Peripheral Neuropathy Related to Connective Tissue Diseases

Subjects: Rheumatology

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Although peripheral neuropathy (PN) is a common complication in connective tissue diseases (CTD) and has been well studied, recent research has shown that PN is more diverse and frequent in different subtypes of CTD than was expected. The incidence of PN in Sjögren's syndrome and rheumatoid arthritis (RA) varies according to different disease subtypes, and the pathogenesis of neuropathic pain in different subtypes of eosinophilic granulomatosis with polyangiitis (EGPA) may also differ. Neurogenic inflammation, autoantibody-mediated changes, ischemia of the vascular wall and metabolic mechanisms have been shown to contribute to the pathogenesis of PN in CTD. Moreover, allergic inflammation has been recently identified as a possible new mechanism producing peripheral neuropathic pain associated with MPO-ANCA negative EGPA patients. Glucocorticoids are routinely used to relieve pain caused by PN. However, these steroids may cause hyperalgesia, exacerbate neuropathic pain, and activate the early phase of pain induction and produce hyperalgesia. Recently, neuroactive steroids, such as progesterone, tetrahydroprogesterone and testosterone, have been shown to exert protective effects for several PN symptoms, and in particular neuropathic pain. Neuroactive steroids will be an interesting topic for future research into PN in CTD.

connective tissue disease | peripheral neuropathy | pathogenesis | diagnosis | treatment

1. Introduction

Connective tissue diseases (CTD) are chronic inflammatory autoimmune diseases induced by antibodies or T-cell responses directed against self-antigens, which can affect all body systems, including the central nervous system (CNS) and peripheral nervous system (PNS) [1]. When the PNS is involved in CTD, peripheral neuropathy (PN) is the most common complication [2], which comprises a heterogeneous group of disorders, such as mononeuropathy, polyneuropathy and mononeuritis multiplex. PN may be a manifestation or a characteristic sign of immune system dysfunction, with variable prevalence and prognosis in CTD. Therefore, rapid recognition and treatment are essential. However, due to a varied complex spectrum of overlapping clinical manifestations, PN is an under-diagnosed complication in CTD and a particular challenge for rheumatologists and neurologists. Glucocorticoids and immunosuppressants are usually administered as basic and routine treatments of PN in CTD. However, as reported in experimental models of neuropathic pain, glucocorticoids may cause hyperalgesia, exacerbate neuropathic pain, and activate the early phase of pain induction and indeed produce hyperalgesia [3]. A possible strategy to find an effective treatment for PN is shifting the focus to new biological targets and relevant

molecular events in the PNS; in particular, neuroactive steroids are a highly promising therapeutic option [4] as these steroids can modulate PNS functions.

2. Prevalence and clinical manifestations

Axonal sensory polyneuropathy and sensorimotor polyneuropathy can be characterized by paresthesia and defects (including mild touch, proprioception and vibration sensation) in the distal part of the symmetrical limb, mainly affecting the distal end of the lower limbs, and may be accompanied by burning pain in the feet. In addition to the above manifestations, motor weakness may be present in sensorimotor polyneuropathy, which is usually mild and limited to the extensor muscles of the toes or feet [5].

Small-fiber neuropathy (SFN) is an algetic esthesioneurosis that usually results in burning pain and arises in the early stage of several systemic diseases such as diabetes, amyloidosis and CTDs [6]. The main manifestations of small fiber neuropathy are numbness, burning sensation, electric pain, pricking, pruritus, involving the limbs, trunk or the proximal part of the face [5]. Motor neuron disease is characterised as paresis, atrophy and bundle fibrillation, mainly in the distal limb [5]. Besides, SFN consists of two different types, which may be underestimated. The first is called “length-dependent” SFN, which is a neuropathic pain arising in a distal “stocking-and-glove” distribution reported by the patients. The conventional model of this distal neuropathic pain is related to equivalent skin biopsy markers of the most distal axonal degeneration. These markers include reduced intra-epidermal nerve-fiber density (IENFD) of amyelinic nerves. Compared to the proximal leg, the fiber density is decreased at the distal leg. While, concerning the second type of the disease which is called “non-length-dependent” SFN, patients suffer from heterodox and atypical models of neuropathic pain which involves the face, truncus and proximal arms and legs. However, skin biopsy results reveal that this non-conventional model of proximal neuropathic pain is related to skin biopsy markers which show that neuronal degeneration affects the most proximal component in the PNS—the dorsal root ganglia (DRG). Under the circumstances, the IENFD in the distal leg is not decreased any more compared to that in the proximal leg [6].

As a heterogeneous group of neurological disorders, the reported prevalence and clinical manifestations of PN in CTD varies widely (Table 1). As shown in Table 1, the main studies during the last 5 years have focused on systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and rheumatoid arthritis (RA). It is still worth mentioning that up to one-third of PN cases have a non-CTD aetiology including infection, drug toxicity or metabolic diseases. The final attribution of PNS involvement in CTD is therefore a relevant and challenging clinical issue [7][8].

2.1 Systemic Lupus Erythematosus (SLE)

Among the studies that have investigated the prevalence of PN in autoimmune diseases in recent years, SLE was one of the major diseases studied. In 2019, Shaban et al. [9] reported that the prevalence of PN-SLE was 3.4–7.5% in their research review. Moreover, cross-sectional studies in recent years have revealed that PN is a very common complication in SLE, with the prevalence ranged from 1.5% to 36%, as highlighted in **Table 1** [8][10][11][12][13][14], and

which was positively related to the level of disease activity [8][11][12][13][14]. The large degree of variation in PN prevalence in these studies was mainly attributed to the sample size, the different features of each group such as drug use, disease activity and/or ethnicity. PN symptoms were usually observed in the first 5 to 7 years of SLE being diagnosed [10][14], but PN events were a component of the first symptoms once SLE had been diagnosed [13]. Neurodiagnostic analysis revealed a predominance of sensory-motor involvement and axonal patterns [10][11][13][14]. Although polyneuropathy was the main form of PN manifestation, about half of the polyneuropathy events were attributed to non-SLE, mononeuritis multiplex and cranial neuropathies likely related to SLE [12]. The most common nerves affected by PN in SLE were the peroneal nerves, followed by the tibial and sural nerves, while ulnar and median nerves were less affected [10]. The most frequent cranial neuropathies were II, followed by VIII, VII, V, VI, IX, III, I and IV [13].

Although Guillain–Barré Syndrome (GBS) is a rare manifestation of SLE, which falls under the category of PNS-SLE, it was not mentioned in these studies. It is, however, important to remember that GBS can be one of the main causes of morbidity and mortality in PN-SLE patients [15][16].

In conclusion, SLE patients are easily susceptible to PN, but neurodiagnostic analysis of PN-SLE varies widely. PN-SLE should be given greater recognition. Further studies should focus on the differences between individual subtypes of neuropathy to explore the different pathologies and guide diagnosis and treatment.

2.2 Sjögren's Syndrome (SS)

SS is the second most common chronic autoimmune rheumatic disease, including primary Sjögren's syndrome (pSS) and secondary Sjögren's syndrome (sSS). We found six valid cross-sectional studies and one cohort study that discussed the prevalence and clinical features of PN in SS [17][18][19][20][21][22][23]. In the studies on pSS, the reported prevalence of PN events ranged from 19% to 72% and could be the initial manifestation [17][18][19][20][21][22][23]. Only one cross-sectional study from China in 2018 compared pSS with sSS and reported that sSS patients had a higher prevalence of PN events than pSS patients (31.1% vs. 19%) [17]. Several previous studies found a higher frequency of symmetric sensorimotor polyneuropathy and symmetric sensory polyneuropathy [24][25], but mononeuropathy or mononeuritis multiplex was the most common pattern in these studies [21][22][23] It is difficult to estimate the precise determination of the prevalence of these manifestations, partly due to the criteria-related variations for inclusion of patients and those related to the recruitment of patients studied, and the manifestations considered. However, in addition to the above two forms of PN manifestations, cranial neuropathy (mainly trigeminal neuropathy) and entrapment neuropathy (mainly carpal tunnel syndrome) are not rare. An acute or a subacute onset was observed more frequently for multiple cranial neuropathies. Atypical presentations included pure motor neuropathies [18], hypertrophic neuropathy [26] and ganglionopathy [21].

