Infectious Neuropathies

19

Sergio Ferrari, Sara Mariotto, Tiziana Cavallaro, Gianmaria Fabrizi, and Salvatore Monaco

19.1 Introduction

Infectious agents are common causes of *neuropathy* in endemic areas, while they are rarely observed in other regions. However, in the current era characterized by quick and easy migration processes, the knowledge of the main infectious neuropathies is required. In the course of infectious diseases, the peripheral nervous system (PNS) may be affected by direct infiltration of peripheral nerves, indirect damage induced by immune and inflammatory responses, or therapy-induced toxicity.

19.2 Hepatitis C Virus (HCV)-Related Neuropathies

PNS is frequently affected in the course of *HCV infection*. Peripheral nerve involvement can be due to a direct viral damage, the presence of *cryoglobulinemia* (CG), and the multiple comorbidities that affect HCV-infected patients. CG is the most frequent extrahepatic manifestation of HCV infection, detectable in up to 50 % of patients, and is the most important risk factor for the peripheral nerve involvement. Cryoglobulins (CGs) are cold-precipitable immunoglobulins, which deposit in small- and medium-sized vessels and cause ischemic damages, lymphocytic microvasculitis, and/or necrotizing arteritis, with polymorphonuclear cell infiltration. Three types of CG are recognized: type I consists of monoclonal immunoglobulin (Ig), and type II is a mixture of monoclonal and polyclonal Ig, while type III is composed of polyclonal Ig. "Mixed cryoglobulinemia" (MC) is defined by either type II or III CG and in up to 95 % of cases is associated with chronic HCV/HIV

S. Ferrari, MD (✉) • S. Mariotto, MD • T. Cavallaro, MD • G. Fabrizi, MD • S. Monaco, MD
Section of Neurology, Departments of Neurological, Biomedical and Movement Sciences, University of Verona, Italy. Policlinico GB Rossi, Piazzale L.A. Scuro, 10, Verona 37134, Italy
e-mail: sergio.ferrari@ospedaleuniverona.it; sara.mariotto@gmail.com; tiziana.cavallaro@ospedaleuniverona.it; gianmaria.fabrizi@univr.it; salvatore.monaco@univr.it

C. Angelini (ed.), *Acquired Neuromuscular Disorders: Pathogenesis, Diagnosis and Treatment*, DOI 10.1007/978-3-319-29514-5_19

infection. About 17–60 % of patients with CG develop peripheral neuropathy (PN), often at disease onset [1, 2]. Neuropathy is rarely seen in patients with HCV infection and type I CG. In our experience axonal polyneuropathy is the main presented form, pathologically characterized by perivascular infiltrates, endoneurial purpura, and microangiopathy, overall suggesting an ischemic pathogenesis linked to endoneurial microcirculation obstruction [3]. Conversely, in patients with HCV-associated MC, the PNS involvement is frequently observed and is more severe when a higher cryocrit is present. *Pathological features* are consistent with axonal degeneration, loss of myelinated fibers (Fig. 19.1) and small-vessel vasculitis or necrotizing arteritis of medium-sized vessel with consequent ischemic nerve damage [4]. In the less frequently reported cases of HCV-associated neuropathy without CG, the vascular and perivascular inflammation can be due to a direct HCV damage or HCV-induced autoimmune mechanisms. Actually, HCV active replication has never been demonstrated in the PNS, and the observation of HCV-RNA in epineurial cells, in close relationship with mononuclear inflammation, is in favor of an immune-mediated pathogenesis [5, 6]. According to previously reported studies, the most frequent form of neuropathy observed in HCV-infected patients is a length-dependent symmetric sensory or sensorimotor axonal polyneuropathy, clinically characterized by distal sensory loss and weakness. More recent reports describe sensory neuropathy as the most prevalent neuropathic form of HCV infection [7].

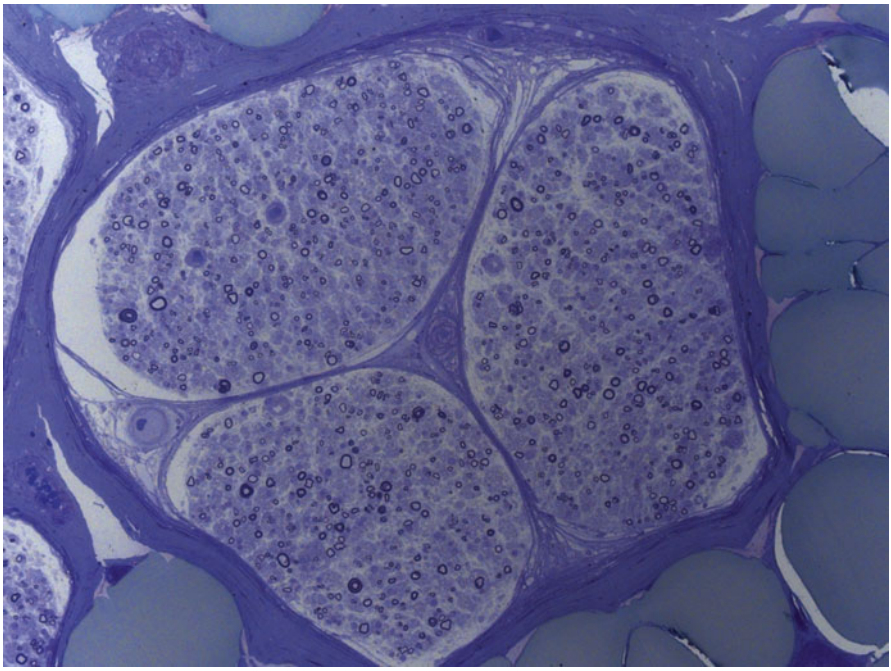

Fig. 19.1 Sural nerve fascicles showing asymmetric loss of myelinated fibers in a patient with cryoglobulinemic neuropathy and HCV infection (toluidine blue, original magnification ×50)

