Abstract. Peripheral neuropathies are a vast group of diseases with heterogeneous aetiologies, including genetic and acquired causes. Several haematological disorders may cause an impairment of the peripheral nervous system, with diverse mechanisms and variable clinical, electrophysiological and pathological manifestations. In this practical review, we considered the main phenotypes of peripheral nervous system diseases associated with lymphoproliferative disorders.

The area of intersection of neurological and haematological fields is of particular complexity and raises specific problems in the clinical practice of lymphoproliferative disorders. The personal crosstalk between neurologists and haematologists remains a fundamental tool for a proper diagnostic process which may lead to successful treatments in most cases.

Keywords: Neuropathy, Monoclonal gammopathy, Amyloid, Nerve biopsy, Peripheral nervous system, MGUS, Lymphoma, POEMS.

Introduction. The peripheral nervous system (PNS) consists of sensory, motor, and autonomic neurons that lie outside the confines of the central nervous system. It is a conceptual artifice rather than a concrete anatomical definition, as most neurons with peripheral projection lie partly within the peripheral and partly within the central nervous system.

Peripheral neuropathies are diseases with heterogeneous aetiologies, including genetic and acquired causes. Several haematological disorders may cause an impairment of the peripheral nervous system, with diverse mechanisms and variable clinical, electrophysiological and pathological manifestations.

Peripheral neuropathies may be classified into distinct phenotypes based on different clinical, electrophysiological and pathological criteria. Clinically, we distinguish two great groups: symmetric polyneuropathies and focal neuropathies. Both groups may be further differentiated in demyelinating and axonal forms, according to the predominant target of the disease process that is myelin sheath or axon, respectively.

In this practical review, we considered the main phenotypes of peripheral nervous system diseases...
and the lymphoproliferative disorders which may be associated with.

**Focal Neuropathies.** In several acquired and hereditary conditions, the involvement of the PNS may be limited to a single nerve (mononeuropathy) or a few nerves (multiple mononeuropathy or multifocal neuropathy). This condition can be easily differentiated from symmetric polyneuropathy on the clinical ground, but the electrophysiological examination is helpful in confirming the multifocal nature of nerve involvement and may indicate the presence of predominant or exclusive axonal or demyelinating pattern.

**Vasculitic neuropathy.** Primary and secondary vasculitis are a leading cause of focal neuropathies and should firstly be considered in the differential diagnosis of focal neuropathies, especially if painful. In a minority of cases vasculitis give rise to a generalized, but asymmetric, neuropathy. Inflammation of the small epineural arteries leads to their occlusion with a secondary ischemic injury of the nerve fibres. Vasculitic neuropathies may occur in the context of widespread, multiorgan involvement, or, less commonly, may represent the only manifestation of the disease (non-systemic vasculitic neuropathies). Haematological diseases associated with vasculitis neuropathy include cryoglobulinemia, eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss disease), and some forms of paraproteinemias (Figure 1).

**Figure 1.** Sural nerve biopsy from a patient with vasculitic neuropathy. H&E staining shows massive lymphocites infiltration of epineural vessels with fibrinoid necrosis.

Cryoglobulinemia refers to the presence of circulating immunoglobulins that precipitate at cold temperatures. Types II mixed cryoglobulinemia is the form most frequently associated with neuropathy. Hepatitis C virus (HCV) is present in 80–90% of patients with types II of cryoglobulinemia. When no underlying disorder is detected, the condition is termed essential. In patients with HCV-related cryoglobulinemia, about 65% develop a neuropathy. However, most cases have a distal, predominantly sensory polyneuropathy with a very slowly progressive course, which is related to HCV infection per se rather than to vasculitic damage. Additional features of the cryoglobulinemic syndrome include purpura, skin ulcers, arthralgias, sicca syndrome, Raynaud’s phenomenon, glomerulonephritis, and lymphadenopathy. Rheumatoid factors and hypocomplementemia occur in the majority of patients.

Churg-Strauss disease is characterized by blood eosinophilia greater than 10%, asthma, pulmonary infiltrates. Involvement of PNS occurs in 60-70% of patients.

