

Always Keep in Mind the Neurological Complications of Connective Tissue Diseases-Review

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Received date: May 20, 2014, Accepted date: Jul 24, 2014, Published date: Jul 31, 2014

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Abstract

Both central and peripheral nervous system complications are frequent and varied in vasculitides associated with connective tissue disorders. In many cases the neurological disorders have a typical clinical course or even an early onset that all clinicians should be aware of them. The neurological manifestations are mainly caused by direct effect of the connective tissue diseases, as well as side effects of corticosteroids and other immunosuppressive therapies. The purpose of this short review is to update the major neurological disorders in various vasculitides, accurate diagnosis and management.

Keywords: Neurological disorders; Central and peripheral nervous system; Vasculitides; Immunosuppressive therapies

Introduction

Connective tissue diseases cover a wide range group of multisystem inflammatory disorders of muscle, joints, and skin often sharing the common feature of vasculitis [1-3]. Both immune mediated changes in the vasculature and ischemia of the vessels walls, as a hallmark of vasculitis, are the main causes of symptoms of the central nervous system (CNS) and peripheral nervous system (PNS). Initial evaluation includes a comprehensive clinical assessment, serological tests, histology and radiology.

For this purpose, it is practical to use the classification of vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (CHCC2012) [4]:

- 1) Large vessel vasculitis (Takayasu arteritis Giant cell arteritis)
- 2) Medium vessel vasculitis (Polyarteritis nodosa)
- 3) Small vessel vasculitis (Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), Microscopic polyangiitis, Granulomatosis with polyangiitis (Wegener's), Eosinophilic granulomatosis with polyangiitis (Churg-Strauss))
- 4) Variable vessel vasculitis (Behçet's disease (BD) Cogan's syndrome)
- 5) Single-organ vasculitis: The involved organ and vessel type should be included in the name (e.g., cutaneous small vessel vasculitis, testicular arteritis, central nervous system vasculitis)
- 6) Vasculitis associated with systemic disease (e.g., rheumatoid vasculitis, lupus vasculitis)
- 7) Vasculitis associated with probable etiology (e.g., hydralazine-associated microscopic polyangiitis, hepatitis B virus-associated vasculitis, hepatitis C virus-associated cryoglobulinemic vasculitis)

Neurological events are likely to be fatal without judicious use of immunosuppression, thus, prompt diagnosis leads to avoid pervasive

injury and disability. This review aims to update recent information on vasculitis with the most common neurological complications, their diagnosis and management.

Polyarteritis Nodosa (PAN)

Neurologic manifestations are very common in PAN due to systemic necrotizing vasculitis affecting small and medium arteries causing ischemia leading to thrombosis or bleeding [1-4]. CNS symptoms occur relatively late in the course of the disease causing multifocal encephalopathy in 40% of patients, depending on the region in which lesions appear. Patients with PAN typically demonstrate neurological signs such as personality disorders and memory, atypical persistent headaches, aphasia, hemiplegia, visual disturbance (blurred, hemianopia), seizures, transverse myelitis and subarachnoid hemorrhage. Up to 65% of patients present with various disorders including as mononeuritis multiplex (almost typical and generally painful manifestation of the disease) and distal symmetric sensorimotor polyneuropathy [2,5]. Suralis nerve biopsy is a useful diagnostic tool in identifying necrotizing vasculitis with infiltrating lymphocytes [5,6]. PAN patients without poor-prognosis factors at diagnosis, treated initially with corticosteroids alone, are seen to have excellent long-term survival [7]. However, relapses are frequent in severe disease with neurologic, renal or cardiac manifestations, cyclophosphamide plus corticosteroids may improve the poor outcome [7,8].

Allergic Granulomatosis (Churg-Strauss syndrome)

Churg-Strauss syndrome is a rare form of systemic vasculitis occurring in patients with asthma and blood eosinophilia, according to the American College of Rheumatology 1990 criteria [9]. Neurological findings in allergic granulomatosis are caused by systemic necrotizing vasculitis with eosinophil infiltrates affecting small vessels. CNS events are rare, and resemble nodular polyarteritis [1,5,8,10]. CNS involvement may include paralysis of seventh cranial nerve and phrenic nerve palsy, cerebral hemorrhage or infarction, convulsions and coma, but these occurrences are much less typical.

