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Peripheral Neuropathy in Connective Tissue Diseases

Mouna Snoussi, Faten Frikha and Zouhir Bahloul

Abstract

Connective tissue diseases are characterized by different organ disorders due to loss of immune system tolerance to autoantigens. Peripheral neuropathy is one of the features of these diseases with variable frequency; it is more prevalent in Sjögren syndrome. Peripheral neuropathy is often seen in the course of the disease. Nonetheless, it may be also a presenting sign or the unique feature of immune system dysfunction. Neuropathies in connective tissue diseases are related mainly to vasculitic disorder. It requires prompt diagnosis and treatment to improve its outcome. Peripheral neuropathy in connective tissue diseases could be multifocal and asymmetric, or confluent and symmetrical. This chapter reviews the clinical, diagnostic and therapeutic features of neuropathies associated with the common diffuse connective tissue diseases.

Keywords: peripheral neuropathy, vasculitis, connective tissue disease, treatment, electromyography, nerve biopsy

1. Introduction

Connective tissue diseases (CTDs) are defined as a group of acquired diseases resulting from persistent immune-mediated inflammation. They are generally the consequence of autoimmune dysregulation resulting in generation of autoreactive T cells or autoantibodies [1]. Immune disorders can affect any organ of the human body responsible for multisystem involvement. The CTDs classily include systemic lupus erythematosus (SLE), Sjögren syndrome (SS), systemic sclerosis (SSc), dermatomyositis and polymyositis (PM/DM), undifferentiated CTD (UTCD) and overlap syndromes such as mixed CTD (MCTD). Most clinicians do not include systemic necrotizing vasculitis, e.g. polyarteritis nodosa, Churg-Strauss syndrome and Wegener's granulomatosis in the category of CTD [1]. Peripheral neuropathies (PN) may complicate many different systemic autoimmune diseases. PN in CTD large clinical, histopathological and pathogenic spectrum [2]. We aim in this chapter to precise the epidemiology, the pathogenesis, the diagnosis and the treatment of neuropathies in CTD including systemic lupus erythematosus (SLE), Sjögren syndrome (SS), dermatomyositis and polymyositis (PM/DM), systemic sclerosis (SSc) and mixed CTD (MCTD).

2. Epidemiology of peripheral neuropathy associated with connective tissue diseases and its topographic distribution

PN is one of the clinical features of CTD with variable frequency and prognosis. It is often seen in the course of the disease. However, it may also be a presenting

Vasculitic neuropathy
Mononeuropathy multiplex
Asymmetrical polyneuropathy
Distal symmetrical polyneuropathy
Distal axonal polyneuropathy
Compression neuropathy
Sensory neuronopathy
Trigeminal sensory neuropathy
Other types of neuropathies associated with connective tissue disease
Acute demyelinating polyneuropathy
Chronic demyelinating polyneuropathy

Table 1.
Types of neuropathies associated with CTD (adapted from neuropathies in connective tissue disease/Richard K) [12].

sign or the unique feature of immune system dysfunction [3]. The prevalence of PN is different in the literature series depending on the type of CTD and the means of diagnosis. The incidence of PN in SS is 10–60%, and many of these patients (40–93%) present with neuropathy as the sentinel symptom [4]. PN in SLE patients ranges from 25 to 50% based on electrodiagnostic studies. Curiously, the incidence drops to only 5% based on clinical criteria [5, 6]. Finally, PN is rarely associated with the other CTD, namely, SSc, MCTD, DM and PM [4].

PN refers to the part of a spinal nerve distal to the root and plexus. It is a damage or a disease affecting nerves [7–9]. Neuropathy affecting one nerve is called “mono-neuropathy” and neuropathy affecting multiple nerves in the same areas on both sides of the body is named “symmetrical polyneuropathy”. When separate nerves in disparate areas of the body are affected, the neuropathy is called mononeuritis multiplex, multifocal mononeuropathy or multiple mononeuropathy [8, 10, 11]. Types of neuropathies that are associated with CTD are outlined in **Table 1**.

3. Pathogenesis of peripheral neuropathy in connective tissue diseases

The principal components in the pathogenesis of peripheral nerve lesions in diffuse CTD are ischemia due to vasculitis and immune abnormalities. Generally, most of patients have a combination of the ischemic, immunological and metabolic mechanisms of damage to the peripheral nervous system. Nevertheless, one component may be predominant in a different stage of the disease. In systemic scleroderma, the greater role is played by ischemic mechanisms, mainly in the initial states of the disease, while SLE may involve the participation of immunological mechanisms, especially in acute and subacute disease with high level of autoimmune activity [13].

