Review

Peripheral nervous system involvement in systemic lupus erythematosus: a review of the evidence

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ABSTRACT

In the past years the peripheral nervous system (PNS) involvement in systemic lupus erythematosus (SLE) has received little attention despite its potential significant impact. The true prevalence of PNS in SLE reported in studies is variable and strongly influenced by American College of Rheumatology (ACR) case definition that includes seven PNS manifestations (acute inflammatory demyelinating polyradiculoneuropathy, autonomic disorder, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy). Other peripheral manifestations, such as chronic inflammatory demyelinating polyradiculoneuropathy and small fibre neuropathy, not included in the ACR nomenclature, have not been well characterised in SLE. The aim of this review is to focus on epidemiology, pathogenesis, diagnosis and clinical features of all possible different expressions of PNS involvement in SLE, with the final objective to profile the patient's clinical characteristics.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune-mediated disease, characterised by the production of autoantibodies and immune-complexes deposition that can affect multiple organs and systems including both the central (CNS) and peripheral nervous system (PNS).

In past decades many studies have evaluated the CNS manifestations, while only a limited number focused on the PNS ones. To date, little is known about the actual prevalence and the demographic and specific immunological factors of peripheral neuro-lupus. In addition the final attribution of PNS involvement to SLE is a relevant and challenging clinical issue because up to one third of peripheral neuropathies (PN) recognises a non-SLE aetiology (1).

The 1999 American College of Rheumatology (ACR) provided the definitions for 7 peripheral manifestations related to SLE (2), but a revisiting of this classification including small fibre neuropathy has been advised by some Authors (1, 3). This review will focus on epidemiology, pathogenesis, diagnosis, clinical features and treatment of peripheral neuropsychiatric SLE (NPSLE).

Epidemiology

The true prevalence of PNS involvement in SLE reported in studies is highly variable and strongly influenced by ACR nomenclature. The case definition included acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barrè syndrome, GBS), autonomic disorder, single/multiple mononeuropathy, myasthenia gravis (MG), cranial neuropathy, plexopathy and polyneuropathy (2).

The importance of the PNS involvement was clearly recognised once again in the new 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (4); here the neurologic criterion was substantially implemented by including a larger number of neurologic manifestations of SLE related to a PNS involvement - like mononeuritis multiplex, peripheral or cranial neuropathy – not included in the original 1997 revised classification criteria for lupus (5). Most of the studies that evaluated the NP involvement in SLE, applying the 1999 ACR nomenclature, are typically retrospective cohort and consider together the peripheral and central involvement (4).

The prevalence of PNS complications ranged between 2 and 10%, with a higher predominance of polyneuropathies (2–3%) and mononeuropathies (single

or multiple: 0.5–1%), compared to rare or unusual events like GBS (0.1%), MG (0.1%) and plexopathy (<0.1%) (6–8). Unterman's meta-analysis assessed the prevalence of NPSLE in the light of the publication of the 1999 ACR nomenclature analysing retrospective and prospective studies. This work confirmed that CNS involvement was more frequent than the peripheral one, accounting for the 93.1% of all neurological manifestations. The rarest events were plexopathy, GBS, MG and autonomic dysfunction (7).

More recent studies have focused on the selective involvement of PNS. In the study of Oomatia (1), in addition to complying with the ACR criteria for NPSLE, patients had to meet the definitions of peripheral neuropathy provided by the Task Force of the American Academy of Neurology and the American Academy of Physical Medicine and Rehabilitation. The prevalence of PNS involvement was 6% (123/2097 of the patients), with 67% of the events (82 of 123) attributable to SLE. Among the peripheral neuropathies, the axonal pattern was the most frequent, observed in 46 cases (56.1%) divided into sensory polyneuropathy (19 cases; 23.2%), sensorimotor polyneuropathy (21 cases; 25.6%) and mononeuritis (6 cases; 7.3%). In this study, close attention was paid to small fibre involvement, not included in the original ACR nomenclature, but resulting more frequent than others and demonstrated by skin biopsy in 17.1% of patients (14 of 82). Toledano *et al*. (9) reported an overall prevalence of PNS involvement of 13.5% in their SLE cohort, with 36.6% of patients presenting with polyneuropathy (mainly sensory-motor axonal polyneuropathy) and 23.7% of mononeuropathy / mononeuritis multiplex; only manifestations included in ACR nomenclature were recorded in this study. Florica *et al*. have found a similar prevalence of sensory (25%) and sensory-motor (20%) axonal polyneuropathy (10). In this cohort, the prevalence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), another manifestation not included in the ACR case definition, was more frequent (5.3% of the cases) than in other reports.

Recent advances in pathogenesis of PNS involvement in SLE

Despite significant advances in understanding the pathogenesis, the causes of acute and chronic immune neuropathies remain largely unsolved. Reasonably no single pathogenetic mechanism is thought to be responsible for the variety of PNS pictures occurring in SLE. We report some conceivable emerging key concepts.

Neurogenic inflammation

Neurogenic inflammation is mediated by the release of different neuropeptides such as calcitonin gene-related protein, substance P, nitric oxide and chemokines resulting in vasodilatation, increasing vascular permeability and cell trafficking (Fig. 1) (11, 12). A key communication between immune cells and nociceptors is through cytokines. Upon activation of cytokine receptors, signal transduction pathways are activated in sensory neurons leading to downstream phosphorylation of membrane proteins including transient receptor potential ion channels and voltage-gated channels. In humans, an increased number of proinflammatory cytokines (IL-1-beta, IL-6, TNF-alpha) is reported in nerve biopsy from patients with painful neuropathies, especially in patients with vasculitic neuropathies (13). IL-1-beta and TNF-alpha are directly sensed by nociceptors which express the cognate receptors and induce activation of map kinases leading to increased membrane excitability. The mediators released from sensory neurons in periphery directly attract and activate immune innate cells (dendritic, mast cells) and adaptative immune cells such as T lymphocites. Nerve growth factor and prostaglandin E2 are major inflammatory mediators released from immune cells that act on sensory neurons inducing peripheral sensitisation and hyperalgesic phenomena (14). Moreover after an injury, this natural inflammatory response could facilitate the pathogenetic activity of anti-neural autoantibodies (Fig. 1) (15).

Whilst the cascade of autoimmune response activation targeting PNS structure remains elusive, it is reasonable to hypothesise that different combinations of molecules released by nociceptors and distinct afferent stimulation induced in periphery could create a chronic pain sensation (16).

Autoantibodies

The role of autoantibodies is a bridging condition between the concept of neurogenic inflammation and the pathogenesis of humoral-mediated axonal or myelin damage.