On the other hand, PNS involvement is noted in about 60% of patients, mainly in the form of mononeuritis multiplex or symmetric mild sensory axonal neuropathy [2,3,8-11]. The neuropathy is caused mainly by nerve ischemia due to occlusion of vasa nervorum. The result of this infarction is a loss of sensory and motor axons. Nerve biopsy is characteristic and useful to confirmed the diagnosis and Churg and Strauss reported three primary histopathologic alterations: (1) eosinophilic tissue infiltration, (2) necrotizing vasculitis and (3) extravascular granulomas. The inflammatory process in CSS tends to affect smaller epineurial arterioles than in systemic vasculitis [11].

We conclude that, Churg-Strauss syndrome complicated frequently with polyneuropathy, and as remission depends on immunosuppressive therapy, it is important to recognize it in the early stage. The diagnosis of polyneuropathy is based on clinical and electrophysiological studies, but precise histology, immunohistochemistry and morphometric study of the peripheral nerve biopsy maybe decisive in establishing the diagnosis.

Rheumatoid Arthritis

Rheumatoid arthritis is the most common disease of the connective tissue that mainly affects the joints. Symptoms of the nervous system often primarily due to vasculitis and damage resulting from the pressure applied by rheumatoid nodules [1,5,12] CNS involvement is uncommon in rheumatoid arthritis and presents vasculitis –like symptoms, such as strokes, seizures, and meningitis (probably due to rheumatoid nodules).

Recent theories on the pathogenesis of rheumatoid arthritis suggest that the synovial cells of these patients chronically express an antigen that triggers the production of the rheumatoid factor (RF) involving infiltration of polymorphonuclear leukocytes Destructive synovitis results in ligamentous laxity and bony erosion with atlantoaxial subluxation, being the most common cervical deformity associated with RA. Since a neurologic deficit is noted in only 7-34% of cases, many patients with pain and radiographic criteria for instability do not develop neurologic sequelae. However, 10% of patients die from brainstem compression [13]

PNS complications are very common and depend on the cause of the injury, localization and severity

Sensory peripheral neuropathy - attributed to vasculitis which characterizes the disease, though the pathogenesis remains unknown. According to clinical and electrophysiological findings aesthetic impairment is recorded in over 75% of patients. Neuropathy is predominantly axial and manifests with mild sensory symptoms in the extremities, characterized by a symmetric and progressive disease course [2,3].

Mononeuritis multiplex is less frequent in rheumatoid arthritis but has a more severe clinical course.

Peripheral entrapment neuropathy is caused by direct pressure on a single nerve. The nerves most commonly affected are the median nerve (carpal tunnel syndrome), the ulnar nerve in the elbow, Guyon's canal at the wrist, medial or lateral plantar nerve in the tarsal canal, and the peroneal nerve.

Sensorimotor peripheral neuropathy in the upper and lower limbs is more severe and carries a poor prognosis.

Muscle weakness and muscle atrophy, especially with proximal localization, are frequent in patients with rheumatoid arthritis. Muscle

biopsy reveals evidence of myositis in about 40% of patients, while levels of muscle enzymes are always elevated [11].

Treatment of rheumatoid arthritis can cause various side effects. Gold is the cause of Guillain-Barre in 1% of patients characterized by sudden onset and rapidly progressive muscle weakness. Albeit rare, cranial nerve palsies, transverse myelitis and seizures have also been noted. Chloroquine may cause headaches, psychotic disorders, neuropathy and myopathy, while D- penicillamine is often responsible for the disturbances in taste, inflammatory myopathy or myasthenia. Hearing disorders, particularly at high frequencies are associated with high doses of salicylates, as well as with the known side effects of corticosteroids [11]. Demyelination observed in RA patients receiving anti-TNF α treatment, could be attributed to the unmasking of latent pre-existing Multiple Sclerosis (MS), the emergence of a new demyelinating episode (either MS or MS like), or to the incidental coexistence of the two disorders [14].

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem organ involvement, heterogeneity of clinical features, and variety in degree of severity with similarities with others autoimmune disease. Thus, lupus mimickers may present as a lupus-like condition (i.e., 2 or 3 criteria) or as one meeting the classification criteria for SLE [15]. Multiple sites may be involved within the nervous system, often in the early stages, especially among young people [1,4,7,16]. CNS manifestations range from 33% to 75% among patients with SLE, mimicking other neurological conditions. Clinical characteristics could be classified into the following groups [16]:

A. Non-thrombotic disease of the CNS in which antibodies against structural components of the CNS, immune complexes, vasculitis and non-vascular lesions are considered mainly responsible. In a recent review of 180 studies, CNS involvement in SLE was characterized by headache (23.73%), seizures (13.56%) and cognitive impairment (8.47%). Depression and anxiety were frequently observed (73.15% and 23.95%, respectively). [13]. Seizures occur in 15% to 50% of patients, more likely in the early stages of the disease or even a few years before the diagnosis of lupus are associated with the duration and severity of disease .