In conclusion, PN events are common in SS. Further studies should focus on the differences in the incidence and clinical patterns of PN events between sSS and pSS. PN might help to establish new international classification criteria and clinical practice guidelines for pSS in the future.

2.3 Systemic Sclerosis (SSc) or Scleroderma

There have been few studies on PN-SSc in recent years, with varying sample sizes and definitions for PN events (some studies used questionnaires to define neuropathic pain). Raja et al. [27] and Paik et al. [28] performed cross-sectional studies and reported that the prevalence of PN-SSc varied from 28% to 36.6%. A systematic review from Turkey concluded that trigeminal neuropathy (TN) (16.5%), peripheral sensorimotor polyneuropathy (14.3%), and carpal tunnel syndrome (CTS) (6.6%) were the most frequent forms of PN-SSc [29], and individual cases of TN in SSc were mainly reported in the last 5 years. In the studies by Yagci et al. [29] and Sriwong PT et al. [30], the prevalence of median neuropathy in SSc was about 35%. Most CTS in patients with SSc were asymptomatic. Autonomic nervous system (ANS) dysfunction, especially cardiac autonomic functions may occur in SSc [31][32], leading to an increased sympathetic modulation and decreased vagal at rest and a blunted autonomic response to orthostatism [31][32]. Most of these changes were detectable in the advanced and fibrotic forms of SSc. [33]. More well-designed studies are still needed.

2.4 Polyarteritis Nodosa (PAN)

One small sample size cross-sectional study from India calculated the prevalence of PN in PAN [34]. The prevalence was 88.9% (22 of 27 cases), the main form of which was axonal injured-sensorimotor mononeuritis multiplex [34]. De Boysson et al. [35] and Imboden et al. [36] mentioned that between 65% and 85% of PAN patients presented with PNS disorders. Polyneuropathy, radiculopathies, lumbar or brachial plexopathies have been reported. Acute neuropathy can also occur in necrotizing vasculitis, but very few cases have been reported [37].

In summary, among CTD, PNA has a high prevalence of PN. The mechanism is arteritis of the vasa nervorum, leading to ischemic neuropathy [36]. Mononeuritis multiplex is the main form of PN manifestation, probably because PAN mainly affects the moderate vessels, which supply slightly larger nerves.

2.5 Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

In 2019, Bischof et al. [38] carried out a large cross-sectional study. Nine hundred and fifty-five patients were identified as ANCA-associated vasculitis (AAV), among which 572 were granulomatosis polyangiitis (GPA), 218 microscopic polyangiitis (MPA) and 165 EGPA. The prevalence of PN involvement was 65% in EGPA, 23% in MPA and 19% in GPA. In another two retrospective cohort studies, Zhang et al. [39] and Cho et al. [40] reported that the prevalence of PN events in EGPA was between 46.4% and 75%. Unlike PAN, PN-EGPA patients were characterized by polyneuropathy. Some researchers speculated the reason is that EGPA primarily affects small vessels which supply terminal nerves but PAN mainly affects the moderate vessels, which supply slightly larger nerves. Nishi et al. [41] compared sural nerve biopsy specimens of 27 PN-EGPA patients with positive MPO-ANCA and 55 PN-EGPA patient specimens with negative MPO-ANCA, and found that the MPO-ANCA positive group was mainly characterized by vasculitis in epineurial vessels, while the MPO-ANCA negative group was mainly characterized by eosinophil infiltration, suggesting that the pathogenesis of PN-EGPA comprises at least 2 distinct mechanisms (possible mechanisms are briefly described in Section 2.2 and Section 2.3 below). Further larger

scale studies are needed to clarify the clinical and pathological relationships between ANCA positivity and PN involvement in EGPA patients.

PN in EGPA primarily affected the lower extremities, with peroneal nerve involvement being the most frequent and severe. The sensory neuropathy was distributed mostly asymmetrically in the distal portion of the limbs, while the main manifestations of motor neuropathy were foot drop and muscle weakness. AVV patients may also have symptoms of autonomic dysfunction which is independent of the disease duration and its severity [42]. Atypical manifestations include acute sciatic nerve neuropathy [43] and mimicking GBS [44].

Mononeuritis multiplex and distal symmetrical polyneuropathy, mixed neuropathy and lower limbs involvement are predominant PN manifestations in MPA patients [45][46]. Symmetrical sensorimotor polyneuropathy is rare in GPA [47], with only one case report in the last 5 years, characterized by CTS and tennis elbow as prodromes [48].

2.6 Rheumatoid Arthritis (RA)

PN in RA was mainly reported as small sample sizes in cross-sectional studies in the past 5 years. Kaeley et al. [49] reported that the prevalence of PN-RA was 75.3%. Interestingly, the incidence of PN varied according to the different subtypes of RA. Kumar et al. [50] reported that the prevalence of PN in seropositive RA patients and seronegative RA patients was 34.4% vs. 15.4, respectively. Further studies are required to clarify the clinical and pathological relationships between seropositive and seronegative RA patients.

Previous studies have shown that the types of PN-RA are pure sensory, distal axonal sensory-motor, mononeuritis multiplex and entrapment neuropathy [51]. However, Kaeley et al. [49] found that pure motor neuropathy was not rare. Autonomic dysfunction also occurred in RA, characterized by heart rate responses to a deep breath (HRD), heart rate response to standing (HRS), blood pressure response to hand grip and sudomotor function impairment [52]. Rare but serious peripheral nerve manifestations included ischemic neuropathies caused by necrotizing arteritis of the vasa vasorum [53].

2.7 Other CTDs

2.7.1 Giant Cell Arteritis (GCA) and Takayasu Arteritis (TAK)

Studies on PN in GCA and TAK were mainly reported as individual cases during the past 5 years. A literature review by Bougea et al. [47] found that PN complications affected 15% of GCA patients. The main neuropathic complication of GCA was CTS, and mononeuritis multiplex and distal symmetrical sensorimotor polyneuropathy were uncommon [47]. Bilateral acute brachial radiculoplexopathy is a rare PN event in GCA, which presents as a “man-in-the-barrel” syndrome (diplegia of the upper extremities in which mobility of the head and lower limbs is preserved) [54][55]. Duval [54] and Calle-Lopez [55] reported this rare neurological complication of GCA, suggesting that GCA should be considered in patients over 50 years old who manifest with peripheral nerve clinical features such as brachial diplegia, and without other demonstrable causes. Also some cases with atypical symptoms such as compressive common peroneal neuropathies [56] have been reported.

PN involvement of TAK is much rarer. Isolated cranial nerve palsies was reported to be due to the involvement of the internal carotid artery or its branches [47]. Vasculitic neuropathy in TAK may cause a subacute sensorimotor deficit in a cervicobrachial plexus distribution [47]. Although TAK rarely affected the axillary artery, Kim et al. [57] reported a case of a right axillary artery aneurysm in a young female TA patient, which led to brachial plexus injury and compression, causing neurological complications.

In summary, PN in systemic vasculitis also requires a consideration of non-vasculitic neuropathies factors, especially compression neuropathies.

2.7.2 Behçet Syndrome (BD)

PNS involvement in BD is extremely rare, only isolated cases of distal symmetrical polyneuropathy and mononeuritis multiplex have been reported [47]. A retrospective study from Korea in 2015 reported the overall prevalence of CTS among BD patients was 0.8% [58]. The nerve dysfunction or PN in BD is an axonal type of distal polyneuropathy and predominantly involves the lower extremities [51]].