Finally, vasculitis may be one of the mechanisms by which IgM paraproteinemia damages the peripheral nerves (see after). Vasculitis should be considered when acute, focal nerve lesion occurs in the setting of the classic indolent IgM polyneuropathy or in asymptomatic individuals.

**Neurolymphomatosis.** Infiltration by lymphomatous cells of the PNS is a rare and frequently ignored complication of non-Hodgkin lymphoma. Direct invasion of lymphoma cells into the PNS may occur in patients with a previous diagnosis of lymphoma but may represent the first and unique manifestation of the haematological malignancy, a condition defined as primary neurolymphomatosis. Nerve roots and plexi are more frequently involved; other sites include cranial nerves, sciatic nerve and cauda equine. Lymphomatous cell invasion induces demyelination and subsequent axonal degeneration in the portion distal from the infiltration site. Differential diagnosis with inflammatory radiculo-plexo-neuropathies and other forms of focal inflammatory neuropathies is challenging. Severe pain and the progressive course despite immunomodulating therapies should raise the
Figure 2. Sural nerve biopsy from a patient with primary multifocal lymphoma of peripheral nervous system. Immunohistochemistry with anti-CD20 (green) and DAPI (blue) confirms diffuse infiltration of one nerve fascicle by lymphomatous cells.

Immunoglobulin infiltration. Multiple mononeuritis have been described as the predominant clinical manifestation in rare patients with Waldenström's macroglobulinaemia in which the underlying mechanism is a massive light and heavy chain deposition within the nerves resulting in massive fascicular hyalinosis (Figure 3 A-D). In these cases, protein accumulation in the endoneurium and epineurium behaves differently from amyloid as it does not stain with Congo Red. The presence of polyneuropathy is currently considered an indication to start treatment in smouldering Waldenström macroglobulinemia.

Others. Focal neuropathies due to direct infiltration of malignant cells have been occasionally reported in patients with acute myeloid leukaemia. Inflammatory asymmetric radiculoplexopathy is a very rare complication of stem cell transplantation.

Demyelinating and Axonal Polyneuropathies. Peripheral nerve disorders are traditionally classified as primary demyelinating or axonal. In demyelinating neuropathies, segments of myelin sheath may be damaged leaving the axon anatomically intact. On the contrary, in axonal neuropathies, there is a loss of motor or sensory axons while the myelin sheath of the surviving fibres is normal. The electrophysiological examination is able to differentiate demyelinating from axonal neuropathies, thus helping in clinical practice and offering clues since causes of demyelinating and of axonal forms are different.

Demyelinating polyneuropathies. The myelin sheath is the primary target in numerous genetic and acquired conditions, the latter including Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), Demyelinating Polyneuropathy associated with IgM paraproteinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome, and Guillain Barré Syndrome (GBS).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Guillain Barré Syndrome. CIDP and GBS are immune-mediated diseases of peripheral nerves, usually occurring as isolated conditions. There is evidence that they may be associated with haematological diseases, particularly lymphoma, which may act as predisposing conditions.

CIDP may have a chronically progressive or relapsing course and responds to immune modulating or immunosuppressive treatments. In typical CIDP there is a symmetric motor/sensory disorder with proximal and distal weakness and areflexia with electrophysiological signs of demyelination, including conduction slowing, temporal dispersion and/or conduction block. Although abnormalities in both cellular and humoral immunity have been shown, the causes of CIDP remain largely unknown, and no specific antigen has been identified. Recently, antibodies against paranodal axo-glial proteins, resulting in conduction alteration without overt demyelination, have been detected in demyelinating neuropathies, but these conditions represent a distinct subgroup of CIDP. Near always CIDP is an idiopathic condition, while in a minority of cases it has been described in association with various disorders and in these cases, it may be more difficult to recognise. A recent review has shown that haematological diseases, particularly non-Hodgkin lymphoma, are the malignancies most commonly associated with CIDP. CIDP frequently precedes...
Figure 3 A-D. Sural nerve biopsy from a patient with massive light chains nerve deposition. H&E staining shows hyalinosis of one fascicle, just near to a normal one (A). Immunohistochemical analysis with anti-lambda (B) and anti-kappa light chains antibodies (C and D) shows immunoreactivity in the form of patchy staining in the endoneurium and epineurium only for anti-kappa light chain antibodies (C and D).