Sensory neuropathy can be distinguished in symmetric or asymmetric forms, the latter variants including *large-fiber sensory neuropathy* (LFSN) and *small-fiber sensory neuropathy* (SFSN). LFSN usually manifests with sensory loss, paresthesias, numbness, and cramps, while SFSN is characterized by burning feet, tingling, restless leg syndrome, and sometimes a non-length-dependent pattern suggestive of ganglionopathy [8]. In some cases the damage of both small and large fibers may coexist. *Mononeuropathies* and *mononeuropathy multiplex* (MM), characterized by stocking-glove asymmetric neuropathy or overlapping forms have also been reported. In a prospective clinical, neurophysiological, and skin biopsy study recently reported, Biasiotta and colleagues described 47 subjects with PN and 29 with neuropathic pain in a series of 69 patients with HCV-related CG. The authors describe a prevalence of predominantly sensory distal polyneuropathy and report the relevance of nociceptive pathway damages. They also note an association between neuropathy, age, and HCV infection rather than CG [9]. Unusual forms of HCV-associated neuropathy are those of pure *motor polyneuropathies* [10] and *autonomic neuropathies* [11]. Cranial nerve damages have been anecdotally described as an involvement of the abducens, facial, and motor trigeminal nerves. Intriguingly, the spectrum of PN in the course of HCV infection is not limited to axonal forms, but encompasses a number of demyelinating conditions. The association between *Guillain-Barré syndrome* (GBS) and non-A, non-B hepatitis has been described before the discovery of HCV [12] and, more recently, in patients with chronic HCV infection [13]. Acute inflammatory demyelinating polyneuropathy (AIDP), the demyelinating variant of GBS, has been described in a single case with subclinical HCV infection during the pre-convalescent phase [14]. As for chronic forms of neuropathy, few reports describe an association between HCV infection and *chronic inflammatory demyelinating polyneuropathy* (CIDP) [15]. This form can be also seen as an uncommon side effect in patients treated with *IFNα* which could have immunomodulating effects as a reduction of proinflammatory cytokines and, at the same time, could play a major role in triggering immune-mediated mechanisms [16]. A single case of Lewis-Sumner syndrome, an asymmetric form of CIDP, has been described in the course of HCV infection; these patients improved after high-dose intravenous immunoglobulins (IVIG) and methylprednisolone treatment, relapsed after administration of INFα and ribavirin, and finally recovered after the discontinuation of INF coupled with e.v. methylprednisolone [17]. We recently reported an intriguing association between HCV infection and neuropathy with *anti-MAG* (myelin-associated glycoprotein) antibodies, which is usually reported in association with hematological disorders or, more rarely, with primary amyloidosis, cryoglobulinemic vasculitis, Charcot-Marie-Tooth type 1, or amyotrophic lateral sclerosis and HCV infection [18]. This neuropathy is usually characterized by a distal demyelinating disorder that involves large fibers and manifests as sensory ataxia, mild motor involvement, and hand intention tremor. Significant weakness and small-fiber neuropathy are encountered in few atypical cases. We studied a cohort of 59 consecutive patients with neuropathy and chronic HCV infection who had undergone nerve biopsy. We detected CG in 39 patients (18 cases with axonal polyneuropathy, 11 with overlapping MM, and 10 with MM). In 14 patients,

CG has not been detected, but they resulted positive for rheumatoid factor (RF); 10 of them had an axonal polyneuropathy, 1 an overlapping form, and 3 cases an MM. Surprisingly, in 3 of the 6 patients without CG or RF, IgM monoclonal gammopathy with anti-MAG activity was detected. Nerve biopsy showed loss of fiber and ongoing segmental demyelination with onion bulb formation, mild perivascular infiltrates of lymphocytes and monocytes at the epineurial level in one case, and endoneurial edema and microangiopathy in the other one. IgM and complement deposition has been observed on myelin sheaths in all three cases. The high association between anti-MAG neuropathy and HCV infection could be the result of the production of monoclonal and polyclonal immunoglobulins triggered by HCV-induced B-cell expansion. These data are supported by the recent description of a significant association between anti-GM1 gangliosides and anti-sulfatide antibodies and HCV-related PN. As for the treatment of HCV-related neuropathy, *antiviral therapy* is the first therapeutic choice, but studies with rituximab have also been performed. According to a recent Cochrane review, high-quality studies are lacking, and there are insufficient data to make an evidence-based decision [19].

19.3 Human Immunodeficiency Virus (HIV)-Related Neuropathies

PN is considered the most common neurological complication of *HIV infection*, even after the introduction of *combination antiretroviral therapy* (cART). The increase in life expectancy is linked to a prolonged exposure to neurotoxic antiretroviral therapies and their potential complications. Various types of PN have been reported in association with HIV infection, including distal symmetric polyneuropathy, *toxic neuropathy* induced by antiretroviral drugs, demyelinating neuropathies, mononeuropathy multiplex, diffuse infiltrative lymphocytosis syndrome (DILS), and progressive polyradiculopathy [20]. The diagnosis and appropriate treatment of PN in the course of HIV infection represent a challenge also for expert neurologist and for consultant in infectious diseases. The difficulty lies in the overlap between the different forms of PN and the frequently unusual clinical presentations.