3.1 Vasculitic neuropathy

The immunopathogenesis of vasculitis in CTD is still unclear. The accumulation of immune complexes in the vasa nervorum initiates the leukocytoclastic reaction, which is characterized by segmental fibrinoid necrosis and transmural inflammatory cell infiltration. Vasculitis induces the occlusion of vasa nervorum at the

epineurial arteries and produces nerve infarction. Nerve infarcts typically lead to axonal degeneration [14]. Demyelination and conduction block may occur transiently but are usually not a predominant or persistent finding [15]. The clinical and electrophysiological features of neuropathies correlate with the rapidity of onset of ischemia. Acute ischemia induces the development of mononeuropathy, while prolonged circulatory insufficiency is associated with chronic polyneuropathy. The compression-ischemic mechanism leads to the formation of tunnel syndromes [13, 14, 16, 17]. The Peripheral Nerve Society task force has recently proposed a classification that categorizes vasculitic neuropathy into primary systemic vasculitides, secondary systemic vasculitides including CTD and nonsystemic or localized vasculitis on the basis of disease associations [18].

3.2 Autoimmune disorders

Patients with diffuse CTD may have IgG and IgM anticardiolipin antibodies in their serum, which are associated with severe signs of neural lesions, as demonstrated by electromyogram [13]. Moreover, serum levels of anti-nerve growth factor (NGF) antibodies are greater than normal in 32.1% of patients with diffuse CTD. Increased serum levels of anti-NGF are associated with high disease activity and more severe nervous system involvement [13].

3.3 Metabolic disorder

Peripheral nervous system abnormalities in CTD are also explained by metabolic disorder secondary to aggressive therapy, multiorgan pathology and endocrine abnormalities in these patients. Metabolic disorder may induce a reaction of demyelization and axon dystrophy in severe cases [13].

4. Clinical practice guidelines of peripheral neuropathy in CTD

In CTD neuropathic symptoms often start gradually and then get worse. Deep proximal aching pain is the first sign in the affected limb. Burning pain in the cutaneous distribution of the affected nerve is frequent. Weakness and numbness usually appear over several hours to several days after the pain. The delay of the former symptoms is explained by the nerve infarction. On physical examination, most patients have pain and temperature sensory loss in the distribution of the affected nerve. A few patients have impairment of vibration and position sense. Hyporeflexia is also rare except in the ankles. In fact, tendon reflexes other than at the ankle are lost only if the femoral, musculocutaneous, or radial nerves are affected proximally [12, 18, 19]. The quantitative sensory testing (QST) is a tool to analyse the perception in response to external stimuli of controlled intensity. It has been used for the early diagnosis and follow-up of small fibre neuropathies. Although the QST is time-consuming and it is modified also in non-neuropathic pain as in rheumatoid arthritis and inflammatory myalgia, it cannot be taken alone as a conclusive demonstration of PN [20]. The QST is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components (grade A) [20]. According to EFNS international guidelines, to evaluate hyperalgesia in PN, it is recommended to use simple tools such as a brush and at least one high-intensity weighted pin-prick or von Frey filament. The evaluation of pain in response to thermal stimuli

is best performed by using the thermotest which is recommended for pathophysiological research or treatment trials. The DN4 may be a useful instrument for the daily diagnostic of PN in CTD [21].

5. Diagnosis and clinical results

In patient with multiorgan involvement and mononeuropathy multiplex, the diagnosis of vasculitic neuropathy is usually easy. However, the diagnosis may be more difficult in less typical presentations of CTD or when peripheral neuropathy is the unique manifestation of the disease. The diagnosis of peripheral neuropathy in CTD particularly in atypical situation is based first on clinical and physical examinations. Electromyography confirms even an underlying axonal neuropathy. The most characteristic electromyographic finding in vasculitic neuropathy described in the previous series is axonal degeneration with multifocal distribution. The typical feature is a low sensory nerve and compound muscle action potential amplitudes in a non-length-dependent distribution with normal or minimally reduced conduction velocities [15, 17, 22, 23]. A partial conduction block is rare, and it is seen transiently and early in stage of nerve ischemia [12]. Laboratory tests may be helpful in establishing the presence of systemic vasculitis or identifying previously undiagnosed connective tissue disease. Evaluation of patients with suspected neuropathy in CTD should include liver and kidney function tests, erythrocyte sedimentation rate, urinalysis as well as a complete blood count. The choice of immunological test including rheumatoid factor, antinuclear antibody, cryoglobulins, antineutrophil cytoplasmic autoantibody and serum complement depends on the clinical presentation of the patient. Nerve biopsy may be helpful in demonstrating vasculitic process. A concomitant muscle specimen is useful to increase diagnostic yield because of the patchy distribution of vasculitic lesions [18].