PNS involvement occurs in about 5-14% of patients with lymphoma. Besides the nerve infiltration and CIDP, mentioned above, other causes are chemotherapy-induced neuropathy, amyloid neuropathy, paraneoplastic neuropathy and Varicella-Zoster (VZV) infection of ganglia/nerves. Since CIDP is a condition responding to specific treatments, a careful electrophysiological examination is required to identify the presence of demyelinating features typical of CIDP.

Guillain-Barre syndrome (GBS) is an acute disorder affecting peripheral nerves and nerve roots with maximum severity within four weeks from disease onset. GBS may be classified into variants based on clinical features and electrodiagnostic findings. The most common variant is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), while acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), Miller Fisher syndrome, pharyngeal-cervical-brachial variant, cranial polynirritis, and acute pandysautonomia account for a minority of cases.

GBS is usually an idiopathic condition but in rare cases is associated with lymphoma and in even much rare cases precedes the haematological disease. GBS has rarely described after stem cell transplantation for haematological diseases, possibly caused by an immune reconstitution syndrome or by a paraneoplastic phenomenon.

Finally, in rare cases, an acute polyradiculoneuropathy mimicking GBS may be the presenting manifestation of acute myeloid leukaemia.

Chronic Demyelinating symmetric polyneuropathy and paraproteinemia. Coexistence of neuropathy and paraproteinemia...
and monoclonal gammopathy represents a common and challenging problem in clinical practice. Monoclonal proteins may occur in the context of several haematologic malignancies or, more frequently, as a monoclonal gammopathy of undetermined significance (MGUS). MGUS is relatively common in the general population, with a prevalence of 3% to 4% among individuals older than 50 years,\textsuperscript{21} so that its presence in a patient with neuropathy may be coincidental. Furthermore, 11% of individuals with MGUS show a progression to multiple myeloma or another plasma-cell or lymphoid disorder over the time.\textsuperscript{22} Finally, the relationship between paraproteinemia and neuropathy is multifaceted, as several pathogenic mechanisms are involved with variable clinical, electrophysiological pathologic manifestations. Depending on the type of M protein three major types of MGUS are considered: IgM MGUS, non-IgM MGUS (which includes IgG and IgA MGUS), and light-chain MGUS.

If the paraproteinemia is detected in association with a demyelinating polyneuropathy, diagnostic and pathogenic consideration differ for each of these three groups:

a) IgM MGUS and demyelinating neuropathy:
- Demyelinating neuropathy and IgM paraproteinemia. IgM paraproteinemic neuropathy represents an established and well-characterised entity, as it shows peculiar clinical, electrophysiological and pathologic characteristics, which allow a clear differentiation from CIDP.\textsuperscript{23-24} The clinical picture in that of “distal acquired demyelinating symmetric” (DADS) sensory and motor neuropathy. Most patients have distal paresthesias, sensory ataxia, frequent hand tremor with little or no weakness of tibia-peroneal muscles. The neuropathy has an indolent course, usually with little functional impairment over time. If in this context a rapid deterioration occurs, the possibility of a vasculitic injury should be considered. Electrophysiological signs are also characteristic and include slowing of conduction velocities with particularly increased distal motor latencies, without conduction blocks. Pathologic examination of nerve biopsy shows typical widening of myelin lamellae and irregular myelin folding while little or no demyelination is observed (Figure 4 A-B). In about 50% of patients with IgM paraproteinemic neuropathies, the M protein binds to myelin-associated glycoprotein (MAG).\textsuperscript{23-24} In anti-MAG negative patients\textsuperscript{25-26} reactivity against gangliosides and their complexes were detected in 35% of cases.