Nodes of Ranvier may be a vulnerable target for autoimmunity due to the intrinsic elevated number of potential antigens and because of the crucial permeability of blood-nerve barrier in nodal and juxtaparanodal structures (Fig. 1). A process of molecular mimicry may act as the starting motif to target different specific antigens within nerve structure. Carbohydrate sequences of the glycoconjugate-related glycolipids of myelin membrane are present in the lipopolysaccharide fraction of microorganism such as Campylobacter jejuni, Haemophilus influenzae and Mycoplasma pneumoniae. Autoantibodies can explain part of the pathogenesis of both axonal and demyelinating forms of GBS, where many of these glyconjugates act as target antigens (17–19) resulting in a block of neuronal voltage-gated sodium channels (20). In PNSLE manifestations the positivity of anti-ganglioside antibodies is frequent (15–24% of reactivity especially to a monosialoganglioside) (21).

The role of routinely assessed autoantibodies is conflicting. In a case-control study on asymptomatic cranial involvement in SLE, Gaber *et al*. (22) reported an association with anti-ribosomal-P antibodies (odds ratio [OR] 5.4, 95% confidence interval [CI] 1.002–1.03, p=0.002), anti-dsDNA (OR 1.01, 95%CI 1.2–24.8, p=0.032) and altered electrophysiological testing (electrical blink reflex, visually and brainstem auditory evoked potentials). Conversely other studies did not find an association with antinuclear antibodies, anti double-stranded DNA (anti-dsDNA), antiphospholipid antibodies or low complement (1, 10).

Histopathology

Histological studies demonstrated perivascular mononuclear or T-cells infil-

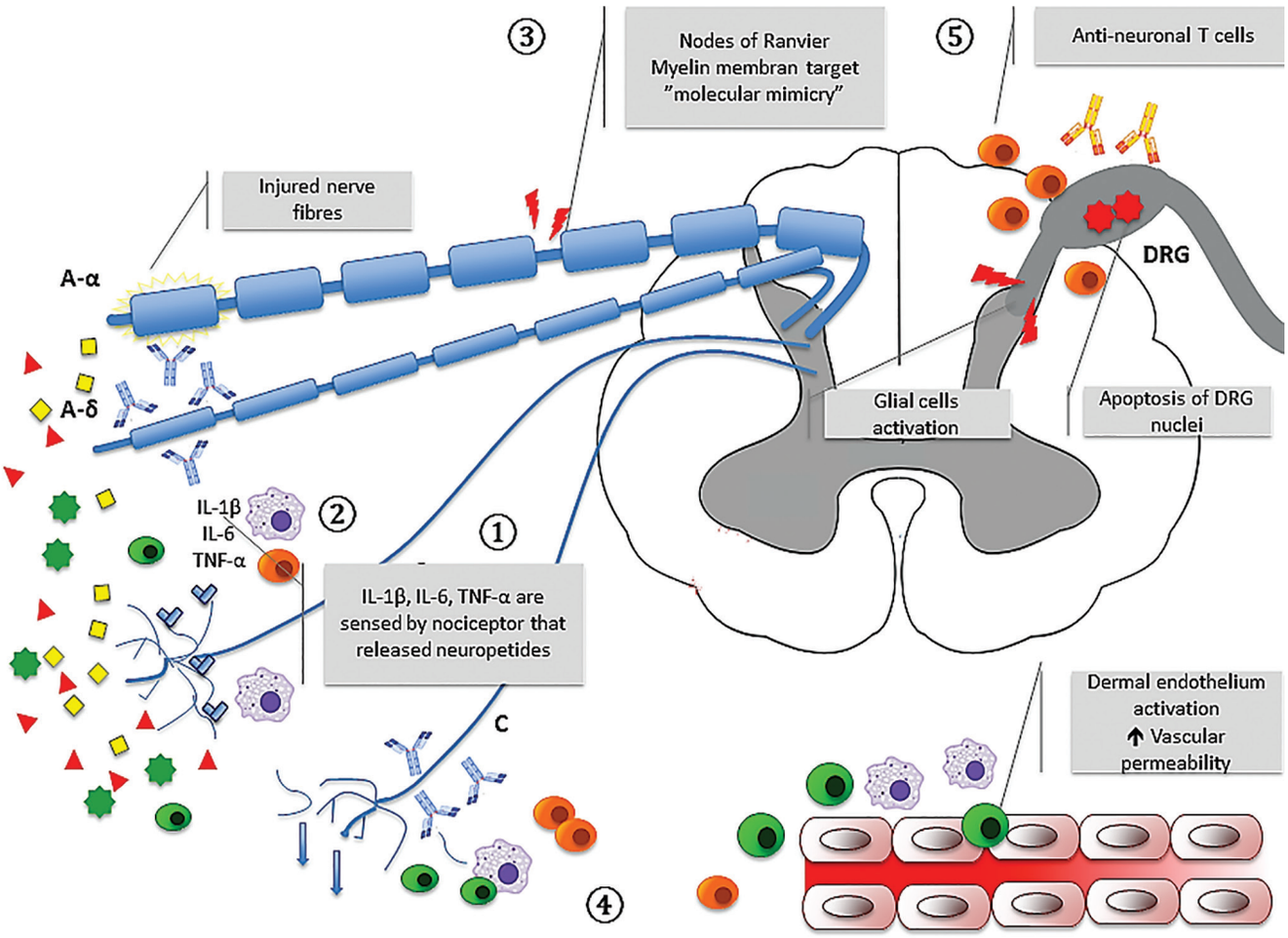

Fig. 1. Pathogenesis of peripheral nervous system involvement in systemic lupus erythematosus.
Different pathogenetic mechanisms could explain large and small fibre neuropathy. The figure illustrates some emerging key concepts.
Neurogenic inflammation: (1) In humans, an increased number of proinflammatory cytokines (IL-1-Beta, IL-6, TNF-alpha) is reported in nerve biopsy from patients with painful neuropathies, especially in patients with vasculitic neuropathies. IL-1-Beta, IL-6, TNF-alpha are directly sensed by nociceptors which express the cognate receptors. Nociceptors can release different neuropeptides such as calcitonin gene-related protein and substance P resulting in vasodilatation and increasing vascular permeability. (2) The mediators released from sensory neurons in periphery directly attract and activate immune innate cells (dendritic, mast cells) and adaptative immune cells such as T lymphocytes.
Autoantibodies: (3) Nodes of Ranvier may be, interestingly, a vulnerable target for autoimmunity due to the intrinsically elevated number of potential antigens and because of the crucial permeability of blood nerve barrier in nodal and juxtaparanodal structures. A process of molecular mimicry may act as the starting motif to target different specific antigens within nerve structure.
Mechanisms implicated in small fibre neuropathy (4) Length-dependent small fibre neuropathy: immunoglobulin deposit on the surface of nerves and the activation of dermal vascular endothelium lead to decreased intraepidermal nerve fibre density of unmyelinated fibres. (5) Non-length-dependent ganglionopathy: the hypothesised pathogenetic mechanisms include the presence of anti DRG-antibodies, apoptosis of the DRG nucleus or axons and reduced apoptosis of anti-neuronal directed T-cell.
DRG, dorsal root ganglion; IL-1β, interleukin 1-beta; IL-6, interleukin-6; TNF-α, tumour necrosis factor alpha.

trates in polyneuropathies (23) and a vasculitis-associated pattern of ischaemic and inflammatory damage in vasculitic neuropathy (24-26).