B. Thrombotic disease of the CNS that is mainly due to anticardiolipin antibodies and vasculitis. The most frequent clinical manifestations of this group are:

1. Occlusive vascular lesions involving the spinal cord (10% of patients have been affected) [11]

2. Chorea: may be the first clinical manifestation of SLE, occurring in 1% to 4% of patients, mainly children or young patients.

3. Ballismus: a rare complication, more common among young people attributed to sub thalamic nucleus infarction.

4. Cerebellar ataxia may appear alone or be accompanied by other disorders associated with the antiphospholipid syndrome.

C. Intracranial bleeding, particularly subdural and subarachnoid haemorrhage occurs in 40% of patients due to coagulation abnormalities seen in SLE.

The complications of the peripheral nervous system in SLE are rare, and arise in approximately 10% of patients, due to vasculitis.

Trigeminal neuropathy may precede other symptoms of the disease by several years, with distal symmetric sensory or sensorimotor polyneuropathy being the most commonly observed sub-acute or chronic with mild to moderate symptoms. Few cases of acute or chronic inflammatory demyelinating polyradiculoneuropathy have been reported [17].

Generally, myopathies in SLE take the form of inflammatory myopathies when appearing in the acute phase of the disease or as secondary side effects such as hypokalemia, resulting from treatment with corticosteroids or hydroxychloroquine [16]

Systemic Sclerosis (SS)

Systemic sclerosis is characterized by widespread microvasculopathy and diffuse tissue fibrosis affecting the skin and other systemic organs, particularly the heart, lungs, and gastrointestinal tract. Previously considered a rare event, neurological complications in SS have been increasingly recognized [1,5]. In a recent review of 180 studies, CNS involvement in SLE was characterized by headaches (23.73%), seizures (13.56%) and cognitive impairment (8.47%). Depression and anxiety were most frequently observed (73.15% and 23.95%, respectively), followed by myopathy (51.8%), trigeminal neuropathy (16.52%), and peripheral sensorimotor polyneuropathy (14.25%) [13], the most common peripheral neuropathy recorded in patients with SS is carpal tunnel syndrome (1% to 10%) [2,3,18]. Trigeminal neuropathy occurred most frequently in young women with PSS in overlap with other disorders, particularly mixed connective tissue disease with clinical evidence of myositis. Some patients experience symptoms such as proximal muscle weakness and display increased muscle enzymes, but few show evidence of inflammatory myopathy on muscle biopsy. Corticosteroids and cyclophosphamide may be effective [18]

Polymyositis - Dermatomyositis

Dermatomyositis is defined as an inflammatory angiopathy affecting the muscles (polymyositis) and skin (dermatomyositis) [7]. Overlapping with malignancy or other connective tissue diseases, this condition appears in up to 15% of patients. Dermatomyositis is traditionally considered to be due to a complement-mediated microangiopathy but the factors responsible for complement activation remain uncertain. Recent studies have emphasised the importance of the type I interferon pathway in the pathogenesis of the disease and have identified autoantibodies with specificities for different clinical subgroups of patients. Polymyositis is characterised by a cytotoxic T cell response targeting as yet unidentified muscle antigens presented by MHC Class I molecules, and can occur in isolation but is more often part of a multi-systemic overlap syndrome. The immune-mediated necrotising myopathies are heterogeneous and are distinguished from polymyositis by the sparseness of inflammatory infiltrates and recognition of an association with specific autoantibodies such as anti-SRP and anti-HMGCR [19].

The muscle biopsy is the most crucial test for establishing the diagnosis, but also the most common cause of misdiagnosis due to erroneous interpretation. In dermatomyositis, the inflammation is predominantly perivascular or in the interfascicular septae and around rather than within the fascicles [20]. In polymyositis, multifocal lymphocytic infiltrates surround and invade healthy muscle fibres we view the diagnosis of polymyositis as definite if a patient has an acquired, sub-acute myopathy, raised concentrations of serum creatine

kinase, and primary inflammation in the muscle biopsy [21]. The diagnosis of dermatomyositis is definite if the myopathy is accompanied by the characteristic rash and histopathology. If no rash is detected but the biopsy sample is typical for dermatomyositis, the diagnosis is probable dermatomyositis [21].