6. Particularity of PN in each CTD

6.1 Peripheral neuropathy in Sjögren syndrome

Sjögren syndrome is a CTD more prevalent in women at the age of menopause. It is characterized by sicca syndrome and other extra-glandular symptoms. Peripheral nervous involvement in Sjögren syndrome (SS) is reported with variable frequency because of diverse methods for detection of neuropathy and may precede the onset of the disease or be the initial diagnostic clue [24]. The most common feature is symmetrical distal sensory neuropathy, autonomic neuropathy and trigeminal sensory neuropathy. Mononeuritis multiplex, chronic inflammatory demyelinating neuropathy and motor neuropathy are less common [8].

6.1.1 Ganglionopathies

Sensory ganglionopathy is characterized by an impairment of kinesthetic awareness. Patients have the profound handicap of proprioceptive sense affecting larger joints. Electromyogram shows unelicitable sensory nerve action potentials, with preservation of compound motor action potentials [25]. When MRI is performed, it can reveal T2 hyperintensities limited to the gracile and cuneatus tracts of the dorsal spinal cord with sensory neuronopathies [26]. There are two mechanisms evoked in the pathogenesis of gangliopathies in SS. First, the cellular autoimmunity, confirmed by the infiltration of mononuclear and predominantly T cells in

the dorsal root ganglia, is associated with cellular degeneration in the absence of vasculitis [25, 27, 28]. Second, recent studies have suggested that the presence of antibodies against the G-bodies, which are a subcellular aggregation of noncoding RNA intermediates and proteins, is associated to neuropathy [29, 30]. Moreover, It was reported that antineuronal antibodies were seen more frequently in Sjögren patients with severe peripheral neuropathy (PN) complications [25].

6.1.2 Small fibre neuropathies

Small fibre neuropathy is the most common PN manifestation of SS. It is a painful, sensory neuropathy affecting the nociceptive A-alpha and unmyelinated C-fibres. Small fibre neuropathy is reported with variable frequency. In the Hopkins Green Sjögren cohort, it was described as the most frequent manifestation [31]. The onset of small fibre neuropathy is usually subacute to chronic, occurring over weeks to months, although cases with hyperacute evolution of hours to days have been reported [27]. The cardinal clinical symptom of isolated small fibre neuropathy is an excruciating burning pain. The physical examination reveals a selective impairment in small-fibre modalities of pinprick and temperature, with relatively preserved vibratory sense and proprioception. The diagnosis of small fibre neuropathy is based on skin biopsy, which assesses the low density of intraepidermal nerve fibres [25, 32].

6.1.3 Sensorimotor polyneuropathies

The majority of studies reported that axonal polyneuropathies as the most frequent type of PN in SS. The onset of sensorimotor polyneuropathy is usually subacute or chronic. The axonal sensory neuropathies are characterized by proprioceptive sensory loss and motor reflexes, and there are diminished sensory nerve action potentials in electromyogram [25]. The sensory symptoms, however, are gradually accompanied by muscle weakness in a distal, symmetrical distribution [32].

6.1.4 Multiple mononeuropathy

It is the transduction of vasculitic neuropathy, and it is very uncommon in SS reported in 0–5% in previous studies. It is usually associated with extra-glandular manifestations [25, 27, 33–35]. Patients with SS and presenting mononeuritis multiplex should be assessed for cryoglobulinemia polyclonal (types II and III) rather than monoclonal (type I) mainly when there is high-titer rheumatoid factor positivity or when there is disproportionate C4 hypocomplementemia, with normal levels of C3. When nerve biopsy is performed, it may show a lymphocytic or necrotizing vasculitis [32].

6.1.5 Cranial neuropathies

The most common cranial neuropathy in SS is the trigeminal neuropathy, which is usually progressive and can be bilateral and requires symptomatic treatment. Motor dysfunction of cranial nerves is less common, and the facial nerve is the most cranial nerve targeted. The acute onset of cranial neuropathy is due to vasculitic mechanism especially when associated with equally rapid development of multiple mononeuropathies in the extremities [25].