19.3.1 Distal Symmetric Polyneuropathy (DSP)

DSP is the most common form of neuropathy in the course of HIV infection. Its prevalence in cART era ranges from 20 to 60 % [21]. According to some studies, the most important risk factors for DSP are age, height, and stavudine exposure, while it seems not associated with decreased *CD4* count or increased viral load [22]. On the contrary, other studies identify the lower CD4 nadir reached during HIV infection as the leading risk factor for DSP [23]. The clinical presentation of DSP is characterized by a distal symmetric predominantly *sensory neuropathy* with painful feet and hyperpathia. Neurological examination reveals decreased or absent ankle

tendon reflexes with impaired pinprick and vibration sensations. Distal muscle weakness is usually mild or absent. According to recent studies, *autonomic dysfunction* including orthostatic hypotension, gastroparesis, diarrhea, constipation, urinary incontinence, sexual dysfunction, sweating, and pupillary abnormalities is commonly associated with DSP in HIV subjects [24]. Electrophysiological studies may be useful to confirm a length-dependent axonal polyneuropathy with small or absent sural sensory nerve action potentials. It also allows to distinguish between DSP and PNS demyelinating conditions as CIDP. Total Neuropathy Score (TNS) [25] and Brief Peripheral Neuropathy Screen (BPNS) [22] are the main clinical tools used to assess DSP. TNS has been validated in diabetic neuropathy and analyzes both the grading of sensory, motor, and autonomic symptoms and signs and nerve conduction studies. BPNS is a quick and easy clinical score that includes questions about neuropathic symptoms, examination of vibration at the great toe, and ankle reflexes. The *neuropathological features* of DSP at sural nerve biopsy are usually characterized by loss of myelinated and unmyelinated fibers with variable extent of axonal degeneration and macrophage infiltration. Demyelinating features are more rarely observed and are considered secondary to axonal damage. The direct detection of HIV in nerve fascicles has been rarely observed indicating the variable nature of this form [26]. Autoptic series show that fiber loss and axonal degeneration prevail in the distal regions of peripheral nerves rather than in the proximal ones, confirming the length-dependent nature of this polyneuropathy. Distal *skin biopsies* may show a loss of the epidermal nerve fiber that correlates with neuropathic pain scores [27]. The differential diagnosis of DSP always requires the exclusion of other causes of neuropathy such as alcoholism, diabetes mellitus, vitamin B12 deficiency, monoclonal gammopathy, and uremia. Moreover, in the course of *antiretroviral therapy*, the patient may present with a clinical picture similar to DSP. Finally, the introduction of *cART* can induce per se DSP through the toxicity due to antiretroviral reverse transcriptase inhibitors as didanosine, zalcitabine, and stavudine. DSP associated with antiretroviral therapy has usually a faster onset and a more rapid course compared to HIV-DSP. Actually, the exact cause of axonal damage of small myelinated and unmyelinated nerve fibers in patients with HIV-DSP has not been established. A direct neuronal damage induced by HIV infection is unlikely since neurons do not express CD4 receptor that is required for the entry of the virus into the cells. Soluble HIV viral gene products as gp120 and viral protein R (*Vpr*) were used in experimental models in order to assay neurotoxicity. Gp120 is a coat glycoprotein that mediates the binding and transmission of HIV into cells by interaction with CD4 receptor via C-C chemokine receptor type 5 (CCR5). Vpr is a protein with cytotoxic effects that modulates HIV infectivity and increases oxidative stress. Recent in vitro studies suggest a primary role of *macrophage activation* in the induction of sensory neuron damage due to an indirect action of HIV protein gp120 that stimulates macrophages by CCR5 binding. These data are confirmed by the inhibitory effect of gp120-induced tumor necrosis factor gene expression, obtained with maraviroc, a CCR5 antagonist [28]. Since pain is the major symptom in patients with HIV-DSP, pain management is the main target of current treatment. Off-label *treatments* include the use of different classes of drugs: nonsteroidal inflammatory drugs, topical agents

(lidocaine and capsaicin), tricyclic antidepressants (amitriptyline, duloxetine), anticonvulsant agents (gabapentin, pregabalin, lamotrigine), and opioids (oxycodone, morphine, and fentanyl patch). In clinical practice a combination of different drugs with distinct specific mechanisms of action is frequently needed to achieve relief from neuropathic pain. A recent meta-analysis of seven randomized double-blind studies demonstrated the efficacy of high-dose (8 %) *capsaicin patch* in single application: 41 % of patients with HIV-DSP obtained 30 % relief of neuropathic pain, and 7 % had complete analgesia starting within few days after treatment and lasting after an average of 5 months [29]. *Pregabalin* resulted to be effective in a small placebo-controlled trial but failed to show relief of pain according to a randomized double-blind placebo-controlled trial [30]. As shown in a placebo-controlled trial performed by Abrams and colleagues, smoked *cannabis* produced a significant reduction of pain in DSP [31]. Among the disease-modifying drugs, human recombinant nerve growth factor (hrNGF) seems to be more effective than placebo; however in a more recent open-label study, hrNGF did not cause an improvement in the severity of neuropathy [32]. Given the lack of concordance of the different studies, this drug has been withdrawn in patients with HIV-associated neuropathy. According to literature, other disease-modifying drugs, as acetyl-L-carnitine, prosaptide, and peptide T, did not show significant efficacy in DSP.