2.7.3 Mixed Connective Tissue Disease (MCTD)

Previous studies suggested that the prevalence of PN-MCTD is approximately 10% to 17% [59], among which trigeminal neuralgia is often associated with MCTD [60]. Bilateral facial nerve palsy with facial swelling can also present in MCTD, and is known as Melkersson–Rosenthal syndrome [61]. Vasculitic neuropathy may be concomitant and manifest as distal symmetric neuropathy [62]. Compressive neuropathies such as CTS can also be observed [62].

2.7.4 Dermatomyositis (DM) and Polymyositis (PM)

Previous studies showed a prevalence of 7.5% in DM/PM patients with polyneuropathy [46]. In 2016, Irie et al. [63] analyzed 9 cases of PN-DM/PM and confirmed that the main form of PN-DM/PM manifestation was axonal neuropathy. Unfortunately, there were no well-designed studies on neuromyositis.

2.7.5 IgG4-Related Disease (IgG4-RD)

IgG4-RD can affect a wide range of visceral nerves including those innervating the kidney, prostate gland, epicardium, abdominal aorta, retroperitoneum and mesentery. The nerves comprising Auerbach's plexus of the intestinal wall were most extensively involved [64]. This might be one mechanism of the intense pain experienced by IgG4-related retroperitoneal fibrosis patients. The involvement of extremities nerves has only rarely been reported [65].

2.8 Peripheral Neuropathies Caused by Immunotherapy

Janus kinase (JAK) inhibitors have been used to treat RA and other CTDs, basically targeting different molecules in the same signal pathway [66]. In a study of JAK1 and JAK2 inhibitor treatment of myelofibrosis, new-onset

treatment-related peripheral neuropathy was observed in 22% of patients (sensory symptoms) [67]. Whether the side effects such as PN will occur in the JAK inhibitors treatment of RA needs further study.

PNS involvement in ankylosing spondylitis (AS) and psoriatic arthritis (Pisa) were mainly related to tumor necrosis factor-α (TNF-α) antagonists, such as infliximab, adalimumab and etanercept [68]. In 2015, Tsouni et al. [69] studied the clinical, electrophysiological and frequency of anti-TNF-α (α-TNF) medication-induced neuropathies (ATIN) in patients with inflammatory disorders. Of 2017 patients treated with α-TNF medication, 12 were diagnosed as ATIN with a prevalence of 0.60% and an incidence of 0.4 cases per 1000 person-years. Six patients had focal or multifocal peripheral neuropathies. During the last 5 years, a number of cases of axonal neuropathy [70] or multifocal-motor-neuropathy-like disease [71] associated with the use of infliximab have been reported. Some TNF-α antagonists have been associated with the occurrence of GBS [72]. Patients treated with TNF-α antagonists can develop a GBS-like disease within the first 6 months after the start of therapy, and the symptoms can persist for up to 2 years [5].

Table 1. Prevalence and clinical manifestation of PN in patients with CTD.

Authors	Prevalence/ Constituent Ratio (%)	Patients (N)	Type of Study	Main Electrodiagnostic Tests Pattern	Main Form of PN Manifestation
Systemic lupus erythematosus					
Xianbin et al. [8]	1.5%	4924	Cross-sectional	Sensory (67.5%), motor (49.3%)	Polyneuropathy +++ Mononeuropathy ++ Cranial neuropathy ++ Myasthenia gravis ++
Toledano et al. [10]	17.7%	524	Cross-sectional	Sensory-motor (56%), axonal 80.3%	Polyneuropathy +++ Mononeuropathy ++ Cranial neuropathy +
Saigal et al. [11]	36%	50	Cross-sectional	Sensory-motor, axonal	-
Bortoluzzi et al. [12]	6.9%	1224	Cross-sectional	Sensory-motor (25%)	Polyneuropathy +++ Cranial neuropathy +++ Mononeuropathy ++ Mononeuritis multiplex +
Hanly et al. [13]	7.6%	1827	Cohort	Sensory-motor (71%), sensory (16.1%) axonal (41.7%), demyelination (21.7%)	Polyneuropathy +++ Mononeuropathy ++ Cranial neuropathy ++ Mononeuritis multiplex ++

Authors	Prevalence/ Constituent Ratio (%)	Patients (N)	Type of Study	Main Electrodiagnostic Tests Pattern	Main Form of PN Manifestation
Fargetti et al. [14]	1.8%	2074	Cohort	Sensory-motor (68.4%), axonal (49.3%)	Polyneuropathy +++ Mononeuropathy ++ Polyradiculoneuropathy + Cranial neuropathy +
Sjögren's syndrome					
Ye W et al. [17]	19% pSS 31.1% sSS	415 pSS 151 sSS	Cross-sectional	-	-
Seeliger et al. [18]	44 SS + PNP	108 PNP	Cross-sectional +case-control	Motor (100%), sensory (89%) axonal (36%), demyelinating (23%), both (41%)	-
Carvajal Alegria et al. [19]	16%	392	Cohort	Sensory (57%), sensory-motor (33%)	Mononeuritis multiplex Polyneuropathy Cranial neuropathy
Przyńska-Mazan et al. [20]	63.9%	61 pSS	Cross-sectional	Sensory-motor axonal (47.5%), demyelination, both (5.1%)	Polyneuropathy +++ Mononeuropathy +++ Entrapment neuropathy ++ Mononeuritis multiplex ++
Sireesha et al. [21]	-	20 pSS 1 sSS	Cross-sectional	-	Mononeuritis multiplex +++ Ganglionopathy ++ Trigeminal neuropathy ++
Jaskólska et al. [22]	72%	50 pSS	Cross-sectional	Sensory-motor axonal (22%)	Entrapment neuropathy +++ Mononeuropathy ++ Cranial neuropathy +
Jaskólska et al. [23]	46%	50 pSS	Cross-sectional	Sensory-motor (47%)	Mononeuropathy ++ Cranial neuropathy ++
Systemic sclerosis (scleroderma)					
Raja et al. [27]	36.6%	60	Cross-sectional	Sensory (65%), motor (53%)	Polyneuropathy +++ Mononeuropathy ++

Authors	Prevalence/ Constituent Ratio (%)	Patients (N)	Type of Study	Main Electrodiagnostic Tests Pattern	Main Form of PN Manifestation
					Entrapment neuropathy ++
Paik et al. [28]	28%	60	Cross-sectional	Sensory-motor axonal, no demyelinating	-
* Yagci et al. [29]	29.2%	24	Cross-sectional	-	Entrapment neuropathy Polyneuropathy
* Sriwong et al. [30]	38%	50	Cohort	-	Median neuropathy at the wrist
Polyarteritis nodosa					
Sharma et al. [34]	88.9%	27	Cross-sectional	Axonal sensory-motor (81.8%)	Mononeuritis multiplex
Eosinophilic granulomatosis with polyangiitis					
Bischof et al. [38]	19% 23% 65%	572 GPA 218 MPA 165 EPGA	Cross-sectional	Sensory-motor (32%), sensory (16%), motor (5%)	Mononeuritis multiplex +++
Zhang et al. [39]	46.4%	110 EPGA	Retrospective cohort	-	Polyneuropathy +++ Mononeuritis multiplex ++
Cho et al. [40]	75%	61 EPGA	Retrospective cohort	Sensory (44/46), motor (24/46)	Mononeuritis multiplex +++ Mononeuropathy ++ Polyneuropathy ++
Nishi et al. [41]	-	82 EPGA	Retrospective	Axonal	-
Rheumatoid Arthritis					
Kaeley et al. [49]	75.28%	89	Cross-sectional	Asymmetrical sensorimotor axonal neuropathy, pure motor	Mononeuritis multiplex Entrapment neuropathy
Kumar et al. [50]	34.4% (seropositive)	60	Cross-sectional	-	-

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Authors	Prevalence/ Constituent Ratio (%)	Patients (N)	Type of Study	Main Electrodiagnostic Tests Pattern	Main Form of PN Manifestation
	15.38% (seronegative)				

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* Studies focused on carpal tunnel syndrome. PN, peripheral neuropathy; pSS, primary Sjögren's syndrome; sSS, secondary Sjögren's syndrome; PNP, polyneuropathy; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; Prevalence/Constituent ratio: +: <10%; ++: 10–30%; +++: >30%.