6.1.6 Demyelinating neuropathies

Demyelinating neuropathy is a rare manifestation of SS [32, 33]. Cases of chronic idiopathic demyelinating polyneuropathy have been the subject of case

reports in Sjögren patients but have not been substantially described in larger case series. The most common neurophysiologic finding in demyelinating neuropathies was demyelination of the motor nerves [36–38]. The onset of this neuropathy is subacute and characterized by severe proximal and distal weakness and proprioceptive sensory deficit. Treatment with steroid and sometimes with intravenous immune globulins may be effective [32, 39].

6.1.7 Autonomic neuropathy

Autonomic neuropathy is the rarest type of peripheral nerve involvement in SS because it is usually underdiagnosed. The clinical manifestations of autonomic neuropathy will vary depending on the organs which are affected. Symptoms range from urinary symptoms to severe disabling postural hypotension [27, 32, 38]. In recent studies, autonomic dysfunction is associated with the severity of fatigue in patients with primary SS. However, no association was detected between autonomic dysfunction and exocrine function in these patients [32, 40].

6.2 Peripheral neuropathy in systemic erythematosus lupus

Systemic lupus erythematosus is a multisystem autoimmune disorder with a broad spectrum of clinical presentations as cutaneous, renal and articular manifestations (**Figure 1**). Affected patients typically have subacute or chronic distal symmetrical polyneuropathies with predominant sensory symptoms. Distal symmetrical axonal degeneration is the major feature of most cases, although other types of peripheral neuropathy have been described [12, 41]. Oomatia reported the subtypes of peripheral neuropathy (PN) attributable to SLE in a group of 82 patients out of 2097 and detailed in **Table 2** [42]. Other features such as Guillain-Barré syndrome, plexopathy and autonomic neuropathy are very low in all series

Figure 1.
Butterfly rash in systemic lupus erythematosus.

Type of peripheral neuropathy	Frequency no. (%)
Axonal neuropathies	46 (56.1)
Sensory axonal polyneuropathy	19 (23.2)
Sensorimotor axonal polyneuropathy	21 (25.6)
Mononeuritis multiplex	6 (7.3)
Small fibre neuropathies	14 (17.1)
Demyelinating polyneuropathies	
Acute inflammatory demyelinating polyneuropathy	1 (1.2)
Sensory demyelinating polyneuropathy	1 (1.2)
Mixed axonal-demyelinating sensorimotor polyneuropathy	3 (3.6)
Plexopathy	1 (1.2)

Table 2.
Type of peripheral neuropathy in SLE (adapted from peripheral neuropathies in systemic lupus erythematosus/ Oomatia et al.) [42].

[41]. In recent data, small fibre neuropathy is more frequent in SLE, and the decreased intraepidermal nerve fibre density of unmyelinated fibres is a diagnostic test [42]. The mechanisms of peripheral neuropathy in SLE are unclear. Several factors have been reported particularly small-vessel vasculitis and lesions induced by autoimmune antibodies and immune complexes. In series, where nerve biopsy is performed, the anatomopathologic aspect was perivascular mononuclear cell infiltration and variable intimal thickening without necrotizing vasculitis. The presence of necrotizing vasculitis is possible and constitutes a prognostic factor of the disease [12, 41, 43]. Endoneurial mononuclear cell infiltration and increased class II antigen expression were also noticed [12, 43].

6.3 Peripheral neuropathy in systemic sclerosis

Systemic sclerosis is a rare connective tissue disease with a prevalence of 1 in 10,000 [44]. It is characterized by symmetrical, widespread thickening of the skin (**Figure 2**) [45]. The prevalence of peripheral neuropathy is unknown with reported ranges in retrospective studies varying from 0.01 to 14% of patients [46, 47]. Vascular-dependent neuropathy is the principal mechanism inducing a distal symmetric, mainly sensory polyneuropathy as in other connective tissue diseases [13, 46, 47]. Cranial mononeuropathies can also occur, mainly the trigeminal nerve, leading to numbness and dysesthesias in the face. Rarely the seventh and ninth cranial neuropathies are affected [11]. The electrophysiological features are those of sensory axonopathy [11]. Rare cases of mononeuritis multiplex have been mentioned in the course of limited SSc (CREST: calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia) and are due to a necrotizing vasculitis [11].