This neuropathy does not respond to many of the immune therapies that are effective in CIDP. There is very low-quality evidence of benefit from rituximab.\textsuperscript{27}

![Figure 4 A-B](https://example.com/figure4.png)

**Figure 4 A-B.** Sural nerve biopsy from a patient with anti-MAG demyelinating polyneuropathy. Ultrastructural examination at electron microscope shows typical widening of inner myelin lamellae (A and B).
Demyelinating neuropathy with IgM paraproteinemia and Ophthalmoplegia. Chronic Ataxic Neuropathy with Ophthalmoplegia, M-protein, cold Agglutinins and Disialosyl antibodies (anti-ganglioside, anti-GD1b, and anti-GQ1b) (CANOMAD syndrome) is a rare phenotype associated with an IgM MGUS. The clinical picture is characterised by a chronic neuropathy with marked sensory ataxia and areflexia, and with relatively preserved motor function in the limbs. In addition, 90% of cases have oculomotor and bulbar muscles impairment as fixed or as relapsing-remitting features. The IgM antibodies are cold agglutinins in 50% of cases.

b) Non-IgM MGUS and demyelinating neuropathy:
Demyelinating neuropathy with IgG or IgA paraproteinemia. When a non-IgM paraproteinemia is found in a context of a demyelinating neuropathy, the most likely situation is that it represents a casual combination of an otherwise typical CIDP with an MGUS. This explanation is based on the observation that the neuropathy has no peculiar clinical, electrophysiological or pathological aspect and no reactivity to nerve antigen has been observed in these cases. Responses to therapy are not different in CIDP patients with or without IgG or IgA paraproteinemia.

- Demyelinating neuropathy with IgG or IgA paraproteinemia, with atypical aspects. When a demyelinating neuropathy associated with non-IgM monoclonal component behave differently from typical CIDP, the POEMS syndrome should be considered. In this condition, a multitude of clinical and laboratory signs may accompany the polyneuropathy. Clinical alerts include skin changes (hyperpigmentation, hypertrichosis, acrocyanosis, flushing, white nails), oedema, pleural effusion or ascites, papilledema, weight loss, severe muscular deterioration not responding to usual therapies used in CIDP. The detection of thrombocytosis/polycythaemia and/or organomegaly (spleenomegaly, hepatomegaly or lymphadenopathy) are additional elements. The electrophysiological examination also shows a more severe pattern than in CIDP, with marked reduction of motor amplitudes and presence of fibrillation potentials, expression of severe axonal loss. The M protein is IgG or IgA, almost always λ. The evidence of osteosclerotic bone lesions at radiologic skeletal studies and of elevation of vascular endothelial growth factor (VEGF) are crucial for the diagnosis. The diagnosis of POEMS syndrome is made in a demyelinating polyneuropathy with M protein when one of the major criteria and at least one of the minor criteria are present. In conclusion, though POEMS is easily mistaken for CIDP, the diagnosis is relatively simple if it is considered.

c) Light-chain MGUS and demyelinating neuropathies:
AL amyloidosis is an axonal neuropathy (see after), but in some cases, a slight slowing of conduction velocities and an increase of distal and F waves latencies may be misleading, and CIDP may be erroneously diagnosed.

Axonal neuropathies. Axonal neuropathies encompass a vast group of genetic and acquired conditions, whose etiologic definition is more difficult than for demyelinating neuropathies. Three main groups of axonal neuropathies may be present in haematological disorders: sensory neuronopathies, length-dependent polyneuropathies, and axonal polyneuropathy associated with paraproteinemia.

Sensory neuronopathies. Sensory neuronopathies (SNs) or ganglionopathies encompass a group of disorders characterised by primary degeneration of sensory neurons whose cell body is located in the dorsal root ganglia (DRG). These cells are particularly susceptible to circulating agents, including antibodies or toxins, because capillaries are fenestrated in the DRG, and the blood-nerve barrier is looser than normally. On the contrary, in nerve trunks, capillaries are not fenestrated, and endothelial cells are united by tight junctions resulting in a true blood-nerve barrier with a restricted permeability. SNs represent the most frequent manifestation of paraneoplastic neurological syndromes, but may also be caused by immunologic diseases as Sjögren syndrome, by HIV, EBV, VZV, HTLV-1 virus infection and by toxic agents as pyridoxine, cisplatin, carboplatin, oxaliplatin. The typical clinical manifestation is an asymmetric, non-length-dependent sensory impairment with subacute onset. Sensory ataxic or painful neuropathy may be predominant, depending on the type of neurons involved. Chronic forms also exist and are generally
idiopathic. Paraneoplastic sensory neuronopathy is associated with small-cell lung cancer and less frequently with bronchial carcinoma, breast and ovarian cancer. HL and NHLs may rarely cause paraneoplastic neurological syndromes, mainly cerebellar degeneration and dermatomyositis while sensory neuronopathy is reported in very few cases. Notably, onconeural antibodies which are detected in the majority of cases of paraneoplastic neuropathies associated with small cell lung carcinoma are generally absent in patients with lymphoma.34,35