3. Pathogenesis

In CTD, neurogenic inflammation, autoantibodies-mediated changes, ischemia of the vascular wall and metabolic mechanisms are believed to contribute to the pathogenesis of PN and to be predominant in different diseases. Despite significant advances in our understanding the pathogenesis, no single pathogenetic mechanism is thought to be responsible for PN in CTD. Next we discuss the possible mechanisms underlying disease pathogenesis.

3.1 Peripheral neuropathies associated with neurogenic inflammation

An increase in proinflammatory cytokine concentrations has been found in patients with vascular neuropathy [7]. Nociceptors located in nerve endings can sense IL-1β and TNF-α directly and induce activation of MAP kinases, resulting in increased membrane excitability. In addition, MAP activation leads to the release of different neuropeptides such as calcitonin gene-related protein, substance P, nitric oxide and chemokines, which subsequently cause vasodilatation, increases in vascular permeability and cell trafficking [7]. On the other hand, these mediators released from sensory neurons in the periphery directly attract and activate immune innate cells and adaptative immune cells such as T lymphocytes [7]. Nerve growth factor and prostaglandin E2 are major inflammatory mediators released from immune cells that act on sensory neurons inducing peripheral sensitization and hyperalgesic phenomena [7].

3.2 Hypothetical mechanisms underlying allergic inflammation-related neuropathic pain (NeP)

The sural nerve biopsy specimens of PN-EGPA patients with negative MPO-ANCA were mainly characterized by eosinophil infiltration [41], suggesting that allergic inflammation was an underlying mechanism in MPO-ANCA negative EGPA patients. Through animal experiments, Fujii et al. [73] found that peripheral nerve damage caused by allergic inflammation [illegible] for allergic individuals, increased [illegible] immunity may lead to anti-plexin D1 antibody production via molecular mimicry with environmental allergens. Anti-plexin D1 antibodies can damage primary pain-conducting neurons, thus inducing neuropathic pain [73]. In addition, the overproduction of ET-1 in inflamed skin tissues and sera may induce blood-brain barrier (BBB) hyperpermeability and activate microglia and astroglia through the ET-1/EDNRB pathway in allergic inflammation, thus causing NeP [73].

4. Eva Falvo; Silvia Diviccaro; Roberto Cosimo Melcangi; Silvia Giatti; Physiopathological Role of Neuroactive Steroids in the Peripheral Nervous System. *International Journal of Molecular Sciences* **2020**, *21*, 9000, 10.3390/ijms21239000.
5. V. Casteleyn; K. Hahn; W. Stenzel; E. Siegert; Periphere Nervenbeteiligung bei rheumatischen Erkrankungen. *Zeitschrift für Rheumatologie* **2019**, *78*, 339-351, 10.1007/s00393-019-0621-z.
6. Julius Birnbaum; Clifton O. Bingham; Non-length-dependent and length-dependent small-fiber neuropathies associated with tumor necrosis factor (TNF)-inhibitor therapy in patients with rheumatoid arthritis: Expanding the spectrum of neurological disease associated with TNF-inhibitors. *Seminars in Arthritis and Rheumatism* **2013**, *43*, 638-647, 10.1016/j.semarthrit.2013.10.007.
7. Alessandra Bortoluzzi; Ettore Silvagni; Federica Furini; Matteo Piga; Marcello Govoni; Peripheral nervous system involvement in systemic lupus erythematosus: a review of the evidence.. *Clinical and experimental rheumatology* **2018**, *37*, 146-155.
8. Wang Xianbin; Wang Mingyu; Xu Dong; Li Huiying; Xu Yan; Zhang Fengchun; Zeng Xiaofeng; Peripheral Neuropathies Due to Systemic Lupus Erythematosus in China. *Medicine* **2015**, *94*, e625-e625, 10.1097/md.0000000000000625.
9. Amir Shaban; Enrique C. Leira; Neurological Complications in Patients with Systemic Lupus Erythematosus. *Current Neurology and Neuroscience Reports* **2019**, *19*, 97, 10.1007/s11910-019-1012-1.
10. Pilar Toledano; Ramón Orueta; Ignasi Rodríguez-Pintó; Josep Valls-Solé; Ricard Cervera; Gerard Espinosa; Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre. *Autoimmunity Reviews* **2017**, *16*, 750-755, 10.1016/j.autrev.2017.05.011.
11. Renu Saigal; Rajat Bhargav; Laxmikant Goyal; Abhishek Agrawal; Pradeep Mital; Dileep Wadhwani; Peripheral Neuropathy in Systemic Lupus Erythematosus: Clinical and Electrophysiological Properties and their Association with Disease Activity Parameters.. *The Journal of the Association of Physicians of India* **2015**, *63*, 15-19.
12. A Bortoluzzi; M Piga; E Silvagni; A Chessa; A Mathieu; M Govoni; Peripheral nervous system involvement in systemic lupus erythematosus: a retrospective study on prevalence, associated factors and outcome. *Lupus* **2019**, *28*, 465-474, 10.1177/0961203319828499.

3.3 Vasculitic neuropathy

The most possible pathogenesis of vasculitis-related PN is inflammation of precapillary arteries in the nerves [74]. Deposition of immune complexes or T cell-mediated immunity plays a major role in inducing the immunological inflammation and necrosis of vessel wall [74]. The end result of both processes is the induction of immunological inflammation and necrosis of blood vessel walls, which eventually leads in addition to focal or multifocal, axonal, ischemic neuropathy [74].

3.4 Nodes of Ranvier and autoantibodies

A process of molecular mimicry may act as the starting motif to target different specific antigens within the structure of a nerve [7]. Nodes of Ranvier may be a vulnerable target for autoimmunity due to the intrinsically elevated number of potential antigens and the crucial permeability of the blood-nerve barrier in nodal and juxtaparanodal structures [7].

IgG and IgM anticardiolipin antibodies were detected in the serum of CTD patients [75]. The existence of anti-ganglioside antibodies in PN-SLE patients has been found frequently [7], while the chronic inflammatory demyelinating polyneuropathy (CIDP) associated with IgG4 antibodies to neurofascin-155 (NF155) was recently described [76]. These immune antibody markers have been not only proven to be useful in clinical practice but also uncovered novel pathophysiological mechanisms, clinical phenotypes, therapeutic responses and prognosis indicators.

3.5 Metabolic disorders

PNS involvement in CTD can also be caused by metabolic disorders secondary to aggressive therapy, multiorgan pathology and endocrine abnormalities. Metabolic disorders may induce a reaction of demyelinating neuropathy and axon dystrophy in severe cases [75].

4. Diagnosis

4.1 Nerve conduction studies (NCS)

NCS can reveal the asymmetric or multifocal nature of neuropathy. Electromyogram (EMG)/NCS can establish whether patients have sensory-motor neuropathy, sensory neuronopathy or motor neuronopathy. Moreover, EMG/NCS can be applied to distinct polyradiculopathy with mononeuritis multiplex, as both patterns have very similar diffuse, non-length dependent neuropathies. Importantly, EMG/NCS can also be used to identify whether the affected structure of nerves is the axon itself or demyelination. In addition, needle electromyography is very useful in estimating the disease course, the extent of the injury and the existence of a superimposed myopathy [77].