In SLE patients, sparse histopathologic data reported chronic axonal degeneration with reduction of myelinated and demyelinated fibre density, demyelination, inflammatory changes with mononuclear infiltration among nerve fibres, immune complexes deposition and vasculitis with thickening of the vessel wall, cellular infiltration and intimal changes (27).

Risk factors and attribution for PNS involvement in SLE

In SLE, the correct attribution of NP events is of outstanding importance for the patient's care and also to define both pathogenic mechanisms and therapeutic interventions (28-30). Oomatia reported that from a total of 123 SLE patients with PNS manifestations, 33.3% were not attributable to SLE, due to other non-SLE aetiologies like infectious or metabolic (1). Florica *et al*. (10) reported a similar result with 39.6% of the whole PNS events judged not-SLE related. Mononeuritis multiplex was most likely to be SLE-related in agreement with the new classification criteria for SLE that deemed this kind of manifestation to be very specific.

Among clinical and demographic data, comparing patients with and without PNS involvement, an older age at onset of the disease and a higher SLICC/ACR Damage Index (SDI) are traits that are associated with PNS involvement attributed to SLE (1, 10).

Polyneuropathy

Large fibre neuropathy are divided by electrodiagnostic studies into axonal or demyelinating neuropathies, and fuctionally in sensory, motor or sensorimotor (1). The pattern of trunk nerve involvement defines the distinction in poli-, multi- and mononeuropathy (Table I).

Table I. Classification of large fibre neuropathy.

Classification of large fibre neuropathy		
By damaged structure	By functional involvement	By pattern of trunk nerve involvement
- axonal - demyelinating	- sensory - motor - sensorimotor	- polyneuropathy - multineuropathy (multiple mononeuropathy) - mononeuropathy

Polyneuropathy is the most frequent PNS manifestation in SLE, inducing altered sensitivity, atrophic changes or pain. Muscle strength is typically involved later in the process, with weakness of toes extension, ankle dorsiflexion (enhanced by walking on heels) and altered proprioception causing frequent falls. The most common form in SLE is a symmetric distal axonal sensory or sensorimotor neuropathy. The axonal forms typically follow a classic stocking-glove pattern of distribution with a slow proximal spreading.

The diagnosis of polyneuropathy implies a combination of clinical symptoms, signs and electrodiagnostic findings. Nerve conduction studies (NCS) and needle electromyography are essential to make a correct differential diagnosis and to monitor response to therapy. In axonal forms, treatment guidelines suggest to use neurotrophic agents (tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, as duloxetine and venlafaxine and anticonvulsivants such as gabapentin and pregabalin (31, 32)) and glucocorticoids (33). Carbamazepine is used in refractory cases. The association of immunosuppressant therapies (azathioprine, mycophenolate mofetil, cyclophosphamide) should be considered in severe forms (34) while high dose intravenous immunoglobulins (IVIG), plasma exchange (PEX), or rituximab are reserved to selected and refractory cases (35) (Table IV). The only controlled clinical trial designed in SLE patients for severe neuropathy showed that intravenous cyclophosphamide treatment was more effective than pulses of steroids (36), but only 7 cases of polyneuropathy were enrolled. Stojanovich confirmed the efficacy of a low-dose regimen of cyclophosphamide versus methylprednisolone in PNS manifestations (37), but more than 50% of the patients, previously improved, had a subsequent relapse during follow-up, which suggested adopting a maintenance therapy.

Cranial neuropathy

Optic neuropathy (II cranial nerve - CN), the most frequent cranial neuropathy described in SLE (about 1% in SLE cohorts), will not be discussed because it is part of CNS (as well as the olfactory nerve).

Most common cranial neuropathies are, in order of frequency, the eighth, the oculomotor (third, fourth and sixth), the fifth and seventh nerve pairs (33). In the Florica cohort 12.5% (26 pts) of the PNS-SLE were found to have a concomitant cranial neuropathy, with a rare involvement of III, V, VI and VII CN (10), data confirmed by Xianbin *et al*. (12.7% of PNS manifestations) (8). Hanly *et al*. reported a prevalence ranging from 4.3 to 7.4% of all NP events (38). Brey *et al*. described a 2.2% overall prevalence in their SLE population (39), with the predominance of trigeminal involvement.

The differential diagnosis of cranial neuropathies includes Lyme disease, neuro-sarcoidosis, MG, and mid-brain or base-of-skull pathologic processes (2); diagnostic workup for CN involvement in SLE involves electrodiagnostic studies (electromyography and electroneurography). Blink reflex can be examined to investigate functional integrity of V and VII CN; Hess chart could help in distinguishing the correct oculomotor involvement.

VIII is the most frequently affected CN in SLE, resulting in both symptomatic and asymptomatic sensorineural hearing defects (22). Deafness or sudden sensorineural hearing loss, dtziness and tinnitus are the most common symptoms (40).

Oculomotor involvement causes diplopia or blurred vision (nausea and vomiting could be present) with pupil diameter alterations in some cases; one or more nerves could be concomitantly affected (41). The involvement of the medial longitudinal fascicle is also described in SLE, resulting in internuclear ophthalmoplegia (42). VI CN is the most frequently affected among oculomotors (40). A micro-thrombotic vasculopathy related to antiphospholipid antibodies has been advocated as a possible pathogenetic mechanism; viral infections before developing clinical signs are sometimes reported. An overall good clinical outcome for CN neuropathies has been reported (40). Treatment protocols require glucocorticoids alone (at 1 mg/kg per day of prednisone equivalents) or in combination with cyclophosphamide in refractory cases (34, 43) (Table IV). Relapses may occur and a maintenance therapy is useful, using long-term corticosteroids and chronic immunosuppressant regimens; anticoagulation can be considered in antiphospholipid-positive patients (33, 41) (Table IV). PEX is a useful therapeutic approach in progressive palsy (44). A number of retrospective studies described several cases of spontaneous recovery of oculomotor involvement (45).

Mononeuropathy single/multiple

Non-compression mononeuropathy is a vasculitic neuropathy characterised by the damage in one or more (multiplex forms) nerves. Vasculitic insult involves *vasa nervorum* with subsequent Wallerian degeneration of nerve fibres secondary to ischaemic infarction due to occlusion of blood vessels caused by leukocytoclastic vasculitis. Endoneurial immune complex deposition in sural nerve biopsy in SLE neuropathy patient would suggest their possible role in the demyelinating process and axonal damage (27). A positive association with antiphospholipid antibody and cryoglobulinaemia is also suggested (17, 46). Clinically mononeuropathy can manifest as “wrist drop” in case of radial

involvement or "foot drop" in presence of sciatic or peroneal involvement, but manifestations can also occur in other nerves like tibial, ulnar and medial (47). Electrophysiology usually shows a typical focal or multifocal pattern of involvement. As suggested by EULAR recommendations for the management of NPLSE, specific therapy depends upon the nature of the underlying pathogenetic process (33). The reduction of inflammation around the epineurium is the primary goal of treatment. Induction therapy includes systemic glucocorticoids, IV cyclophosphamide (48); in refractory cases, rituximab, IVIG, PEX, azathioprine or mycophenolate mofetil as a maintenance therapy have been used (49) (Table IV).