19.3.2 Demyelinating Neuropathy

Demyelinating neuropathies as *AIDP* and *CIDP* have been reported in acute and chronic forms of HIV infection. Due to the lack of large series and controlled studies, the incidence of AIDP and CIDP in the course of HIV infection is unknown. AIDP frequently occurs in the early stage of HIV infection, sometimes preceding the diagnosis of AIDS, when the immunosuppression is less pronounced. Even if CIDP may occur in early HIV infection, it frequently manifests in more advanced stages of the disease. Cases of *Miller Fisher syndrome* associated with HIV seroconversion and a patient who developed Miller Fisher/AIDP overlap in the presence of serum anti-GQ1b antibodies have been also reported [33]. In these patients, clinical features, disease course, and neurophysiological findings appear similar to that of HIV-negative patients. In accordance, in AIDP cases the nadir of neurological signs is reached within 4 weeks, whereas in CIDP the neurological impairment progresses for more than 8 weeks and may be relapsing and remitting.

Neurophysiological analysis shows slow conduction velocities, increased distal motor and F-wave latencies, and partial conduction blocks, characteristics of demyelinating neuropathies. At *cerebrospinal fluid* (CSF) examination, high protein content is frequently observed, but, at variance with non-HIV inflammatory polyneuropathies, a mild lymphocytic pleocytosis is frequently found. Brannagan et al. reviewed ten cases with HIV-AIDP and observed a CSF with blood cell count of less than 10/mm^3 in seven cases, concluding that the absence of pleocytosis in AIDP patients does not exclude HIV infection [34]. Like in non-HIV patients, *pathological examination* of the peripheral nerve in CIDP cases shows demyelination and

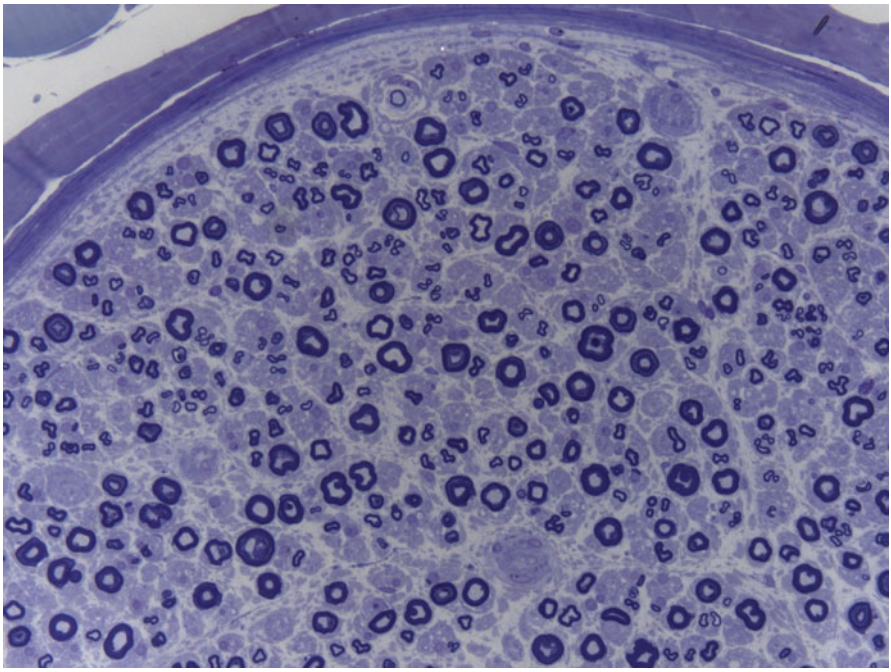

Fig. 19.2 Sural nerve biopsy in a patient with HIV-associated CIDP. Some onion bulb formations are evident at toluidine blue stain (original magnification ×100)

onion bulb formation (Fig. 19.2), infiltration of mononuclear cell of nerve fascicles, and endoneurial edema. *Treatment* of AIDP includes IVIG and *plasmapheresis*. Clinical signs of CIDP may improve with *steroids*, IVIG, or plasmapheresis, but IVIG are considered the treatment with fewer complications. Finally, some data suggest that patients with clinical picture of AIDP and CD4 count less than 50 cell/μL should be treated presumptively for *cytomegalovirus (CMV)* infection, but some cases reported by Brannagan et al. do not support this recommendation [34].

19.3.3 Mononeuropathy Multiplex (MM)

MM, characterized by asymmetric sensorimotor involvement of single nerves, is a rare complication occurring in early and late stages of HIV infection. The initial asymmetric involvement of peripheral nerves may progress, during the evolution of the disease, in a clinical picture simulating a distal symmetric neuropathy. If occurring at the onset of HIV infection, MM is the result of self-limited immune-mediated *vasculitis*. Vasculitis is a rare event in HIV infection and occurs only in 0.3–1.0 % of patients with AIDS either as an isolated process involving peripheral nerves or as a manifestation of a systemic disease. In post-cART era, vasculitis of PNS may present as distal symmetric polyneuropathy [35]. The *pathological features* of nerve

biopsy show focal loss of fibers, variable axonal degenerations, and perivascular epineurial inflammatory cell infiltration with fibrinoid necrosis. In the later stages of the infection, when fewer than 50 CD4 cells/μL are present, MM can be associated with *CMV* infection or, more rarely, with *varicella zoster*, *HCV*, or *lymphomatous infiltration* of nerve. CMV is an opportunistic agent that affects HIV-infected patients with fewer than 50 CD4 cells/μL. Clinical picture of CMV infection includes a multiorgan involvement with retinitis, pneumonia, gastrointestinal system involvement, epididymitis, pancreatitis, cervicitis, hepatitis, encephalitis, and MM or polyradiculopathy. Nerve biopsy shows lymphomonocyte cell infiltration of nerve fascicles and the presence of cytomegalic cells filled with CMV particles.