4.2 Histopathological techniques

13. John G. Hanly; Qiuju Li; Li Su; Murray B. Urowitz; Caroline Gordon; Sang-Cheol Bae; Juanita Romero-Diaz; Jorge Sanchez-Guerrero; Sasha Bernatsky; Ann E. Clarke; et al.Daniel J. WallaceDavid A. IsenbergAnisur RahmanJoan T. MerrillPaul R. FortinDafna D. GladmanIan N. BruceMichelle PetriEllen M. GinzlerM. A. DooleyKristjan SteinssonRosalind Ramsey-GoldmanAsad A. ZomaSusan ManziOla NivedAndreas JonsenMunther A. KhamashtaGraciela S. AlarconElisabet SvenungssonRonald F. van VollenhovenCynthia AranowMeggan MackayGuillermo Ruiz-IrastorzaManuel Ramos-CasalsS. Sam LimMurat InancKenneth C. KalunianSoren JacobsenChristine A. PeschkenDiane L. KamenAnca AskanaseChris TheriaultVernon Farewell Peripheral Nervous System Disease in Systemic Lupus Erythematosus: Results From an International Inception Cohort Study. *Arthritis & Rheumatology* **2019**, *72*, 67-77, 10.1002/art.41070.
14. Simone Fargetti; Michelle R. Ugolini-Lopes; Sandra G. Pasoto; Luciana P. C. Seguro; Samuel K. Shinjo; Eloisa Bonfa; Eduardo F. Borba; Short- and Long-Term Outcome of Systemic Lupus Erythematosus Peripheral Neuropathy. *JCR: Journal of Clinical Rheumatology* **2019**, *27*, S212-S216, 10.1097/rhu.0000000000001201.
15. Nan Zhang; Jie Cao; Meng Zhao; Li Sun; The introspection on the diagnosis and treatment process of a case of Guillain–Barré syndrome (GBS) attributed to systemic lupus erythematosus (SLE). *Medicine* **2017**, *96*, e9037, 10.1097/md.0000000000009037.
16. Ankita D Patil; Niteen D Karnik; Milind Y Nadkar; Vishal A Gupta; Krithika Muralidhara; Suresh Passidhi; Guillain Barré Syndrome, Systemic Lupus Erythematosus and Acute Intermittent Porphyria – A Deadly Trio.. *The Journal of the Association of Physicians of India* **2015**, *63*, 60-3.
17. Wenjing Ye; Siyan Chen; Xinshi Huang; Wei Qin; Ting Zhang; Xiaofang Zhu; Xiaochun Zhu; Chongxiang Lin; Xiaobing Wang; Clinical features and risk factors of neurological involvement in Sjögren's syndrome.. *BMC Neuroscience* **2018**, *19*, 26, 10.1186/s12868-018-0427-y.
18. Tabea Seeliger; Nils K. Prenzler; Stefan Gingele; Benjamin Seeliger; Sonja Körner; Thea Thiele; Lena Bönig; Kurt-Wolfram Sühs; Torsten Witte; Martin Stangel; et al.Thomas Skripuletz Neuro-Sjögren: Peripheral Neuropathy With Limb Weakness in Sjögren's Syndrome. *Frontiers in Immunology* **2019**, *10*, 1600, 10.3389/fimmu.2019.01600.
19. Guillermo Carvajal Alegria; Dewi Guellec; Xavier Mariette; Jacques-Eric Gottenberg; Emmanuelle Dernis; Jean-Jacques Dubost; Anne-Priscille Trouvin; Eric Hachulla; Claire Larroche; Veronique Le Guern; et al.Divi CornecValérie Devauchelle-PensecAlain Saraux Epidemiology of neurological manifestations in Sjögren's syndrome: data from the French ASSESS Cohort. *RMD Open* **2016**, *2*, e000179-e000179, 10.1136/rmdopen-2015-000179.
20. Joanna Perzyńska-Mazan; Maria Maślińska; Robert Gasik; Neurophysiological Features of Peripheral Nervous System Involvement and Immunological Profile of Patients with Primary Sjögren Syndrome. *The Journal of Rheumatology* **2020**, *47*, 1661-1667, 10.3899/jrheum.181464.

The sural nerve is most frequently used for biopsy, which contributes to the determination of the nature and extent of PN [5]. Birnbaum et al. [38] performed nerve biopsies in 31 PN-AAV patients and showed that 55% of patients had definite vasculitis. Similarly, about 80% of PN-EGPA patients had extravascular eosinophils and 57% of the patients had vasculitis, while no extravascular granuloma was observed in the total 40 patients [40].

4.3 Diagnosis of small fibers neuropathy

Somatic and autonomic functional nervous evaluation of SFN involves the sympathetic and parasympathetic autonomic functions, which is realized by determining the psychophysical sensory thresholds (e.g. cold and heat) through quantitative sensory testing (QST), pain-related tests and recording of laser-evoked potentials (LEP), single axon recording utilizing microneurography and tests [78]. In another hand, in 2010, the European Federation of Neurological Societies and the Peripheral Nerve Society joint amended the Guidelines on the Application of Skin Biopsy in the Diagnosis of PN. And a conclusion was made that distal leg skin biopsy with quantification of the linear density of IENFD, adopting universally accepted counting rules, is a reliable and efficient technology to evaluate the diagnosis of SFN [79]. In fact, the process toward the determination of the diagnosis of SFN in individual patients, beginning from the chief complaints of sensory symptoms, is on the basis of the clues from skin biopsy and/or QST results. The combination of clinical signs and abnormal QST and/or IENFD findings can reliably be used to diagnose SFN compared with the combination of abnormal QST and IENFD findings without clinical signs [80].

What's more, current diagnostic technologies for SFN are also composed of quantitative sensory testing with determination of warm and cold detection thresholds (WDT, CDT), recording of LEP and sympathetic skin responses (SSRs), and measurement of electrochemical skin conductance (ESC) utilizing Sudoscan(®) device [81].

4.4 Modern imaging methods

Modern imaging methods allow the precise localization of peripheral nerve damage. Sonoelastography [29] and ultrasonography investigations of the median nerve [82] are emerging techniques to image the median nerve. Researchers have used the ultrasonography investigation of the median nerve to visualize the median nerve in the carpal tunnel, revealing an increased median nerve cross-sectional area (CSA) and decreased echogenicity due to neural edema within the carpal tunnel [51]. Sonoelastography, previously applied to document decreased skin elasticity in patients with SSc, now is also used for median nerve imaging [51].

Diffusion-weighted magnetic resonance neurography (DW-MRN) is another emerging technique that can exploit the greater water diffusion anisotropy in peripheral nerves for improved visualization [83]. Based on the concept of background body and vascular signal suppression for improved visualization of stationary fluid or cellular structures, DW-MRN is applicable to improved visualization of extremity nerves and their lesions in the wrist and palm with adequate image quality, thus providing a supplementary method for conventional magnetic resonance imaging [83].