Neurological complications in the onset of juvenile dermatomyositis include cerebral vasculitis of small to medium-sized vessels (particularly in overlapping syndromes); generalized tonic-clonic convulsions; hypoxic ischemic encephalopathy secondary to cerebral hypoperfusion (with poor myocardial function in some patients); and hypertensive encephalopathy; they can also be consequence of Cyclosporine treatment. Evidence of CNS involvement demands aggressive immunosuppression and multiorgan support. Vasculopathy is a rare but potentially fatal systemic complication of dermatomyositis [19].

Sjögren's Syndrome

In accordance with the American-European Consensus Group (AECG) classification of Sjögren's syndrome (SS), diagnosis requires any four of the six diagnostic criteria [22]:

- 1) Ocular symptoms: dry eyes for over three months, foreign-body sensation, use of tear substitutes more than three times daily
- 2) Oral symptoms: feeling of dry mouth, recurrently swollen salivary glands, frequent use of liquids to aid swallowing
- 3) Ocular signs: Schirmer test performed without anesthesia (<5m in 5 min), positive vital dye staining results
- 4) Oral signs: abnormal salivary scintigraphy findings, abnormal parotid sialography findings, abnormal sialometry findings (unstimulated salivary flow <1.5 mL in 15 min)
- 5) Positive minor salivary gland biopsy findings
- 6) Positive anti-SSA or anti-SSB antibody results

Secondary SS is diagnosed when, in the presence of a connective-tissue disease, the patient displays symptoms of oral or ocular dryness in addition to criteria 3, 4, or 5, as listed above.

CNS complications observed in 15% of patients include stroke, haemorrhage, seizures, aseptic meningoencephalitis, and transverse myelitis; however, the spectrum of neurological complication is not well defined. Additionally, SS with CNS disease may mimic MS [1,4,23]. The peripheral nervous system is the most commonly affected in 30% of patients, mainly in women suffering from SS with peripheral symmetrical sensorimotor polyneuropathy and mononeuritis multiplex [2,3,24]. Sjögren's can also complicate polymyositis and dermatomyositis. In conclusion, although central and peripheral complications of primary SS are difficult to assess, partly because of the wide spectrum of possible manifestations, their incidence is estimated to be approximately 20%. Neuropathy is the most specific complication [24].

Wegener Granulomatosis

Approximately 50% of patients with Wegener's granulomatosis exhibit neurological complications caused by necrotizing granulomatous lesions of small vessel veins. [1-4,7] CNS involvement includes several types depending upon the presence of vasculitic, contiguous extension, or remote granulomatous spread. Granulomas cause basilar meningitis, temporal lobe dysfunction and venous sinus

occlusion [25,26]. Cranial neuropathy of nerves II, VI and VII are also caused by granulomatous lesions [26].

The typical and most frequent PNS complication is mononeuritis multiplex (10% to 22%) symmetrical sensorimotor polyneuropathy with relatively rapid progression, though rare, has also been recorded [27]. Based on the 1994 Chapel Hill Consensus, the diagnosis of Wegener's granulomatosis requires a tissue biopsy (usually a kidney biopsy) showing evidence of vasculitis demonstrated by granulomatous inflammation and necrosis in the involved organs [25]. However, a negative biopsy does not exclude the diagnosis of Wegener disease. As concerns both CNS and PNS involvement, rituximab and infliximab have emerged as potential treatment options for refractory disease [26]. Thirty-three patients with active disease were enrolled in an open prospective trial that reviewed the adjunction of infliximab to standard therapy with the aim of achieving remission within a median follow-up of 12 months. No benefit was demonstrated with the use of anti-TNF- α agents. Current treatment strategies have substantial short-term and long-term adverse effects, and relapses are frequent; thus, less-toxic and more-effective approaches are needed.

Temporal Arteritis

Temporal arteritis, otherwise known as giant cell arteritis, usually occurs in middle or advanced age. Typically, it targets large and medium-sized arteries, with mainly the temporal artery showing evidence of clinical changes. Notwithstanding its name, giant cells are not a precondition for diagnosis; histopathologic features are consistent with diffuse vascular involvement.

Clinical manifestations of the CNS are related to the anatomical region of the carotid artery. The most common and initial symptom is headache, migraine localized in the temporal area, accompanied by fever, malaise, myalgias and anorexia. The temporal artery is often swollen and sensitive to palpation. The most common and serious complication of temporal arteritis is that of unilateral or bilateral loss of vision due to ischemic optic neuropathy.

PNS complications affect 15% of patients and include mononeuritis multiplex or distal symmetrical sensorimotor polyneuropathy [27].

Blood tests reveal lymphocytosis and an increased erythrocyte sedimentation rate, while temporal artery biopsy confirms the presence of inflammation and giant cells.