Inflammatory demyelinating poliardiculoneuropathy

Acute inflammatory demyelinating polyradiculoneuropathy or GBS is an acute, inflammatory and demyelinating syndrome of spinal root, peripheral and occasionally cranial nerves (2). In a retrospective study of 1,100 GBS patients, SLE was diagnosed only in 7 cases (50). The prevalence of GBS in SLE patients ranges between 0.6–1.7% of cases, mainly during the course of the disease. The pathogenesis of GBS as a manifestation of active SLE is not clearly defined and both cell-mediated and humoral processes are implicated. The co-occurrence with infections, frequently observed in immunosuppressed patients, could represent another relevant pathogenetic factor. Autoantibodies reacting with specific neural tissues, such as myelin components, may be produced as part of the broad spectrum of SLE- associated autoantibodies; recently dysfunctional autophagy, a process linked with SLE pathogenesis and type I – Interferon production (51–53), is under investigation in animal models mimicking GBS (54). GBS is characterised by rapidly progressive monophasic course (<1 month), usually without relapsing, determinating a progressive ascending limb weakness usually starting in the inferior distal extremities. Miller-Fisher syndrome is a variant of GBS characterised by the triad of ophthalmoplegia, ataxia, and areflexia, occasionally described in association with SLE (55–57). Diagnostic criteria include supportive evidence by nerve conduction block, slowing of conduction velocity and prolongation of distal latency. Nerve conduction abnormalities may be subtle in early stages and may need repetition (2). Given the usual post-infectious nature of the disease, the first therapeutic approach for the GBS involves the use of high dose IVIG or PEX, in addition to respiratory and cardio-respiratory supporting measures. Otherwise, steroids and immunosuppressants like cyclophosphamide could be an important treatment option in lupus-related GBS (58).

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated non-length-dependent neuropathy (prevalence of 1–7 per 100,000 people) characterised by progressive symmetric or asymmetric demyelinating polyneuropathy (although axonal variants could be present) and albumin-cytologic dissociation on cerebro-spinal fluid (CSF) examination. It was often thought to be the chronic counterpart of GBS (59). The ACR case definition for NPSLE does not include this condition although SLE could be an autoimmune cause of CIDP, as well as infections (Hepatitis B or C, HIV), inflammatory diseases (connective tissue diseases, inflammatory bowel diseases, thyrotoxicosis) and other heterogeneous conditions (lymphomas, diabetes mellitus, transplants, inherited neuropathies, nephrotic syndrome).

Compared to GBS, CIDP rarely involves bulbar tract or autonomic system and presents maximal symptoms in usually more than eight weeks, while GBS reaches nadir within four weeks from the onset. Autoantibodies to Schwann cells and myelin sheath proteins are part of the pathogenetic mechanism in CIDP (17); autoantigens are recognised by a phenomenon of molecular mimicry, as well as in GBS (26) and neurofascin, a protein of the nodes of Ranvier, has been identified as a possible antigenic target for pathogenetic autoantibodies (60). Among pathological findings in CIDP, segmental demyelination and re-myelination, formation of "onion-bulbs" due to Schwann cells proliferation and debris-laden macrophages in endoneurium are enhanced (61). Electrophysiological studies (including sensory and motor nerve conduction studies), spine magnetic resonance imaging (MRI) and CSF analysis support the diagnosis, while nerve biopsy is useful in selected cases (59).

Randomised controlled trials demonstrated the effectiveness of glucocorticoids, IVIG, and plasmapheresis in up to two-thirds of CIDP (62, 63), but studies are needed to characterise preliminary patterns of response to treatment. IVIG represent the first-line treatment; in IVIG-resistant diseases a response to PEX was found in 66% of cases and to glucocorticoids in 58% of cases (64). Among 6 patients with CIDP secondary to SLE (65), Vina *et al*. found an improvement greater than 50% (in subjective report of everyday function and objective neurological examination) in patients treated with IVIG within 1 year from onset of symptoms. Poor IVIG-responders were patients with a later IVIG course and atypical clinical pattern. It is reasonable that a more aggressive treatment approach could result in improving the autoimmune processes on the basis of CIDP. In refractory diseases or to reduce the need for IVIG, immunosuppressants in association to steroids (59) and even rituximab can be effective (66) (Table IV). No evidence-based guidelines are available for maintenance therapy that would be advisable for the majority of patients.

Small fibre neuropathy

Small fibre neuropathy is frequently associated with painful burning sensations; however, its association with SLE is not always defined, and this condition was not included in 1999 ACR case definitions for NPSLE.

Causes of small fibre neuropathy are multiple and heterogeneous (Table II) and no further clinical characteristics distinguish SLE patients. Half of the cases reflect an idiopathic cause (67) and sometimes these symptoms could be confused with fibromyalgia and chronic pain syndrome.

Clinical assessment contemplates careful neurological examination, aimed at excluding clinical signs of large fi-

Table II. Causes of small fibre neuropathy (adapted from Themistocleous *et al*. (67)).

Primary	Secondary	Conditions related / matters of debate
idiopathic small fibre neuropathy	impaired glucose tolerance, diabetes mellitus	complex regional pain syndrome
burning mouth syndrome	infections (HIV, hepatitis C, influenza)	subtypes of fibromyalgia
genetic forms (Fabry's disease, Tangier's, NAv1.7 mutations, NAv1.8 mutations, familial amyloid polyneuropathy) TNF-alpha inhibitors)	drugs (antiretrovirals, Metronidazole, Nitrofurantoin, Linezolid, Bortezomib, Flecainide, statins, alcohol, vitamin B6 toxicity,	chronic pain syndrome
	autoimmune diseases (coeliac disease, sarcoidosis, rheumatoid arthritis, SLE, Sjögren's syndrome, vasculitis, inflammatory bowel disease)	painful channelopathies (inherited erythromelalgia; paroxysmal extreme pain disorder; familial episodic pain syndrome)
	chronic kidney disease	restless leg syndrome
	vitamin B12 deficiency	neurodegenerative conditions
	dyslipidaemia, metabolic syndrome	
	hypothyroidism	
	paraneoplastic syndromes	
	monoclonal gammopathy/amyloidosis	

Table III. A purpose of diagnostic criteria for small fibre neuropathy in diabetes mellitus (69).

Possible	Probable	Definite
presence of length-dependent symptoms and/or clinical signs of small fibre damage	presence of length-dependent symptoms, clinical signs of small fibre damage, and normal sural NCS	presence of length-dependent symptoms, clinical signs of small fibre damage, normal sural NCS, and altered IENF density at the ankle and/or abnormal quantitative sensory testing thermal thresholds at the foot

NCS: nerve conduction study; IENF: intraepidermal nerve fibre.

bre involvement or autonomic nervous system dysfunction and to confirm positive signs as allodynia, hyperalgesia, hyperpathia or the presence of coexisting autonomic impairment with atrophy, dryness or oedema of the surrounding area of the skin. Standard diagnostic methods include Quantitative Sensory Testing (QST) and skin biopsy (Table III) (68, 69).