21. Meena Angamuthu Kanikannan; Yareeda Sireesha; Anjan Pyal; Gampa Sandeep; Megha S Uppin; Rukmini Mridula Kandadai; Shaik Afshan Jabeen; Rajendra Vanaprasad; Liza Rajasekhar; Mathukumilli L Neeharika; et al.Rupam BorgohainPatterns of peripheral neuropathy in Sjogren's syndrome in a tertiary care hospital from South India. *Neurology India* **2019**, *67*, 94-S99, 10.4103/0028-3886.250714.
22. Marta Jaskólska; Magdalena Chylińska; Anna Masiak; Mariusz Siemiński; Marcin Ziętkiewicz; Zenobia Czuszyńska; Żaneta Smoleńska; Zbigniew Zdrojewski; Neuro-Sjögren: Uncommon or underestimated problem?. *Brain and Behavior* **2020**, *10*, e01665, 10.1002/brb3.1665.
23. Marta Jaskólska; Magdalena Chylińska; Anna Masiak; Katarzyna Nowicka-Sauer; Mariusz Siemiński; Marcin Ziętkiewicz; Zenobia Czuszyńska; Zbigniew Zdrojewski; Peripheral neuropathy and health-related quality of life in patients with primary Sjögren's syndrome: a preliminary report. *Rheumatology International* **2020**, *40*, 1267-1274, 10.1007/s00296-020-04543-2.
24. Guillermo Carvajal Alegria; Dewi Guellec; Valérie Devauchelle-Pensec; Alain Saraux; Is there specific neurological disorders of primary Sjögren's syndrome?. *Joint Bone Spine* **2015**, *82*, 86-89, 10.1016/j.jbspin.2014.04.002.
25. Alessia Alunno; Francesco Carubbi; Elena Bartoloni; Paola Cipriani; Roberto Giacomelli; Roberto Gerli; The kaleidoscope of neurological manifestations in primary Sjögren's syndrome.. *null* **2019**, *118*, 192-198.
26. Ajith Sivadasan; Karthik Muthusamy; Bimal Patel; Rohit Benjamin; A. T. Prabhakar; Vivek Mathew; Sanjith Aaron; Mathew Alexander; Clinical Spectrum, Therapeutic Outcomes, and Prognostic Predictors in Sjogren's Syndrome-associated Neuropathy. *Annals of Indian Academy of Neurology* **1970**, *20*, 278-283, 10.4103/aian.AIAN_116_17.
27. Jasmin Raja; Tharshannia Balaikerisnan; Letchumy Praba Ramanaidu; Khean Jin Goh; Large fiber peripheral neuropathy in systemic sclerosis: A prospective study using clinical and electrophysiological definition. *International Journal of Rheumatic Diseases* **2021**, *24*, 347-354, 10.1111/1756-185x.14042.
28. Julie J. Paik; Andrew L. Mammen; Fredrick M. Wigley; Ami A. Shah; Laura K. Hummers; Michael Polydefkis; Symptomatic and Electrodiagnostic Features of Peripheral Neuropathy in Scleroderma. *Arthritis & Rheumatism* **2015**, *68*, 1150-1157, 10.1002/acr.22818.
29. Ilker Yagci; Ozge Kenis-Coskun; Tugba Ozsoy; Gulsen Ozen; Haner Direskeneli; Increased stiffness of median nerve in systemic sclerosis.. *BMC Musculoskeletal Disorders* **2017**, *18*, 434, 10.1186/s12891-017-1793-9.
30. Pornhathai T. Sriwong; Patpiya Sirasaporn; Chingching Foocharoen; Kannikar Srichompoo; Median neuropathy at the wrist in patients with systemic sclerosis: two-year follow-up study. *Reumatologia/Rheumatology* **2018**, *56*, 294-300, 10.5114/reum.2018.79500.

5. New treatments

5.1. Glucocorticoids with immunosuppressants as basic therapy

In 2010, the guidelines of the Society for Neurology of USA recommended (with evidence level B) vasculitic peripheral neuropathy shock therapy with glucocorticoids, possibly in combination with immunosuppression as basic therapy [84]. Major treatment recommendations were: (1) corticosteroid (CS) monotherapy for at least 6 months as first-line treatment; (2) combination therapy applied to rapidly progressive and non-systemic vasculitic neuropathy and patients who progress on CS monotherapy; (3) immunosuppressive options including cyclophosphamide, azathioprine, and methotrexate; (4) cyclophosphamideapplies to severe neuropathies, generally administered in IV pulses to reduce cumulative doses and the associated side effects; (5) combination therapy for patients achieving clinical remission, followed by continued maintenance therapy for 18-24 months with azathioprine or methotrexate [84].

5.2. Neuroactive steroids in neuropathic pain

Glucocorticoids are routinely used to relieve pain. However, as reported in experimental models of neuropathic pain, glucocorticoids may contribute to hyperalgesia, exacerbate neuropathic pain, activate the early process of pain induction and induce hyperalgesia [3]. Therefore, concerns have been raised about the use of glucocorticoids for pain treatment [3] and a new strategy is needed. Neuroactive steroids (i.e., steroid hormones synthesized by peripheral glands and those directly synthesized in the nervous system) represent critical physiological regulators of PNS function and can have protective impacts on several symptoms of PN including neuropathic pain [4]. Falvo et al. [4] summarized the role of neuroactive steroids for the treatment of neuropathic pain thus: progesterone prevents pain-related behaviors, like allodynia and hyperalgesia, in different models of neuropathic pain; tetrahydroprogesterone reduces thermal and mechanical hyperalgesia by enhancing the activity of the γ-amino butyric acid-A receptor and by blocking T-type Ca^{2+} channels; testosterone exerted anti-nociceptive effects in neuropathic rats; 17β-estradiol caused pain attenuation and a decrease of neuropathy-induced gliosis after sciatic nerve ligature; moreover, it exerted protective effects on neuropathic pain via estrogen receptors by inhibiting microglia activation and the production of inflammatory mediators. These observations support the view that neuroactive steroids may provide an interesting topic for neuropathic pain research in the near future.

31. Ugur Nadir Karakulak; Sercan Okutucu; Mehmet Levent Şahiner; Naresh Maharjan; Elifcan Aladag; Ali Akdogan; Levent Kilic; Ergun Baris Kaya; Kudret Aytemir; Lale Tokgozoglu; et al. Assessment of cardiac autonomic nervous system involvement in systemic sclerosis via exercise heart rate recovery.. *Medical Principles and Practice* **2014**, *24*, 17-22, 10.1159/000368359.

32. Marijana Tadic; Maja Zlatanovic; Cesare Cuspidi; Ana Stevanovic; Vera Celic; Nemanja Damjanov; Vesna Kocijancic; Systemic sclerosis impacts right heart and cardiac autonomic nervous system. *Journal of Clinical Ultrasound* **2017**, *46*, 188-194, 10.1002/jcu.22552.

33. Gabriel Dias Rodrigues; Eleonora Tobaldini; Chiara Bellocchi; Alessandro Santaniello; Monica Caronni; Adriana Severino; Marco Froldi; Lorenzo Beretta; Pedro Paulo Da Silva Soares; Nicola Montano; et al. Cardiac autonomic modulation at rest and during orthostatic stress among different systemic sclerosis subsets. *European Journal of Internal Medicine* **2019**, *66*, 75-80, 10.1016/j.ejim.2019.06.003.

34. Aman Sharma; Benzeeta Pinto; Aadhaar Dhooria; Manish Rathi; Manphool Singhal; Varun Dhir; Kusum Sharma; Mahesh Parkash; Manish Modi; Rajesh Vijayvergiya; et al.Saroj K. SinhaRitambhra NadaRanjana MinzSurjit Singh Polyarteritis nodosa in north India: clinical manifestations and outcomes. *International Journal of Rheumatic Diseases* **2016**, *20*, 390-397, 10.1111/1756-185x.12954.

35. Hubert de Boysson; Loïc Guillevin; Polyarteritis Nodosa Neurologic Manifestations. *Neurologic Clinics* **2019**, *37*, 345-357, 10.1016/j.ncl.2019.01.007.

36. John B. Imboden; Involvement of the Peripheral Nervous System in Polyarteritis Nodosa and Antineutrophil Cytoplasmic Antibodies–Associated Vasculitis. *Rheumatic Disease Clinics of North America* **2017**, *43*, 633-639, 10.1016/j.rdc.2017.06.011.

37. Joe James; James Jose; Nallaveettil Kesavan Thulaseedharan; Acute Necrotizing Vasculitic Neuropathy due to Polyarteritis Nodosa. *Oman Medical Journal* **2018**, *33*, 253-255, 10.5001/omj.2018.46.

38. Antje Bischof; Veronika K. Jaeger; Robert D. M. Hadden; Raashid A. Luqmani; Anne-Katrin Pröbstel; Peter A. Merkel; Ravi Suppiah; Anthea Craven; Michael P. Collins; Thomas Daikeler; et al. Peripheral neuropathy in antineutrophil cytoplasmic antibody-associated vasculitides. *Neurology - Neuroimmunology Neuroinflammation* **2019**, *6*, e615, 10.1212/nxi.0000000000000615.