19.3.4 Progressive Lumbosacral Polyradiculopathy (PLP)

Progressive lumbosacral polyradiculopathy (PLP) starting with back and leg pain and evolving into paraparesis with sensory and sphincter dysfunction has been frequently observed in HIV-infected subjects pre-cART era [36]. PLP usually occurs in the late stages of HIV infection in concomitance with low count of CD4 lymphocytes. Usually PLP is related to *CMV* infection, but it can be caused by different conditions including mycobacterial, syphilis, cryptococcus, herpes simplex infection, and lymphomatous infiltration [20]. The diagnosis includes *CSF* examination with polymerase chain reaction amplification to detect viral agents, mycobacterial and cryptococcus antigen testing. In our experience cytofluorimetric analysis of CSF is helpful and should be recommended in the suspect of lymphomatous meningoradiculitis. *Electrophysiological study* shows denervation in paraspinal muscles followed by denervation potential in the legs in the course of disease progression. Contrast-enhanced MRI can reveal enhancement of nerve roots [37]. *Treatment* for CMV infection should be started early in clinical suspicion of PLP and include ganciclovir, valganciclovir, foscarnet, cidofovir, and fomivirsen.

19.3.5 Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

Diffuse infiltrative lymphocytosis syndrome (*DILS*) is a rare multisystem syndrome described in HIV-infected patients and characterized by persistent blood polyclonal CD8 T-cell lymphocytosis and organ infiltration [38]. This syndrome may affect the salivary glands, lymph nodes, lungs, liver, kidneys, digestive tract, and PNS. *Polyneuropathy*, *aseptic meningitis*, and *facial nerve palsy* are the neurological abnormalities most frequently reported. DILS neuropathy usually presents as a painful and symmetric neuropathy. Electrophysiological examination shows signs of axonal neuropathy. Nerve biopsy is characterized by angiocentric CD8 T-cell infiltration without vessel wall necrosis and abundant expression of HIV p24 protein in macrophages [39]. In these patients, chronic HCV infection and *immune reconstitution inflammatory syndrome* (*IRIS*) are the principal differential diagnosis

to be considered. *Treatment* of DILS consists mainly of *cART*, but *steroids* may also be added when organ infiltration persists.

19.3.6 IRIS and Peripheral Nervous System

IRIS is an aberrant immune response due to the restoration of the immune system that occurs in the cART era. IRIS is defined as an unmasking or paradoxical worsening of a pre-existing infection in the presence of rapid decrease of viral load and recovery of *T-cell* immunity. In the course of IRIS, peripheral nerve involvement can occur in subjects previously affected by *Mycobacterium leprae* infection, inflammatory demyelinating radiculopathy, and cryptococcal radiculoplexopathy. IRIS-associated *AIDP* has also been described. *Treatment* is controversial and includes the use of *anti-inflammatory*, *corticosteroids*, *IVIG*, and *plasmapheresis*.

19.4 Leprosy

Mycobacterium leprae (*ML*) is an obligatory intracellular agent with tropism for macrophages and Schwann cell, which infects the skin and peripheral nerves resulting in chronic inflammation and neuropathy. The prevalence of leprosy is declining but, according to WHO data, it remains a common cause of neuropathy in 17 highly endemic countries. About 81 % of all new cases occur in three countries: Brazil, India, and Indonesia [40]; however, it is a worldwide problem since new cases have also been reported in travelers from endemic areas. Transmission of ML occurs via nasal mucosa and is followed by hematogenous spread. According to the classification of Ridley and Jopling, leprosy is subdivided into different subtypes: tuberculoid (T), borderline tuberculoid (BT), borderline (B), borderline lepromatous (BL), and lepromatous (L). A further form was later defined as indeterminate (I) [41]. The classification is based on the balance between bacterial particles and *immune reaction*. Patients with L form are anergic to the bacillus and examined tissues are rich in mycobacteria. On the other hand, in T form a strong immune reaction with paucity of mycobacteria particles is usually observed. In these latter cases, the immune response is able to limit bacterial growth, but skin lesions and nerve damage are frequently observed. Clinical condition correlates with the entity of activation of cell-mediated immune response to ML. To simplify, the WHO recommended a dichotomic classification into *paucibacillary* (PB) and *multibacillary* (MB) category. PB group includes I, T, BT, B, and BL forms, whereas MB includes BT, B, BL, and L subtypes. The two classifications are considered complementary, but the Ridley and Jopling one fits better with patients' clinical condition and prognosis. The suspect of ML infection is established when *multifocal neuropathy* is associated with hypopigmented, hypoesthetic, or reddish *skin lesions*, even if some patients may present signs of neuropathy in the absence of the characteristic skin lesions. Indeed, 3–10 % of patients present the *pure neuritic form* (PNL) that manifests as PN without any skin lesion. At onset *sensory symptoms* are the most common ones; small fibers