QST in a non-invasive method that explores the function of unmyelinated and thinly myelynated afferent nerves assessing responses to pressure, pinprick, vibration, heat; it requires the active collaboration of the subject and cannot differentiate between central and peripheral causes of sensory loss (70). Skin biopsy assesses morphological alterations, investigating intraepidermal nerve fibre density (IENFD), showing reduction in number of fibres crossing the dermal-epidermal junction, but also alterations in structure of fibres and axonal swelling. So far the quantification of IENFD is the efficient technique to prove diagnosis, showing a decreased IENFD (71) and it is indicated in diagnostic work-up of SLE patients with PN when electrodiagnostic studies are normal (33). More recently, corneal confocal microscopy (CCM) has been purposed as a diagnostic non-invasive tool for early nerve damage in diabetic patients (72).

Recent studies have suggested small fibre neuropathies occur in SLE patients more frequently than other PNS manifestations described in ACR case definitions (1), but available data are scarce.

Goransson *et al*. (73) described a prevalence of 13% of SLE patients with biopsy-proven small fibre neuropathy. Tseng *et al*. found a reduction in IENFD in 82% of SLE patients, compared to healthy controls (74). Oomatia *et al*. characterised 5.9% of SLE patients with PN in their John Hopkins SLE cohort and small fibre neuropathies occurred in 17.1% of cases, 6.1% length-dependent and 11% non-length-dependent (1). In the first group neuropathic pain developed in the distal feet, with a "stocking-glove" distribution. Skin biopsy showed decreased intraepidermal nerve fibre density of unmyelinated fibres suggesting a distal-most axonal degeneration in the area of maximal vulnerability to different causes. In the second group neuropathic pain occured with a patchy, asymmetric or proximal pattern. In skin biopsy, the proximal leg was unorthodoxically more affected than the distal leg, suggesting a different nervous target, which involves DRG (75, 76).

Pathogenetic mechanisms of this selective damage to A-delta and C-fibres are still largely unexplained; a specific immunoglobulin deposit (peripherin-IgG (77) and antisulfatide antibodies (78)) on the surface of nerves or an activation of dermal vascular endothelium are counted, resulting in vulnerability or apoptosis of nerves (79). Elevated pro-inflammatory cytokine-mediated damage and microglial-activation have also been advocated (80, 81) (Fig. 1).

In non-length-dependent ganglionopathy anti DRG-antibodies, apoptosis of the DRG nucleus or axons or reduced apoptosis of anti-neuronal directed T-cells have been described (82), (Fig. 1). Birnbaum evaluated MRI morphology of DRG in small fibre neuropathy, Sjögren's syndrome and underlined

Table IV. Summary of treatment options available for peripheral nervous system involvement in systemic lupus erythematosus.

PNS manifestation	First-line treatment approach	Treatment of refractory cases
polyneuropathy	neurotrophic agents (tricyclic antidepressants, SNRI (duloxetine, venlafaxine), anticonvulsivants (gabapentin, pregabalin)) (31,32) glucocorticoids (1 mg/kg/day of prednisone equivalent) (33) severe forms: immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide) (33,34,36,37)	carbamazepine high dose IVIG, PEX, Rituximab (33,35)
cranial neuropathy	glucocorticoids (1 mg/kg/day of prednisone equivalent) with long-term dosage reduction (33) spontaneous recovery possible for oculomotor involvement (45)	cyclophosphamide (34,43) immunosuppressants as maintenance treatment (33) anticoagulation in presence of aPL-ab (33,41) PEX (44)
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) (33,48,49) IV cyclophosphamide (33,48,49)	Rituximab, IVIG, PEX (49,92) mycophenolate mofetil (49) azathioprine (49)
acute inflammatory demyelinating polyradiculoneuropathy (GBS)	high dose IVIG (58,92) PEX (58) cardio-respiratory supporting measures	glucocorticoids (1 mg/kg/day of prednisone equivalent or pulses of methylprednisolone 1000 mg for 3 days) and immunosuppressants – cyclophosphamide (58)
chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	IVIG (62,64,65,71,92) PEX (59,63) glucorticoids (1 mg/kg/day of prednisone equivalent) (59,62,64,65)	immunosuppressants in association with glucocorticoids (59) Rituximab (66)
small fibre neuropathy	neurotrophic agents (tricyclic antidepressants, SNRI (duloxetine, venlafaxine), anticonvulsivants (gabapentin, pregabalin)) (80) topical anaesthetics (67) analgesics	immunosuppressants (80) IVIG (67,84) psychological support (67)
autonomic nervous system dysfunction	specific symptomatic therapy (88)	IVIG, PEX (88) immunosuppressants (89)
myasthenia gravis	symptomatic treatments (anticholinesterase agents, cardio-respiratory supporting measures). glucocorticoids (1-1.5 mg/kg/day of prednisone equivalent or pulses of 500-2000 mg of methylprednisolone for 3-5 days or 10-20 mg/day of prednisone equivalent followed by dosage increase of 5 mg/day per week until 1 mg/kg/day) plus azathioprine (91). other immunosuppressants (cyclosporine A, methotrexate, micophenolate mofetil, tacrolimus) (91).	Rituximab, eculizumab, cyclophosphamide, IVIG, PEX (91,92)
plexopathy	glucocorticoids? (94)	

PNS: peripheral nervous system; SNRI: serotonin-norepinephrine reuptake inhibitors; IVIG: intravenous immunoglobulins; PEX: plasma exchange; aPL-ab: antiphospholipid antibodies; IV: intravenous; GBS: Guillain-Barrè syndrome; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy.

pathological alterations of ganglions, describing an increase in their size, T2-signal and gadolinium-enhancement (83).

Medication includes antidepressants, anticonvulsants, topical anaesthetics and analgesics. Poor data are available for steroidal or immunomodulatory therapeutical options in autoimmune diseases and are limited to case reports. Recently, a randomised controlled trial with IVIG has been designed in idiopathic small fibre neuropathy (75, 83, 84). Prognosis is characterised by slow progression of the disease with a chronic pain condition.

Rare syndromes

Autonomic nervous system dysfunction

There are still controversies concerning the precise prevalence of autonomic nervous system (ANS) dysfunction, variously reported in 6 to 93% of all SLE patients (85, 86), maybe because symptoms of autonomic dysfunction are non-specific and vary remarkably; moreover, tests to detect autonomic dysfunction are not routinely employed in clinical practice. Criteria for diagnosis of ANS are provided in glossary definition in British Isles Lupus Assessment Group (BILAG) index and by 1999 ACR classification (2, 87). The general management of ANS dysfunction depends on the clinical sever-

ity. Autonomic neuropathies usually require specific symptomatic therapy. If an autoimmune cause of the autonomic neuropathy is found or strongly suspected, immunomodulatory therapy may be considered. IVIG, plasmapheresis (88) and oral immunosuppressant medications have been used successfully (89).