39. Zhaocui Zhang; Suying Liu; Ling Guo; Li Wang; Qingjun Wu; Wenjie Zheng; Yong Hou; Xinping Tian; Xiaofeng Zeng; Fengchun Zhang; et al. Clinical Characteristics of Peripheral Neuropathy in Eosinophilic Granulomatosis with Polyangiitis: A Retrospective Single-Center Study in China. *Journal of Immunology Research* **2020**, *2020*, 1-10, 10.1155/2020/3530768.

40. Hye-Jin Cho; Sehyo Yune; Jin Myoung Seok; Eun Bin Cho; Ju-Hong Min; Yeon Lim Seo; Byung-Jae Lee; Byoung Joon Kim; Dong-Chull Choi; Clinical Characteristics and Treatment Response of

Peripheral Neuropathy in the Presence of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome): Experience at a Single Tertiary Center. *Journal of Clinical Neurology* **2017**, *13*, 77-83, 10.3988/jcn.2017.13.1.77.

41. Ryoji Nishi; Haruki Koike; Ken Ohyama; Yuki Fukami; Shohei Ikeda; Yuichi Kawagashira; Masahiro Iijima; Masahisa Katsuno; Gen Sobue; Differential clinicopathologic features of EGPA-associated neuropathy with and without ANCA. *Neurology* **2020**, *94*, e1726-e1737, 10.1212/wnl.0000000000009309.
42. P. Moog; O. Eren; M. Witt; V. Rauschel; S. Kossegg; A. Straube; M. Grünke; H. Schulze-Koops; Assessment of autonomic function in a cohort of patients with ANCA-associated vasculitis. *Clinical Autonomic Research* **2016**, *26*, 279-285, 10.1007/s10286-016-0364-8.
43. Kazuma Murata; Kenji Endo; Hirosuke Nishimura; Hidetoshi Tanaka; Takaaki Shishido; Kengo Yamamoto; Eosinophilic granulomatosis with polyangiitis presenting as acute sciatic nerve neuropathy resembling lumbar disease. *Journal of Orthopaedic Science* **2015**, *20*, 224-228, 10.1007/s00776-013-0437-7.
44. Carlos Rodrigo Camaralemarroy; Adrian Infante-Valenzuela; Hector J. Villareal-Montemayor; Carlos A. Soto-Rincon; Javier A. Davila-Olalde; Hector J. Villareal-Velazquez; Eosinophilic Granulomatosis with Polyangiitis Presenting as Acute Polyneuropathy Mimicking Guillain-Barre Syndrome. *Case Reports in Neurological Medicine* **2015**, *2015*, 1-3, 10.1155/2015/981439.
45. Li Wang; Jing Li; Min Qian; Wenjie Zheng; Qingjun Wu; Wen Zhang; Xinping Tian; Fengchun Zhang; [Clinical features of microscopic polyangiitis associated with peripheral neuropathy].. *Zhonghua yi xue za zhi* **2015**, *95*, 2190-2193.
46. Federica Arienti; Giulia Franco; Edoardo Monfrini; Alessandro Santaniello; Nereo Bresolin; Maria Cristina Saetti; Alessio Di Fonzo; Microscopic Polyangiitis With Selective Involvement of Central and Peripheral Nervous System: A Case Report. *Frontiers in Neurology* **2020**, *11*, 269, 10.3389/fneur.2020.00269.
47. Anastasia Bougea; Evangelos Anagnostou; Nikolaos Spandideas; Nikolaos Triantafyllou; Evangelia Kararizou; An update of neurological manifestations of vasculitides and connective tissue diseases: a literature review. *Einstein (São Paulo)* **2015**, *13*, 627-635, 10.1590/S1679-45082015RW3308.
48. Christian Geier; Kelly Steed; ‘Carpal tunnel syndrome’ and ‘tennis elbow’ as prodromes for granulomatosis with polyangiitis (formerly Wegener’s granulomatosis). *BMJ Case Reports* **2019**, *12*, 2, 10.1136/bcr-2018-227348.
49. Nidhi Kaeley; Sohaib Ahmad; Monika Pathania; Rajesh Kakkar; Prevalence and patterns of peripheral neuropathy in patients of rheumatoid arthritis. *Journal of Family Medicine and Primary Care* **2019**, *8*, 22-26, 10.4103/jfmpc.jfmpc_260_18.

50. Bharat Kumar; Madhumita P. Das; Arup Kumar Misra; A cross-sectional study of association of serostatus and extra-articular manifestations in patients with rheumatoid arthritis in a teaching hospital. *Journal of Family Medicine and Primary Care* **2020**, *9*, 2789-2793, 10.4103/jfmpc.jfmpc_99_20.
51. Inimioara Mihaela Cojocaru; Manole Cojocaru; Isabela Silosi; Camelia Doina Vrabie; Peripheral Nervous System Manifestations in Systemic Autoimmune Diseases. *MAEDICA – a Journal of Clinical Medicine* **2014**, *9*, 289-294.
52. Vijaita Syngle; Ashit Syngle; Nidhi Garg; Pawan Krishan; Inderjeet Verma; Predictors of autonomic neuropathy in rheumatoid arthritis. *Autonomic Neuroscience* **2016**, *201*, 54-59, 10.1016/j.autneu.2016.07.008.
53. Kimberly DeQuattro; John B. Imboden; Neurologic Manifestations of Rheumatoid Arthritis. *Rheumatic Disease Clinics of North America* **2017**, *43*, 561-571, 10.1016/j.rdc.2017.06.005.
54. Fanny Duval; Idoia Lacoste; Gaël Galli; Hugo Chaumont; Guilhem Solé; François Léger; Nathalie Damon-Perrière; Marie Rouanet; Gwendal Le Masson; Stéphane Mathis; et al. Acute Brachial Radiculoplexopathy and Giant Cell Arteritis. *The Neurologist* **2018**, *23*, 23-28, 10.1097/nrl.0000000000000162.
55. Yamile Calle-Lopez; A F Fernandez-Ramirez; E Franco-Dager; J G Gomez-Lopera; A L Vanegas-Garcia; [«Man-in-the-barrel» syndrome: atypical manifestation of giant cell arteritis].. *Revista de Neurología* **2018**, *66*, 373-376.
56. Richard Conway; Justin A. Kinsella; Eamonn S. Molloy; Peroneal neuropathy in giant cell arteritis. *Rheumatology* **2016**, *56*, 169-170, 10.1093/rheumatology/kew363.
57. Denise Kim; Graham Roche-Nagle; Axillary artery aneurysm combined with brachial plexus palsy due to Takayasu arteritis. *BMJ Case Reports* **2018**, *2018*, 2018, 10.1136/bcr-2017-221863.
58. Jungsoo Lee; Suhyun Cho; Do Young Kim; Zhenlong Zheng; Hoon Park; Dongsik Bang; Carpal Tunnel Syndrome in Behçet's Disease. *Yonsei Medical Journal* **2015**, *56*, 1015-1020, 10.3349/ymj.2015.56.4.1015.
59. Yulei Hao; Liangshu Feng; Yongliang Teng; Yingying Cheng; Jiachun Feng; Management of multiple neurological complications in mixed connective tissue disease. *Medicine* **2018**, *97*, e11360, 10.1097/md.0000000000011360.
60. X J Gao; Y H Li; X W Zhang; S Chen; Y Y Liu; [Clinical analysis of 12 cases of mixed connective tissue disease-associated trigeminal neuropathy].. *null* **2020**, *100*, 938-941.
61. Dorota Jasińska; Jerzy Boczon; Melkersson–Rosenthal syndrome as an early manifestation of mixed connective tissue disease. *European Journal of Medical Research* **2015**, *20*, 1-3, 10.1186/s40001-015-0192-7.