Polymyalgia rheumatic co-exists in 40% of patients with temporal arteritis. Given the significant risk of vision loss, glucocorticoids should be started without delay. A randomized controlled trial of 44 patients showed that maintenance therapy with Infliximab failed to show more efficacy in disease control than that of steroids, and it did not allow a reduction in the dose of steroids required to prevent relapse [28]. A dramatic response to low-dose corticosteroids remains a valuable diagnostic tool in patients for whom diagnosis is uncertain. However, the challenge lies in recognizing atypical cases that lack the more specific manifestations. We conclude that the diagnosis of giant cell arteritis should always be considered in an elderly patient with an unexplained elevation of inflammatory markers and others neglected symptoms such as trismus, facial swelling and chronic dry cough in order to avoid serious complications.

Primary Angiitis of The Central Nervous System (Pacns)

PACNS is a rare inflammatory disorder of the small vessels of the CNS. The histologic findings of PACNS consist of granulomatous inflammation, fibrinoid necrosis of vessel walls or exclusively of lymphocytic cellular infiltrates [29-31]. Subacute or chronic meningeal type form is observed, mainly in men, and present as a headache, or migraine lasting three to six months, followed by focal and generalized neurologic symptoms. Confusion, impaired memory, and problems with attention and concentration constitute signs of cognitive dysfunction. Isolated CNS symptoms include hemiparesis, seizures, ataxia and cranial nerve palsies. The cerebrospinal fluid (CSF) examination shows a slight increase in cells and albumin. Neither neuroradiological findings nor laboratory tests can confirm a definite diagnosis of the disorder. Brain biopsy reveals the characteristic histological lesions of the disease [30]. Since, no controlled therapy studies for CNS angiitis have yet been performed treatment recommendations for PACNS based on protocols for systemic vasculitides with severe organ involvement. A combination of steroids and pulse cyclophosphamide (CYC) is recommended for patients with a poor prognosis [30,31]. With a relapse rate of 25% and reduced survival rate, we recommend that a close follow up of suspected PACNS is mandatory.

Isolated Peripheral Nerve Vasculitis

Peripheral neuropathy lacks evidence of an association with systemic necrotizing vasculitis involvement in other organs [26]. Some studies have identified vascular lesions in the muscles, without a satisfactory explanation of the pathogenesis of the disease. Vasculitis in its primary form affects smaller diameter vessels and mainly the epineurium, not unlike systemic vasculitis. Multiple mononeuritis, asymmetric sensorimotor and sensorimotor distal symmetrical are the most frequent forms [32]. The high rate of symmetrical neuropathy in a study could possibly be due to the considerable delay between the initiation of symptoms and the clinical and neuropathological examination. Isolated peripheral nerve vasculitis should be suspected when there is unexplained polyneuropathy without evidence of systemic involvement. Clinical and neurophysiological studies are essential for the detection of nerve involvement, but the specific diagnosis of isolated peripheral nerve vasculitis may be missed unless a biopsy is performed. Primary vasculitis of PNS responds well to treatment with corticosteroids and its prognosis is good [32].

Behcet 's Syndrome

This multisystem disorder of unknown etiology predominantly affects men with oral and genital ulceration and uveitis, based on the International Criteria for Behcet's Disease [33]. The histology reveals vasculitis of small vessels and perivascular deposition of inflammatory cells in the meninges.

CNS involvement in Behcet's disease, usually called neuro-Behcet's syndrome (NB) in 30% of cases, includes acute type and chronic progressive type. Acute NB is characterized by acute meningoencephalitis with focal lesions, presenting high intensity areas in T2-weighted images or FLAIR images on MRI scans. Cyclosporin A frequently causes acute NB. Acute NB responds to steroid therapy, and is usually self-limiting. By contrast, chronic progressive NB is characterized by intractable slowly progressive dementia, ataxia and dysarthria with persistent elevation of cerebrospinal fluid IL-6 activity

(more than 20 pg/ml). PNS Involvement is extremely rare, although isolated cases have been reported with distal symmetrical polyneuropathy and mononeuritis multiplex [34].

Chronic progressive NB is resistant to conventional treatment with steroid, cyclophosphamide, or azathioprine. However, recent studies suggest the efficacy of low dose methotrexate in chronic progressive NB [35].

Conclusion

The vasculitides and connective tissue diseases provide an avenue for investigating the pathophysiology of immune system among the vasculature of the CNS and PNS. Searching the international bibliography, there is no established, effective treatment for these disorders. Prospective clinical trials are warrant for early recognition of all of the possible medication related side effects. Long-term evaluation of patients is important in order to manage relapses.

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