are affected early, whereas large fibers are involved later. Clinical characteristics of PN in the course of leprosy include mononeuritis, MM, and polyneuropathy. *Mononeuritis* is the most common presentation and usually affects nerves of the upper limbs as ulnar, median, posterior auricular, and superficial radial. Lower limbs can also be affected with the involvement of common peroneal, superficial peroneal, and posterior tibial. Rarely, also cranial nerves, primarily facial and trigeminal ones, are damaged [42]. Typically, in the course of ML infection nerves are enlarged and painful on palpation, and electrophysiological examination shows axonal damage. The use of imaging techniques as *nerve sonography* and MRI may be useful in the diagnosis. Analyzing high-resolution sonography, Visser and colleagues showed that the epineurium of the ulnar nerve is often strikingly thickened in these patients, especially in those with ulnar involvement [43]. Symmetric *polyneuropathy* is rarely reported in leprosy, while regional *autonomic* dysfunctions are frequently observed. Although the diagnosis of leprosy is mainly clinical, peripheral *nerve biopsy* can be helpful especially in atypical cases or in those patients with pure neuritic forms. The definite diagnosis is based on skin smear or biopsy demonstrating granulomatous inflammation or foamy macrophages with acid-fast bacilli (Fig. 19.3).

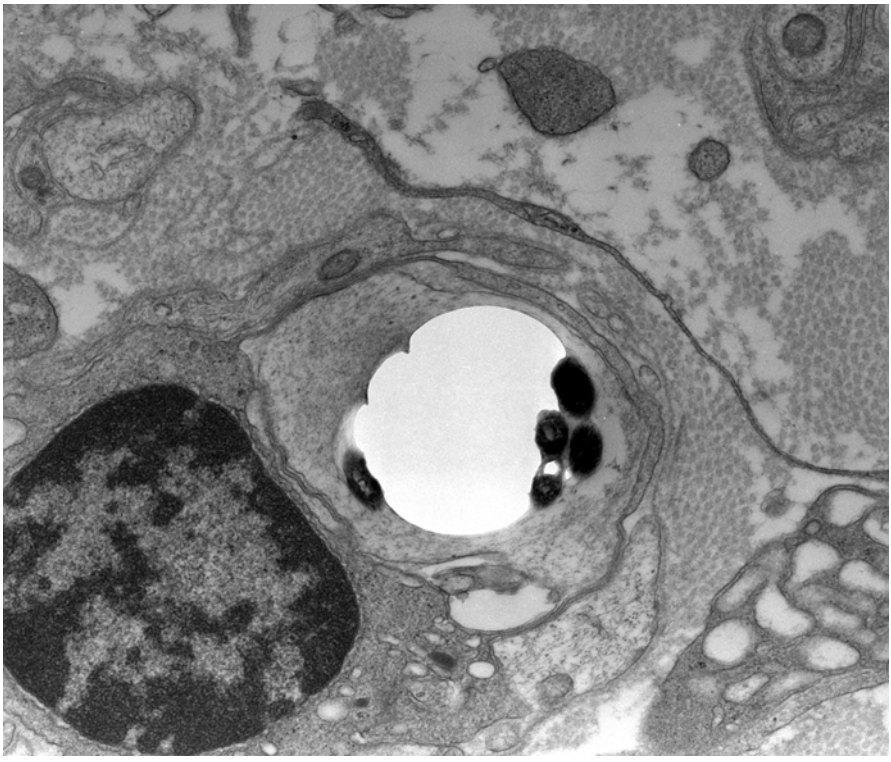

Fig. 19.3 Electron micrograph of sural nerve biopsy in pure neuritic form of leprosy showing a Schwann cell containing *Mycobacterium leprae* organisms (original magnification ×12,000)

19.5 *Borrelia burgdorferi*-Related Neuropathies

The tick-borne spirochete *Borrelia burgdorferi* is responsible of a vector-borne disease, known as Lyme borreliosis, transmitted by the *Ixodes* complex. This *zoonosis*, more diffuse in temperate regions and rural areas, causes a multisystem disease that affects humans as incidental hosts. The skin and the nervous system are the main involved organs. Nervous system involvement can occur through the hematogenous or transneural spread along peripheral nerves, few weeks after a tick bite or in the late and chronic disease [44]. Subacute painful *meningoradiculitis*, which consists of painful migrant burning radiculitis, peripheral motor deficit, and *CSF* inflammation, alone or in combination, is the prevalent manifestation of early neuroborreliosis. Motor damage consists frequently of bilateral and asymmetric peripheral facial nerve palsy. More rarely, III or VI cranial nerve involvement is present, sometimes only observed at MRI [45]. Isolated or concomitant limb paresis often bilateral, asymmetric, and predominantly proximal can occur. These symptoms are consistent with root or plexus lesions and, more rarely, with a distal *mononeuropathy.* Distal *nerve pathology* has been demonstrated in the course of Lyme borreliosis and confirmed by sural nerve findings of small lymphocytic infiltration around endoneurial vessels, perineural fibrosis, and wallerian degeneration [46]. However, nerve involvement in the absence of radicular symptoms or CSF inflammation has been rarely described [44]. *Brachial neuritis*, *Guillain-Barré*, and *CIDP*-like syndrome have also been reported [47, 48]. On the other hand, patients with chronic dermatoborreliosis can develop a distal mainly *sensory neuropathy* in the absence of CSF inflammation. It consists of a mild distal axonal neuropathy probably due to a cutaneous neuritis. Sural *nerve biopsy* show lymphocytic perivasculitis and wallerian degeneration. On the basis of these data, the opportunity to perform the screening for *Borrelia* in patients with PN of unknown etiology, in the absence of the above described symptoms, is still very controversial. Since there is a high percentage of positive *anti-Borrelia IgG* blood test in the general population, the association between polyneuropathy and this infectious agent must be demonstrated by the concomitance of specific markers of active *Lyme borreliosis* as *CFS* pleocytosis, increased protein concentration, intrathecal IgM and IgG synthesis, and PCR positivity in CSF or blood. The data previously reported are mainly referred to European experience, since in American studies the involvement of peripheral nerve has been rarely reported. In early neuroborreliosis, radiculopathy, cranial neuropathy, and MM have been described, while late symptoms as a distal polyneuropathy with mild diffuse stocking-glove process are rarely reported [44]. *Biopsy of sural nerve* shows a prevalent axonal damage with perivascular infiltration [49, 50]. The acute neurological involvement in the course of borreliosis has usually a benign course, but *antibiotics* as penicillin, cephalosporin, ceftriaxone, or oral doxycycline accelerate clinical recovery and prevent the development of new neurological deficit. Also chronic symptoms frequently ameliorate with antibiotic *treatment.* Of note, some patients report long-lasting and relapsing, recurrent, and persistent nonspecific symptoms with negative active *Borrelia* serology. Patients do not improve after antibiotic treatment leading to the idea that the pathogenesis of this condition, known as