62. Syeda Naqvi; Vikash Talib; Razia Aijaz; Zeeshan Ali; Shehroz Bashir; Syed Masroor Ahmad; Shabnam Naveed; Autoamputation and Polyneuropathy in Mixed Connective Tissue Disorder: A Case Report. *Cureus* **2017**, *9*, e1313-e1313, 10.7759/cureus.1313.
63. Takashi Irie; Hiroshi Shigeto; Junpei Koge; Hiroo Yamaguchi; Hiroyuki Murai; Jun-Ichi Kira; Dermatomyositis complicated with asymmetric peripheral neuritis on exacerbation: A case report and literature review. *Clinical and Experimental Neuroimmunology* **2016**, *7*, 373-380, 10.1111/cen3.12332.
64. Mahmoud A AbdelRazek; Nagagopal Venna; John H Stone; IgG4-related disease of the central and peripheral nervous systems. *The Lancet Neurology* **2018**, *17*, 183-192, 10.1016/s1474-4422(17)30471-4.
65. Lingling Zhan; Mengting Fan; Naiqing Cai; Bin Cai; Combination of autoimmune pancreatitis and peripheral neuropathy on an IgG4-related disease patient with 4 years following-up. *Journal of Neuroimmunology* **2020**, *348*, 577378, 10.1016/j.jneuroim.2020.577378.
66. Yen-Ju Lin; Martina Anzaghe; Stefan Schülke; Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. *Cells* **2020**, *9*, 880, 10.3390/cells9040880.
67. A Pardanani; R R Laborde; T L Lasho; C Finke; K Begna; A Al-Kali; W J Hogan; M R Litzow; A Leontovich; M Kowalski; et al.A Tefferi Safety and efficacy of CYT387, a JAK1 and JAK2 inhibitor, in myelofibrosis. *Leukemia* **2013**, *27*, 1322-1327, 10.1038/leu.2013.71.
68. Mahyar Etminan; Mohit Sodhi; Ali Samii; Bruce C Carleton; Abbas Kezouh; J Antonio Avina-Zubieta; Tumor necrosis factor inhibitors and risk of peripheral neuropathy in patients with rheumatic diseases. *Seminars in Arthritis and Rheumatism* **2018**, *48*, 1083-1086, 10.1016/j.semarthrit.2018.09.006.
69. Pinelopi Tsouni; Olivier Bill; Andre Truffert; Christelle Liaudat; François Ochsner; Andreas J. Steck; Thierry Kuntzer; Anti-TNFalpha medications and neuropathy. *Journal of the Peripheral Nervous System* **2015**, *20*, 397-402, 10.1111/jns.12147.
70. Ali Zinebi; Youssef Akhouad; Adil Rkiouak; Ahmed Reggad; Zohour Kasmy; Mostafa Boudlal; Monsef Rabhi; Khalid Ennibi; Jilali Chaari; Neuropathie périphérique sous Infliximab: étude d'une observation. *The Pan African Medical Journal* **2016**, *24*, 271, 10.11604/pamj.2016.24.271.3498.
71. S. Fernández-Menéndez; N. González Nafría; L. Redondo-Robles; M. Sierra-Ausín; R. García-Santiago; A. Saponaro-González; Multifocal-motor-neuropathy-like disease associated with Infliximab treatment in a patient with Crohn's disease. *Journal of the Neurological Sciences* **2015**, *349*, 246-248, 10.1016/j.jns.2015.01.003.
72. Savvas Psarelis; Andreas P. D. Hajineocli; Eleni Hadjicosta; Hugh St. A. Elliott; Paul Johnson; Is secukinumab a safe alternative treatment for ankylosing spondylitis with Guillain Barré syndrome

after anti-TNF-? treatment? Case report and literature review. *Clinical Rheumatology* **2017**, *36*, 1197-1199, 10.1007/s10067-017-3573-1.

73. Takayuki Fujii; Ryo Yamasaki; Jun-Ichi Kira; Novel Neuropathic Pain Mechanisms Associated With Allergic Inflammation. *Frontiers in Neurology* **2019**, *10*, 1337, 10.3389/fneur.2019.01337.
74. Sampaio L, Silva LG, Terroso G, Nadais G, Mariz E, Ventura F.; Vasculitic neuropathy. *Acta Reumatol Port.* **2011 Apr-Jun**, *36(2)*, 102-109.
75. N. N. Spirin; V. A. Bulanova; N. V. Pizova; N. P. Shilkina; Peripheral nervous system lesion syndromes and the mechanisms of their formation in connective tissue diseases. *Neuroscience and Behavioral Physiology* **2007**, *37*, 1-6, 10.1007/s11055-007-0141-1.
76. Nidhi Garg; Susanna B. Park; Con Yiannikas; Steve Vucic; James Howells; Yu-Ichi Noto; Emily K. Mathey; John D. Pollard; Matthew C. Kiernan; Neurofascin-155 IGG4 Neuropathy: Pathophysiological Insights, Spectrum of Clinical Severity and Response To treatment. *Muscle & Nerve* **2017**, *57*, 848-851, 10.1002/mus.26010.
77. Chafic Karam; Peripheral Neuropathies Associated With Vasculitis and Autoimmune Connective Tissue Disease. *CONTINUUM: Lifelong Learning in Neurology* **2020**, *26*, 1257-1279, 10.1212/con.0000000000000917.
78. Astrid Juhl Terkelsen; Pall Karlsson; Giuseppe Lauria; Roy Freeman; Nanna Finnerup; Troels S Jensen; The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. *The Lancet Neurology* **2017**, *16*, 934-944, 10.1016/s1474-4422(17)30329-0.
79. G. Lauria; Sung-Tsang Hsieh; O. Johansson; W. R. Kennedy; J. M. Leger; S. I. Mellgren; Maria Nolano; I. S. J. Merkies; M. Polydefkis; A. G. Smith; et al.C. SommerJ. Valls-Solé 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 Fe-deration of Neurological Societies and the Peripheral Ne. *European Journal of Neurology* **2010**, *17*, 903-e49, 10.1111/j.1468-1331.2010.03023.x.
80. Grazia Devigili; Sara Rinaldo; Raffaella Lombardi; Daniele Cazzato; Margherita Marchi; Erika Salvi; Roberto Eleopra; Giuseppe Lauria; Diagnostic criteria for small fibre neuropathy in clinical practice and research. *Brain* **2019**, *142*, 3728-3736, 10.1093/brain/awz333.
81. J.-P. Lefaucheur; A. Wahab; V. Planté-Bordeneuve; D. Sène; I. Ménard-Lefaucheur; D. Rouie; D. Tebbal; H. Salhi; A. Créange; Hela Zouari; et al.S. Ng Wing Tin Diagnosis of small fiber neuropathy: A comparative study of five neurophysiological tests. *Neurophysiologie Clinique* **2015**, *45*, 445-455, 10.1016/j.neucli.2015.09.012.
82. Soo-Jung Choi; Jae Hong Ahn; Dae Shik Ryu; Chae Hoon Kang; Seung Mun Jung; Man Soo Park; Dong-Rock Shin; Ultrasonography for nerve compression syndromes of the upper extremity. *Ultrasonography* **2015**, *34*, 275-291, 10.14366/usg.14060.

83. Hongjing Bao; Shanshan Wang; Guangbin Wang; Li Yang; Mansoor-Ul Hasan; Bin Yao; Chao Wu; Xu Zhang; Weibo Chen; Queenie Chan; et al.Lebin WuAvneesh Chhabra Diffusion-weighted MR neurography of median and ulnar nerves in the wrist and palm. *European Radiology* **2016**, *27*, 2359-2366, 10.1007/s00330-016-4591-0.

84. Michael P. Collins; P. James B. Dyck; Gary S. Gronseth; Loïc Guillevin; Robert D. M. Hadden; Dieter Heuss; Jean-Marc Léger; N.C. Notermans; John D. Pollard; Gérard Said; et al.Gen SobueA.F.J.E. VranckenJohn T. Kissel Peripheral Nerve Society Guideline* on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. *Journal of the Peripheral Nervous System* **2010**, *15*, 176-184, 10.1111/j.1529-8027.2010.00281.x.