6.4 Peripheral neuropathy in mixed connective tissue disease

Mixed connective tissue disease is defined as the overlap of SLE, SSc and PM, with a high titer of extractable nuclear antigen and its ribonucleoprotein component [48]. Mild distal axonal polyneuropathy was exceptionally reported in 2 of 20 patients with mixed connective tissue disease, but there has not been a detailed study of the neuropathy or its treatment [48].

Figure 2.
Sclerosis of the face in systemic sclerosis.

6.5 Peripheral neuropathy in dermatomyositis and polymyositis

Nerve involvement in patients with DM is mediated through membrane attack complex (MAC) formation, leading to nerve injury. This entity called “neuromyositis” was first reported in 1890 [49]. Further studies showed a frequency of 7.5% in DM or PM patients with polyneuropathy [50]. Neuropathy due to DM is difficult to diagnose due to necessity of excluding other comorbid etiologic conditions and heterogeneity of muscular manifestations [49]. Nerve biopsy may reveal endothelial vascular injury, and immunohistochemical stains revealed increased expression of perivascular VEGF and demyelination associated or not with inflammation [51].

7. Treatment of peripheral neuropathy in CTD

7.1 General approach

There are no treatment guidelines specific to each CTD. In general, the management of PN is based on symptomatic treatment of pain as in other causes of neuropathies. Typically, patients with painful polyneuropathies respond to drugs known to be effective for neuropathic pain, including tricyclic antidepressants and a variety of antiepileptic drugs as gabapentin and pregabalin, which is preferred because of its better bioavailability [52]. Concerning the antidepressants, international guidelines provide the same level of recommendation for nonselective tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs). Most clinical trials showed that the efficacy of SNRIs is lower than that of tricyclic antidepressants. However, tricyclic antidepressants have more side effects in elderly and are contraindicated in patients with glaucoma, prostate hypertrophy or some cardiac conduction disturbances. Venlafaxine is a SNRI who has shown efficacy in painful polyneuropathies of different origins [53]. In CTD, PN is mainly due to vasculitic

and immune abnormalities. So when vasculitic neuropathy is diagnosed, corticosteroids should be promptly introduced to recover sensory and motor deficits [3]. Most authors recommend starting oral prednisone at high dose of 1 mg/kg per day. In severe cases, intravenous pulses of methylprednisolone of one 1 g for 3–5 days might be appropriate for initial treatment. This treatment should be maintained during the subacute phase, and after 6 to 8 weeks, the treatment should be tapered progressively. Immunosuppressant therapy is associated to corticosteroids in severe forms of vasculitic neuropathy or in systemic vasculitic PN. Cyclophosphamide seems to be the most effective drug for induction of remission and improvement of survival in non-viral systemic vasculitides [18]. Most patients need 3–12 months of cyclophosphamide induction therapy before they can be switched to a maintenance immunosuppressant [54]. Immunosuppressant used as a maintenance therapy is azathioprine, methotrexate and mycophenolate mofetil [55]. Intravenous immunoglobulin is a safe treatment used in serious systemic PN with clinical benefit [18].

7.2 Particularities of treatment in each CTD

Therapeutic strategies of small fibre neuropathy in SS are still unclear. Carbamazepine is generally the first-line agent for trigeminal neuralgia. The use

PNS manifestation	First-line treatment approach	Treatment of refractory cases
Polyneuropathy	Neurotrophic agents (tricyclic antidepressants, SNRI (duloxetine, venlafaxine), anticonvulsants (gabapentin, pregabalin)) (glucocorticoids (1 mg/kg/day of prednisone equivalent)) Severe forms: immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide)	Carbamazepine High-dose IVIG PEX Rituximab
Mononeuropathy single/ multiple	Systemic glucocorticoids (1–2 mg/kg/day of prednisone equivalent or pulses of methylprednisolone 500/1000 mg for 3–5 days with long-term dosage reduction) IV Cyclophosphamide	Rituximab, IVIG, PEX Mycophenolate mofetil Azathioprine
Small fibre neuropathy	Neurotrophic agents (tricyclic antidepressants, SNRI (duloxetine, venlafaxine), anticonvulsants (gabapentin, pregabalin)), topical anaesthetics Analgesics	Immunosuppressants IVIG Psychological support
Acute inflammatory demyelinating polyradiculoneuropathy (GBS)	High-dose IVIG PEX Cardiorespiratory supporting measures	Glucocorticoids (1 mg/kg/day of prednisone 1000 mg for 3 days) Equivalent or pulses of methylprednisolone and immunosuppressants – cyclophosphamide
Cranial neuropathy	Glucocorticoids (1 mg/kg/day of prednisone equivalent) with long-term dosage reduction Spontaneous recovery possible for oculomotor involvement	Cyclophosphamide immunosuppressants as maintenance treatment

PNS: peripheral nervous system; SNRI: serotonin-norepinephrine reuptake inhibitors; IVIG: intravenous immunoglobulins; PEX: plasma exchange; GBS: Guillain Barré Syndrom.