Myasthenia gravis

The coexistence of MG is rare in SLE but is not coincidental and the prevalence of MG in SLE is estimated at 1.3%, which is higher than the 0.02% prevalence of MG in general population (43). In most patients MG appeared first and atypical presentations are reported (90). MG expected both symptomatic treatment and immunotherapy. Corticosteroids and azathioprine are considered the first-line treatment, second line immunosuppressive drugs are cyclosporine A, methotrexate, micophenolate mofetil and tacrolimus (91). In severe and refractory cases, rituximab, eculizumab, cyclophosphamide are used as well as IVIG and PEX for prevention and therapy of myasthenic crisis (91, 92). Hydroxycloroquine is considered safe in MG patients with SLE but available data are controversial (93).

Plexopathy

Plexopathies present with signs and symptoms in the area of distribution of the brachial or lumbosacral plexus. The association between neural plexus injury and SLE requires further confirmations, in fact, only few case reports were published in literature so far (1, 7, 94). Oomatia *et al*. reported 1.2% of plexopathy in their John Hopkins's Lupus Cohort (1 patient) (1) and suggested this entity could reflect a coincidental neurologic syndrome occurring in SLE. The rarity and low level of attribution to the underlying SLE of this clinical picture arises some questions about the opportunity of maintaining its inclusion into the ACR 1999 case definition.

Table IV summarises therapeutical options available for each PNS manifestation covered in this review, focusing on first-line approach and treatment of refractory cases.

Conclusions

In this review, we have examined the peripheral involvement in SLE, from epidemiological data to pathogenetic new evidence and the patient's clinical profile and treatment. Although to a lesser extent than CNS, PNS involvement is a well recognised but also underestimated manifestation of NPSLE. Damage accrual and higher age are potential risk factors associated to PNS involvement. Peripheral polyneuropathy is the most common manifestation throughout the studies, followed by cranial nerve neuropathy (7). GBS and plexopathy are extremely rare in SLE suggesting that they may reflect the manifestation of a distinct and coincidental neurologic syndrome rather than a SLE related manifestation (1, 2).

References

1. OOMATIA A, FANG H, PETRI M, BIRNBAUM J: Peripheral neuropathies in systemic lupus erythematosus: clinical features, disease associations, and immunologic characteristics evaluated over a twenty-five-year study period. *Arthritis Rheumatol* 2014; 66: 1000-9.
2. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42: 599-608.
3. BORTOLUZZI A, SCIRÈ CA, GOVONI M: Comment on: Diagnosing and attributing neuropsychiatric events to systemic lupus erythematosus: time to untie the Gordian knot? *Rheumatology* (Oxford) 2017; 56: 856-7.
4. PETRI M, ORBAI A-M, ALARCÓN GS *et al*.: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64: 2677-86.
5. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
6. HANLY JG, SU L, FAREWELL V, MCCURDY G, FOUGERE L, THOMPSON K: Prospective study of neuropsychiatric events in systemic lupus erythematosus. *J Rheumatol* 2009; 36: 1449-59.
7. UNTERMAN A, NOLTE JES, BOAZ M, ABADY M, SHOENFELD Y, ZANDMAN-GODDARD G: Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. *Semin Arthritis Rheum* 2011; 41: 1-11.
8. XIANBIN W, MINGYU W, DONG X *et al*.: Peripheral neuropathies due to systemic lupus erythematosus in China. *Medicine* (Baltimore) 2015; 94: e625.
9. TOLEDANO P, ORUETA R, RODRÍGUEZ-PINTÓ I, VALLS-SOLÉ J, CERVERA R, ESPINOSA G: Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre. *Autoimmun Rev* 2017; 16: 750-5.
10. FLORICA B, AGHDASSI E, SU J, GLADMAN DD, UROWITZ MB, FORTIN PR: Peripheral neuropathy in patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 2011; 41: 203-11.
11. BRAIN SD, WILLIAMS TJ: Interactions between the tachykinins and calcitonin gene-related peptide lead to the modulation of oedema formation and blood flow in rat skin. *Br J Pharmacol* 1989; 97: 77-82.
12. HUGHES SR, WILLIAMS TJ, BRAIN SD: Evidence that endogenous nitric oxide modulates oedema formation induced by substance P. *Eur J Pharmacol* 1990; 191: 481-4.
13. LINDENLAUB T, SOMMER C: Cytokines in sural nerve biopsies from inflammatory and non-inflammatory neuropathies. *Acta Neuropathol* (Berl). 2003; 105: 593-602.
14. SKAPER SD: Nerve growth factor: a neuroimmune crosstalk mediator for all seasons. *Immunology* 2017; 151: 1-15.
15. KOHR D, TSCHERNATSCH M, SCHMITZ K *et al*.: Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen. *Pain* 2009; 143: 246-51.
16. CHIU IM, VON HEHN CA, WOOLF CJ: Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci* 2012; 15: 1063-7.
17. KLEIN CJ: Autoimmune-mediated peripheral neuropathies and autoimmune pain. *Handb Clin Neurol* 2016; 133: 417-46.
18. ANG CW, JACOBS BC, LAMAN JD: The Guillain-Barré syndrome: a true case of molecular mimicry. *Trends Immunol* 2004; 25: 61-6.
19. SHAHRIZAILA N, KOKUBUN N, SAWAI S *et al*.: Antibodies to single glycolipids and glycolipid complexes in Guillain-Barré syndrome subtypes. *Neurology* 2014; 83: 118-24.
20. WEBER F, RÜDEL R, AULKEMEYER P, BRINKMEIER H: Anti-GM1 antibodies can block neuronal voltage-gated sodium channels. *Muscle Nerve* 2000; 23: 1414-20.
21. LABRADOR-HORRILLO M, MARTINEZ-VALLE F, GALLARDO E, ROJAS-GARCIA R, ORDI-ROS J, VILARDELL M: Anti-ganglioside antibodies in patients with systemic lupus erythematosus and neurological manifestations. *Lupus* 2012; 21: 611-5.
22. GABER W, EZZAT Y, EL FAYOUMY NM, HELMY H, MOHEY AM: Detection of asymptomatic cranial neuropathies in patients with systemic lupus erythematosus and their relation to antiribosomal P antibody levels and disease activity. *Clin Rheumatol* 2014; 33: 1459-66.
23. EURELINGS M, VAN DEN BERG LH, WOKKE JHJ, FRANSSEN H, VRANCKEN AFJE, NOTERMANS NC: Increase of sural nerve T cells in progressive axonal polyneuropathy and monoclonal gammopathy. *Neurology* 2003; 61: 707-9.
24. VRANCKEN AFJE, NOTERMANS NC, JANSEN GH, WOKKE JHJ, SAID G: Progressive idiopathic axonal neuropathy--a comparative clinical and histopathological study with vasculitic neuropathy. *J Neurol* 2004; 251: 269-78.
25. COLLINS MP, ARNOLD WD, KISSEL JT: The