"chronic arthropod-borne neuropathy," could be linked to toxins and immunological, autoimmune, or psychological illness rather than the infectious agent [44].

Key Points

- Neuropathy remains the most common neurological complication of HIV infection.
- Different forms of neuropathy may occur during HCV chronic infection, frequently associated with cryoglobulinemia.
- Lepromatous neuropathy may present in pure neuritic form, requiring diagnostic nerve biopsy.
- The association of neuropathy with anti-*Borrelia* IgG antibodies in serum must be confirmed with blood and CSF demonstration of infectious activity.

References

1. Sansonno D, Dammacco F (2005) Hepatitis C virus, cryoglobulinaemia, and vasculitis: immune complex relations. Lancet Infect Dis 5:227–236
2. Robbins SJ, Shaheen AAM, Myers RP (2007) Immunologic complications of the hepatitis C virus. Curr Hepat Rep 6:138–144
3. Bonetti B, Invernizzi F, Rizzuto N et al (1997) T-cell-mediated epineurial vasculitis and humoral-mediated microangiopathy in cryoglobulinemic neuropathy. J Neuroimmunol 73:145–154
4. Vital C, Vital A, Canron MH et al (2006) Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16- year retrospective study of 202 cases. J Peripher Nerv Syst 11:20–29
5. Bonetti B, Scardoni M, Rizzuto N et al (1999) Hepatitis C virus infection of peripheral nerves in type II cryoglobulinaemia. Virchows Arch 434:533–535
6. De Martino L, Sampaolo S, Tucci C et al (2003) Viral RNA in nerve tissues of patients with hepatitis C infection and peripheral neuropathy. Muscle Nerve 27:102–104
7. Yoon MS, Obermann M, Dockweiler C et al (2011) Sensory neuropathy in patients with cryoglobulin negative hepatitis- C infection. J Neurol 258:80–88
8. Bant A, Hurowitz B, Hassan N et al (2007) Complex regional pain syndrome (reflex sympathetic dystrophy) in a patient with essential mixed cryoglobulinemia and chronic hepatitis C. J Pak Med Assoc 57:96–98
9. Biasiotta A, Casato M, La Cesa S et al (2014) Clinical, neurophysiological, and skin biopsy findings in peripheral neuropathy associated with hepatitis C virus-related cryoglobulinemia. J Neurol 261:725–731
10. Costa J, Resende C, De Carvalho M (2003) Motor-axonal polyneuropathy associated with hepatitis C virus. Eur J Neurol 10:183–185
11. Ammendola A, Sampaolo S, Migliaresi S et al (2007) Autonomic neuropathy in mixed cryoglobulinemia. J Neurol 254:215–219
12. Tabor E (1987) Guillain-Barré syndrome and other neurologic syndromes in hepatitis A, B, and non-A, non-B. J Med Virol 21:207–216