Table 3.
Treatment options available for peripheral nervous system involvement in patients with SLE (adapted from PNS involvement in SLE/A. Bortoluzzi et al.) [60].

of other antiepileptic agents such as gabapentin should be prescribed with slow titration to minimize its side effects particularly over somnolence and fatigue. The duration of therapeutic trial should be at least 3 months. The secondary amine tricyclic antidepressants such as nortriptyline and desipramine have fewer anticholinergic side effects and a proven efficacy in neuropathic pain, and so they may be slowly prescribed in patients with SS. The use of new immunosuppressant agents mainly monoclonal antibody directed against CD20 antigen on B cells as rituximab and the tumour necrosis factor (TNF)-alpha inhibitors such as adalimumab has been reported to be efficient in the small fibre neuropathies occurring in SS [25]. The management of axonal polyneuropathy is based on a symptomatic treatment; corticosteroids and immunosuppressors are discussed in the case of motor neuropathy with rapid progression [25]. In the case of multiple mononeuropathy, the presence of vasculitis is associated with a good response to immunosuppressive therapy [34]. There is evidence supporting the use of immunoglobulin therapy in Sjögren-associated sensorimotor and non-ataxic sensory neuropathy from retrospective and observational cohorts and case reports [56, 57].

In SLE, there are no clear guidelines on the treatment of peripheral neuropathy. Induction treatments with glucocorticoids with or without immunosuppressant agents are indicated in the situation of active vasculitic neuropathy [58]. In the case of necrotizing vasculitis, treatment with plasmapheresis, steroids and immunosuppressant has led to improvement [59, 60]. The definitions of response to treatment are variable between studies. Overall, the rate of global response (complete or partial) is more than 50% [41] (**Table 3**).

In SSc, there is not enough data regarding the response of scleroderma-associated neuropathy to immunosuppression [11, 61]. However, this therapy seems to be effective in mononeuritis multiplex and sensorimotor polyneuropathy with inflammatory process [11]. In DM/PM the treatment of PN is based on corticosteroids and immunosuppressant agents depending on the severity of the clinic presentation [51].

PNS, peripheral nervous system; SNRI, serotonin-norepinephrine reuptake inhibitors; IVIG, intravenous immunoglobulins; PEX, plasma exchange; GBS, Guillain-Barré syndrome.

8. Conclusion

8.1 Final considerations

PN is one of the possible neurologic manifestations encountered by physicians in CTD. Coexistence of both conditions is explained by immune-mediated factors particularly a vasculitis of peripheral nerve. Therefore, it is important to take a detailed medical history and examination and then adequate investigations to assess for an underlying systemic autoimmune diseases that may be associated with the neuropathy. Pure sensory and sensorimotor neuropathies are the most common PN features in these disorders. Acute to subacutely evolving multifocal or asymmetric neuropathy suggests a vasculitic cause. This situation constitutes a prognostic factor of the disease and requires prompt treatment with steroids and immunosuppressant agents. The treatment of PN in CTD progresses in three fronts: first, to identify the type of PN through the medical history and physical exam; second, to precise the pathogenic mechanism of neuropathy via clinical presentation, electromyographic data and in unclear situation the nerve biopsy and finally, the efficient control of pain. Corticosteroids remain the mainstay of treatment for vasculitic neuropathy in CTD.

8.2 Futures directions

Although much is known about the PN in CTD, particularly its pathogenesis and its clinical aspects, further experience needs to be gained especially in the treatment with prospective trials to identify indications and precise efficacy for cytotoxic agents, intravenous immunoglobulin, plasma exchange and new biological drugs. In future, we need also further studies to precise clear guidelines to diagnose PN related to CTD such as more specific features in the electromyogram and neuro-muscular biopsy. Moreover, in the treatment approach of PN in CTD, we need further researches to identify curative drugs targeting the pathogenesis pathways rather than the symptomatic and the previous conventional therapy.

Conflict of interest

There is no conflict of interest.

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