neuropathies of vasculitis. *Neurol Clin* 2013; 31: 557-95.
26. MARTINEZ ARM, FABER I, NUCCI A, APPENZELLER S, FRANÇA MC: Autoimmune neuropathies associated to rheumatic diseases. *Autoimmun Rev* 2017; 16: 335-42.
27. BÓDI I, VÁRADI P, POKORNY G *et al*.: Polyneuropathy with endoneurial immune complex deposition as the first manifestation of systemic lupus erythematosus. *Acta Neuropathol* (Berl) 1998; 96: 297-300.
28. GOVONI M, BORTOLUZZI A: Lupus or not lupus? Neuropsychiatric symptom attribution in systemic lupus erythematosus: Strapline: Repetita iuvant. *Rheumatology* (Oxford) 2017; 56: 1639-40
29. FANOURIAKIS A, PAMFIL C, REDNIC S, SIDIROPOULOS P, BERTSIAS G, BOUMPAS DT: Is it primary neuropsychiatric systemic lupus erythematosus? Performance of existing attribution models using physician judgment as the gold standard. *Clin Exp Rheumatol* 2016; 34: 910-17.
30. BORTOLUZZI A, FANOURIAKIS A, APPENZELLER S *et al*.: Validity of the Italian algorithm for the attribution of neuropsychiatric events in systemic lupus erythematosus: a retrospective multicentre international diagnostic cohort study. *BMJ Open* 2017; 7: e015546.
31. FINNERUP NB, ATTAL N, HAROUTOUNIAN S *et al*.: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162-73.
32. ATTAL N, CRUCCU G, BARON R *et al*.: EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17: 1113-e88.
33. BERTSIAS GK, IOANNIDIS JPA, ARINGER M *et al*.: EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* 2010; 69: 2074-82.
34. NEUWELT CM, LACKS S, KAYE BR, ELLMAN JB, BORENSTEIN DG: Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. *Am J Med* 1995; 98: 32-41.
35. LEVY Y, UZIEL Y, ZANDMAN G *et al*.: Response of vasculitic peripheral neuropathy to intravenous immunoglobulin. *Ann N Y Acad Sci* 2005; 1051: 779-86.
36. BARILE-FABRIS L, ARIZA-ANDRACA R, OLGUÍN-ORTEGA L *et al*.: Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann Rheum Dis* 2005; 64: 620-5.
37. STOJANOVICH L, STOJANOVICH R, KOSTICH V, DZJOLICH E: Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). *Lupus* 2003; 12: 3-7.
38. HANLY JG, UROWITZ MB, SU L *et al*.: Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2010; 69: 529-35.
39. BREY RL, HOLLIDAY SL, SAKLAD AR *et al*.: Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. *Neurology* 2002; 58: 1214-20.
40. SALEH Z, MENASSA J, ABBAS O, ATWEH S, ARAYSSI T: Cranial nerve VI palsy as a rare initial presentation of systemic lupus erythematosus: case report and review of the literature. *Lupus* 2010; 19: 201-5.
41. GENEVAY S, HAYEM G, HAMZA S, PALAZZO E, MEYER O, KAHN MF: Oculomotor palsy in six patients with systemic lupus erythematosus. A possible role of antiphospholipid syndrome. *Lupus* 2002; 11: 313-6.
42. GALINDO M, PABLOS JL, GÓMEZ-REINO JJ: Internuclear ophthalmoplegia in systemic lupus erythematosus. *Semin Arthritis Rheum* 1998; 28: 179-86.
43. GOVONI M, BORTOLUZZI A, PADOVAN M *et al*.: The diagnosis and clinical management of the neuropsychiatric manifestations of lupus. *J Autoimmun* 2016; 74: 41-72.
44. KOBAYASHI S, FUJISHIRO N, SUGIYAMA K: Systemic lupus erythematosus with sensorineural hearing loss and improvement after plasmapheresis using the double filtration method. *Intern Med Tokyo Jpn* 1992; 31: 778-81.
45. JOHNSON RT, RICHARDSON EP: The neurological manifestations of systemic lupus erythematosus. *Medicine* (Baltimore) 1968; 47: 337-69.
46. RIVIÈRE E, AUBART FC, MAISONOBE T *et al*.: Clinicopathological features of multiple mononeuropathy associated with systemic lupus erythematosus: a multicenter study. *J Neurol* 2017; 264: 1218-26.
47. KEANE JR: Multiple cranial nerve palsies: analysis of 979 cases. *Arch Neurol* 2005; 62: 1714-7.
48. MATHEW L, TALBOT K, LOVE S, PUVANARAJAH S, DONAGHY M: Treatment of vasculitic peripheral neuropathy: a retrospective analysis of outcome. *QJM Int J Med* 2007; 100: 41-51.
49. MUANGCHAN C, VAN VOLLENHOVEN RF, BERNATSKY SR *et al*.: Treatment algorithms in systemic lupus erythematosus. *Arthritis Care Res* 2015; 67: 1237-45.
50. LENEMAN F: The Guillain-Barré syndrome. Definition, etiology, and review of 1,100 cases. *Arch Intern Med* 1966; 118: 139-44.
51. ZHONG Z, SANCHEZ-LOPEZ E, KARIN M: Autophagy, NLRP3 inflammasome and auto-inflammatory/immune diseases. *Clin Exp Rheumatol* 2016; 34 (Suppl. 98): S12-6.
52. RÖNNBLOM L: The importance of the type I interferon system in autoimmunity. *Clin Exp Rheumatol* 2016; 34 (Suppl. 98): S21-4.
53. WU H, FU S, ZHAO M, LU L, LU Q: Dysregulation of cell death and its epigenetic mechanisms in systemic lupus erythematosus. *Mol ecules* 2016; 22: pii: E30.
54. MULLER S, BRUN S, RENÉ F, DE SÈZE J, LOEFFLER J-P, JELTSCH-DAVID H: Autophagy in neuroinflammatory diseases. *Autoimmun Rev* 2017; 16: 856-74.
55. BUKHARI S, TABOADA J: A Case of Miller Fisher Syndrome and Literature Review. *Cureus* 2017; 9: e1048.
56. OKOH HC, LUBANA SS, LANGEVIN S, SANELLI-RUSSO S, ABRUDESCU A: A Case of Systemic Lupus Erythematosus Presenting as Guillain-Barré Syndrome. Case Rep Rheumatol [Internet]. 2015;2015. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4553270/
57. BINGISSER R, SPEICH R, FONTANA A, GMÜR J, VOGEL B, LANDIS T: Lupus Erythematosus and Miller-Fisher Syndrome. *Arch Neurol* 1994; 51: 828-30.
58. SANTIAGO-CASAS Y, PEREDO RA, VILÁ LM: Efficacy of low-dose intravenous cyclophosphamide in systemic lupus erythematosus presenting with Guillain-Barre syndrome-like acute axonal neuropathies: report of two cases. *Lupus* 2013; 22: 324-7.
59. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--First Revision. *J Peripher Nerv Syst JPNS* 2010; 15: 1-9.
60. NG JKM, MALOTKA J, KAWAKAMI N *et al*.: Neurofascin as a target for autoantibodies in peripheral neuropathies. *Neurology* 2012; 79: 2241-8.
61. LATOV N: Diagnosis of CIDP. *Neurology* 2002; 59 (12 Suppl. 6): S2-6.
62. HUGHES R, BENSA S, WILLISON H *et al*.: Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001; 50: 195-201.
63. HAHN AF, BOLTON CF, PILLAY N *et al*.: Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy. A double-blind, sham-controlled, cross-over study. *Brain J Neurol* 1996; 119 (Pt 4): 1055-66.
64. KUITWAARD K, HAHN AF, VERMEULEN M, VENANCE SL, VAN DOORN PA: Intravenous immunoglobulin response in treatment-naïve chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 2015; 86: 1331-6.
65. VINA ER, FANG AJ, WALLACE DJ, WEISMAN MH: Chronic inflammatory demyelinating polyneuropathy in patients with systemic lupus erythematosus: prognosis and outcome. *Semin Arthritis Rheum* 2005; 35: 175-84.
66. QUEROL L, ROJAS-GARCÍA R, DIAZ-MANERA J *et al*.: Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol Neuroimmunol Neuroinflammation* 2015; 2: e149.
67. THEMISTOCLEOUS AC, RAMIREZ JD, SERRA J, BENNETT DLH: The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol* 2014; 14: 368-79.
68. CRUCCU G, AMINOFF MJ, CURIO G *et al*.: Recommendations for the clinical use of somatosensory-evoked potentials. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 2008; 119: 1705-19.
69. TESFAYE S, BOULTON AJM, DYCK PJ *et al*.: Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33: 2285-93.
70. BACKONJA MM, ATTAL N, BARON R *et al*.: Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain* 2013; 154: 1807-19.