13. Khiani V, Kelly T, Shibli A et al (2008) Acute inflammatory demyelinating polyneuropathy associated with pegylated interferon alpha 2a therapy for chronic hepatitis C virus infection. World J Gastroenterol 14:318–321
14. De Klippel N, Hautekeete ML, De Keyser J et al (1993) Guillain-Barré syndrome as the presenting manifestation of hepatitis C infection. Neurology 43:2143
15. Corcia P, Barbereau D, Guennoc AM et al (2004) Improvement of a CIDP associated with hepatitis C virus infection using antiviral therapy. Neurology 63:179–180
16. Hirotani M, Nakano H, Ura S et al (2009) Chronic inflammatory demyelinating polyneuropathy after treatment with interferon-alpha. Intern Med 48:373–375
17. Caporale CM, Capasso M, Ragno M et al (2006) Lewis-Sumner syndrome in hepatitis C virus infection: a possible pathogenetic association with therapeutic problems. Muscle Nerve 34:116–121
18. Mariotto S, Ferrari S, Monaco S (2014) HCV-related central and peripheral nervous system demyelinating disorders. Inflamm Allergy Drug Targets 13:299–304
19. Benstead TJ, Chalk CH, Parks NE (2014) Treatment for cryoglobulinemic and non-cryoglobulinemic peripheral neuropathy associated with hepatitis C virus infection. Cochrane Database Syst Rev Dec 12:CD010404
20. Ferrari S, Vento S, Monaco S et al (2006) Human immunodeficiency virus-associated peripheral neuropathies. Mayo Clin Proc 2:213–219
21. Schütz SG, Robinson-Papp J (2013) HIV-related neuropathy: current perspectives. HIV AIDS (Auckl) 5:243–251
22. Cherry CL, Affandi JS, Imran D et al (2009) Age and height predict neuropathy risk in patients with HIV prescribed stavudine. Neurology 73:315–320
23. Ellis RJ, Rosario D, Clifford DB et al, and CHARTER Study Group (2010) Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER study. Arch Neurol 67:552–558
24. Robinson-Papp J, Sharma S, Simpson DM et al (2013) Autonomic dysfunction is common in HIV and associated with distal symmetric polyneuropathy. J Neurovirol 19:172–180
25. Cornblath DR, McArthur JC (1988) Predominantly sensory neuropathy in patients with AIDS and AIDS-related complex. Neurology 38:794–796
26. Rizzuto N, Cavallaro T, Monaco S et al (1995) Role of HIV in the pathogenesis of distal symmetrical peripheral neuropathy. Acta Neuropathol 90:244–250
27. Polydefkis M, Yiannoutsos CT, Cohen BA et al (2002) Reduced intraepidermal nerve fiber density in HIV-associated sensory neuropathy. Neurology 58:115–119
28. Moss PJ, Huang W, Dawes J et al (2015) Macrophage-sensory neuronal interaction in HIV-1 gp120-induced neurotoxicity. Br J Anaesth 114:499–508
29. Mou J, Paillard F, Turnbull B et al (2013) Efficacy of Qutenza® (capsaicin) 8% patch for neuropathic pain: a meta-analysis of the Qutenza Clinical Trials Database. Pain 154:1632–1639
30. Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, Whalen E, Emir B, Scott GN, Freeman R, 1066 HIV Neuropathy Study Group (2010) Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology 74(5):413–420
31. Abrams DI, Jay CA, Shade SB et al (2007) Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 68:515–552
32. Schifitto G, Yiannoutsos C, Simpson DM et al, AIDS Clinical Trials Group Team 291 (2001) Long-term treatment with recombinant nerve growth factor for HIV-associated sensory neuropathy. Neurology 57:1313–1316
33. Hiraga A, Kuwabara S, Nakamura A et al (2007) Fisher/Guillain-Barré overlap syndrome in advanced AIDS. J Neurol Sci 258:148–150
34. Brannagan TH 3rd, Zhou Y (2003) HIV-associated Guillain-Barré syndrome. J Neurol Sci 208:39–42

35. Ferrari S, Lanzafame M, Faggian F et al (2004) Painful neuropathy vasculitis in 2 patients with long-standing human immunodeficiency virus-1 infection. Scand J Infect Dis 36:392–393
36. Miller RF, Fox JD, Thomas P et al (1996) Acute lumbosacral polyradiculopathy due to cytomegalovirus in advanced HIV disease: CSF findings in 17 patients. J Neurol Neurosurg Psychiatry 61:456–460
37. Kameda K, Shirano M, Hadano Y et al (2015) Cytomegalovirus polyradiculopathy in three Japanese patients with AIDS. Intern Med 54:513–518
38. Ghrenassia E, Martis N, Boyer J et al (2015) The diffuse infiltrative lymphocytosis syndrome (DILS). A comprehensive review. J Autoimmun 59:19–25
39. Moulignier A, Authier FJ, Baudrimont M et al (1997) Peripheral neuropathy in human immunodeficiency virus-infected patients with the diffuse infiltrative lymphocytosis syndrome. Ann Neurol 41:438–445
40. WHO (2014) Global leprosy update, 2013; reducing disease burden. Wkly Epidemiol Rec 89:389–400
41. Ridley DS, Jopling WH (1966) Classification of leprosy according to immunity. A five group system. Int J Lepr Other Mycobact Dis 34:255–273
42. de Freitas MR, Nascimento OJ, Quaglino EA et al (2003) Small-fiber polyneuropathy in leprosy without skin changes: study of 17 cases. Arq Neuropsiquiatr 61:542–546
43. Visser LH, Jain S, Lokesh B et al (2012) Morphological changes of the epineurium in leprosy: a new finding detected by high-resolution sonography. Muscle Nerve 46:38–41
44. Dryden MS, Saeed K, Ogborn S et al (2015) Lyme borreliosis in southern United Kingdom and a case for a new syndrome, chronic arthropod-borne neuropathy. Epidemiol Infect 143:561–572
45. van Erp WS, Bakker NA, Aries MJ et al (2011) Opsoclonus and multiple cranial neuropathy as a manifestation of neuroborreliosis. Neurology 77:1013–1014
46. Meier C, Grahmann F, Engelhardt A et al (1989) Peripheral nerve disorders in Lyme-Borreliosis. Nerve biopsy studies from eight cases. Acta Neuropathol 79:271–278
47. Muley SA, Parry GJ (2009) Antibiotic responsive demyelinating neuropathy related to Lyme disease. Neurology 72:1786–1787
48. Halperin JJ, Little BW, Coyle PK et al (1987) Lyme disease: cause of a treatable peripheral neuropathy. Neurology 37:1700–1706
49. Mygland A, Skarpaas T, Ljøstad U (2006) Chronic polyneuropathy and Lyme disease. Eur J Neurol 13:1213–1215
50. Logigian EL, Kaplan RF, Steere AC (1990) Chronic neurologic manifestations of Lyme disease. N Engl J Med 323:1438–1444