pending the axonal regeneration, rehabilitation is especially important to maintain joint range of motion and prevent muscle atrophy, with passive range of motion exercises consisting in progressive stretching. The use of braces or splints can also be recommended to enhance balance and posture[25].

Prognosis

The prognosis correlates directly with early diagnosis and treatment.

Several studies also showed better prognosis in combination treatment (cyclophosphamide and prednisolone) versus monotherapy with prednisolone[5,25,28].

Although there is no comparative study, the systemic vasculitic neuropathies have a worse prognosis than non-systemic vasculitic neuropathy, both in terms of survival, and of neurologic deficit[25].

Conclusion

Vasculitic neuropathy most often occurs in the context of a systemic disease, usually a primary systemic vasculitis or a connective tissue disease. Less often, vasculitic neuropathy presents in an isolated fashion, called non-systemic vasculitic neuropathy. The diagnosis is based on a careful history, complete physical examination and selected laboratory assays designed to diagnose or exclude a systemic disease.

Electromyography and nerve conduction studies are useful to distinguish nerve dysfunction from muscular disease and in identifying characteristic patterns of peripheral nerve disease.

The gold standard for the diagnosis of vasculitic neuropathy is a nerve biopsy, usually performed in conjunction with a muscle biopsy. Patients with biopsy proven vasculitis in other organ and pre-

sentation of nerve dysfunction typical of vasculitis do not require nerve biopsy.

Although corticosteroids remain the mainstay of treatment for vasculitic neuropathy, current treatments are becoming more disease specific. Prospective clinical trials of traditional and novel treatments are needed to identify indications and establish efficacy for immunosuppressant agents, intravenous immunoglobulin, and plasma exchange.

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