71. LAURIA G, HSIEH ST, JOHANSSON O *et al*.: European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* 2010; 17: 903-12, e44-49.
72. JIANG M-S, YUAN Y, GU Z-X, ZHUANG S-L: Corneal confocal microscopy for assessment of diabetic peripheral neuropathy: a meta-analysis. *Br J Ophthalmol* 2016; 100: 9-14.
73. GØRANSSON LG, TJENSVOLL AB, HERIGSTAD A, MELLGREN SI, OMDAL R: Small-diameter nerve fiber neuropathy in systemic lupus erythematosus. *Arch Neurol* 2006; 63: 401-4.
74. TSENG M-T, HSIEH S-C, SHUN C-T *et al*.: Skin denervation and cutaneous vasculitis in systemic lupus erythematosus. *Brain J Neurol* 2006; 129: 977-85.
75. GORSON KC, HERRMANN DN, THIAGARAJAN R *et al*.: Non-length dependent small fibre neuropathy/ganglionopathy. *J Neurol Neurosurg Psychiatry* 2008; 79: 163-9.
76. GEMIGNANI F, GIOVANELLI M, VITETTA F *et al*.: Non-length dependent small fiber neuropathy. a prospective case series. *J Peripher Nerv Syst JPNS* 2010; 15: 57-62.
77. CHAMBERLAIN JL, PITTOCK SJ, OPRESCU A-M *et al*.: Peripherin-IgG association with neurologic and endocrine autoimmunity. *J Autoimmun* 2010; 34: 469-77.
78. DABBY R, WEIMER LH, HAYS AP, OLARTE M, LATOV N: Antisulfatide antibodies in neuropathy: clinical and electrophysiologic correlates. *Neurology* 2000; 54: 1448-52.
79. MALIK RA, TESFAYE S, THOMPSON SD *et al*.: Endoneurial localisation of microvascular damage in human diabetic neuropathy. *Diabetologia* 1993; 36: 454-9.
80. HOEIJMAKERS JG, FABER CG, LAURIA G, MERKIES IS, WAXMAN SG: Small-fibre neuropathies--advances in diagnosis, pathophysiology and management. *Nat Rev Neurol* 2012; 8: 369-79.
81. UÇEYLER N, KAFKE W, RIEDIGER N *et al*.: Elevated proinflammatory cytokine expression in affected skin in small fiber neuropathy. *Neurology* 2010; 74: 1806-13.
82. MURATA Y, MAEDA K, KAWAI H *et al*.: Antiganglion neuron antibodies correlate with neuropathy in Sjögren's syndrome. *Neuroreport* 2005; 16: 677-81.
83. BIRNBAUM J, DUNCAN T, OWOYEMI K, WANG KC, CARRINO J, CHHABRA A: Use of a novel high-resolution magnetic resonance neurography protocol to detect abnormal dorsal root Ganglia in Sjögren patients with neuropathic pain: case series of 10 patients and review of the literature. *Medicine* (Baltimore) 2014; 93: 121-34.
84. DE GREEF BTA, GEERTS M, HOEIJMAKERS JGJ, FABER CG, MERKIES ISJ: Intravenous immunoglobulin therapy for small fiber neuropathy: study protocol for a randomized controlled trial. *Trials* 2016; 17: 330.
85. MILOVANOVIĆ B, STOJANOVIĆ L, MILIĆEVIK N, VASIĆ K, BJELAKOVIĆ B, KROTIN M: Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk. *Srp Arh Celok Lek* 2010; 138: 26-32.
86. STOJANOVICH L, MILOVANOVICH B, DE LUKA SR *et al*.: Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. *Lupus* 2007; 16: 181-5.
87. ISENBERG DA, RAHMAN A, ALLEN E *et al*.: BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology* (Oxford) 2005; 44: 902-6.
88. SCHROEDER C, VERNINO S, BIRKENFELD AL *et al*.: Plasma exchange for primary autoimmune autonomic failure. *N Engl J Med* 2005; 353: 1585-90.
89. MODONI A, MIRABELLA M, MADIA F *et al*.: Chronic autoimmune autonomic neuropathy responsive to immunosuppressive therapy. *Neurology* 2007; 68: 161-2.
90. LESZCZYNSKI P, PAWLAK-BUS K: Vocal cords palsy in systemic lupus erythematosus patient: diagnostic and therapeutic difficulties. *Rheumatol Int* 2013; 33: 1577-80.
91. MELZER N, RUCK T, FUHR P *et al*.: Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. *J Neurol* 2016; 263: 1473-94.
92. MAGRO-CHECA C, ZIRKZEE EJ, HUIZINGA TW, STEUP-BEEKMAN GM: Management of neuropsychiatric systemic lupus erythematosus: current approaches and future perspectives. *Drugs* 2016; 76: 459-83.
93. JALLOULI M, SAADOUN D, EYMARD B *et al*.: The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. *J Neurol* 2012; 259: 1290-7.
94. BLOCH SL, JARRETT MP, SWERDLOW M, GRAYZEL AI: Brachial plexus neuropathy as the initial presentation of systemic lupus erythematosus. *Neurology* 1979; 29: 1633-4.