Length-dependent axonal polyneuropathy. In chronic axonal neuropathies, cell bodies of neurons remain intact, at least in the initial phases of the disease, but the axons are impaired in proportion to their length. Since the longest axons are affected earlier, motor and sensory signs begin symmetrically in distal legs and progress to involve distal regions of upper limbs and eventually proximal regions. Electrophysiological examination shows a reduction of the amplitude of sensory and motor potentials while the conduction time (conduction velocities, distal and F wave latencies) is average or slightly altered.

A major problem in clinical practice is that in a significant proportion of patients with chronic axonal neuropathy no aetiology can be identified, despite extensive investigations. This condition, termed Chronic Idiopathic Axonal Polyneuropathy (CIAP), affects people usually in the sixth-seventh decades of life and accounts for about 30% of neuropathy cases.36 CIAP is characterised by prominent or isolated sensory symptoms with numbness and tingling in the feet, or sensory ataxia, while motor impairment is less severe.59 CIAP has an indolent and usually “benign” course with phases of stabilisation.

Axonal sensory-motor polyneuropathy is a rare manifestation of a paraneoplastic syndrome and the association with lymphoma has been described in isolated cases.34

Axonal polyneuropathy associated with paraproteinemia. Since CIAP and MGUS are highly prevalent in people over 50 years of age, the possibility of a chance association should be considered. Accurate follow-up is recommended in order to detect possible changes in both conditions.

If the polyneuropathy shows a course which appears atypical for CIAP and in particular if motor weakness and atrophy occur in legs and hands, or painful paraesthesias become prominent, the possibility of AL amyloidosis must be considered. Other critical red flags include weight loss, renal involvement, diarrhoea alternated with constipation, postural hypotension, cardiomyopathy. The diagnosis of amyloidosis is straightforward if considered.

Primary systemic AL amyloidosis is a disease characterised by diffuse deposition of amyloid fibrils derived from immunoglobulin light chains which, instead of forming the α-helical configuration, became misfolded and forms a β-pleated sheet. Amyloid deposits are found mainly in the heart, kidney, gastrointestinal tract, and peripheral nervous system. AL amyloidosis may be secondary to Multiple Myeloma in 10% of cases. Twenty per cent of patients with systemic AL amyloidosis present with an axonal sensory-motor and autonomic polyneuropathy.30 The monoclonal protein is usually IgG or IgA, but in a minority of cases, AL amyloidosis is associated with IgM.38-39

Diagnosis is based on the demonstration of amyloid deposits, confirmed by Congo Red staining, in heart, peripheral nerves, rectum, abdominal fat or salivary glands (Figure 5 A-B). Importantly, the presence of an MGUS in patients with systemic amyloidosis does not necessarily imply a diagnosis of primary AL amyloidosis, as hereditary amyloidosis may be identified in about 10% per cent of patients with a presumptive diagnosis of AL amyloidosis.40-41 Late-onset, sporadic, familial amyloid polyneuropathy caused by TTR (transthyretin) gene mutations may be easily misdiagnosed as AL.42 so mutational analysis of TTR should not be overlooked when managing amyloidosis, also considering the new promising therapeutic options.43-45

Conclusions. The area of intersection of neurological and haematological fields is of particular complexity and raises several problems in clinical practice, mainly when the peripheral nervous system is involved, as happens with a certain frequency in some lymphoproliferative diseases.

A proper cultural approach is needed as in most conditions the diagnosis is simple if considered. The personal crosstalk between
neurologists and haematologists remains a fundamental tool for a proper diagnostic process which may lead to successful treatments in most cases.

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