Infectious Neuropathies

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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 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 by therapy-induced toxicity.

19.2 Hepatitis C Virus (HCV)-Related Neuropathies

PNS is frequently affected in the course of *HCV infection*. Peripheral nerves 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 neuropathy (PN). Cryoglobulins (CGs) are cold-precipitable immunoglobulins, which deposit in small and medium size vessels and cause ischemic damages, lymphocytic microvasculitis, and/or necrotizing arteritis, with polymorphonuclear cell infiltration. Three types of CG are recognized, type I is a monoclonal immunoglobulin (Ig), type II is a mixture of monoclonal and polyclonal Ig, while type III is composed of polyclonal Ig. "Mixed CG" (MC) is defined by either type II or III CG and in up to 95%

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of cases is associated with chronic HCV/HIV infection. About 17–60% of patients with CG develop peripheral neuropathy, 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 higher cryocrit is present. *Pathological features* are consistent with a small vessel vasculitic or necrotizing arteritis of medium-sized vessel with consequent ischemic nerve damages (Fig. 19.1) [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. HCV active replication has never been demonstrated in the PNS and the observation of nonreplicative HCV-RNA in epineurial cells, in close relationship with mononuclear inflammation, is in favor of an immune-mediated pathogenesis [5, 6]. Russi et al. demonstrated the presence of HCV genomic RNA sequences and HCV-E2 viral antigen in sural nerve biopsies from patients with peripheral neuropathy and chronic HCV infection, with and without cryoglobulinemia. These data further support an immune-mediated mechanism in nerve damage triggered by viral infection [7].

Accordingly to previously reported studies, the most common form of neuropathy observed in HCV-infected patients is a length-dependent symmetrical sensory or sensorimotor axonal polyneuropathy, clinically characterized by distal sensory loss and weakness. Other reports describe sensory neuropathy as the most prevalent neuropathic form of HCV infection [8]. Sensory neuropathy can be distinguished in symmetric or asymmetric forms, the latter variants including *large-fiber sensory neuropathy* (LFSN) and *small-fiber sensory polyneuropathy* (SFSN). LFSN usually manifests with sensory loss, paresthesias, numbness, and cramps while SFSN is characterized by burning feet, tingling, restless leg syndrome and sometimes with a

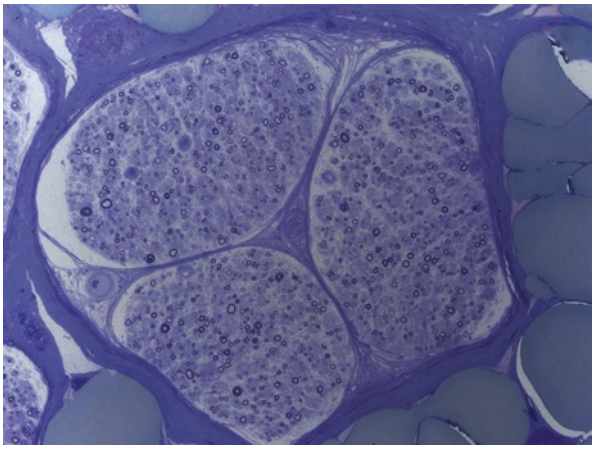

Fig. 19.1 Sural nerve biopsy in a patient with HIV-associated CIDP. Some onion bulb formations are evident in toluidine blue stain (original magnification ×100)

non-length-dependent pattern suggestive of ganglionopathy [9]. 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, 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 [10]. Unusual forms of HCV-associated neuropathy are pure motor polyneuropathies [11] and autonomic neuropathy [12]. Cranial nerves damages have been anecdotally described as an involvement of the abducens, facial, and motor trigeminal nerves. Intriguingly, the spectrum of PN in 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 [13], and, more recently, in patients with chronic HCV infection [14]. *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 [15]. As for chronic forms of neuropathy, few reports describe an association between HCV infection and *chronic inflammatory demyelinating polyneuropathy*-CIDP [16]. This form can also be 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 favoring immune-mediated mechanisms [17]. A single case of the Lewis-Sumner syndrome, an asymmetric form of CIDP, has been described in 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 IV methylprednisolone [18]. We 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 [19]. 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 or 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 a MM. Surprisingly, in 3 of the 6 patients without CG or RF, and 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 have been observed on myelin sheaths. 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 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. After the introduction of direct-acting antiviral agents, sustained virologic response has been achieved in the majority of patients with cryoglobulinemic vasculitis [20]. According to Cochrane review, high quality studies are lacking, and there are insufficient data to make an evidence-based decision [21].

19.3 Human Immunodeficiency Virus (HIV)-Related Neuropathies

PN is considered the most common neurological complication of *HIV infection*, affecting actually 21% of patients, even after the introduction of *combination antiretroviral therapy* (cART) [22]. The increase life expectancy in 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 symmetrical polyneuropathy, *toxic neuropathy* induced by antiretroviral drugs, demyelinating neuropathies, mononeuropathy multiplex, diffuse infiltrative lymphocytosis (DILS), and progressive polyradiculopathy [23]. The diagnosis and appropriate treatment of PN in 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 Symmetrical Polyneuropathy (DSP)

DSP is the most common form of neuropathy in course of HIV infection. Its prevalence in cART era ranges from 20 to 60% [24]. 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 [25]. On the contrary, other studies identify the lower CD4 nadir reached during HIV infection as the leading risk factor for DSP [26]. 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 are commonly associated with DSP in HIV subjects [27]. 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) [28] and Brief Peripheral Neuropathy Screen (BPNS) [28] are the main clinical tools used to assess DSP. TNS has been validated in diabetic neuropathy and analyzes both the grading of sensory, motor, 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 great toe and ankle reflexes. The *neuropathological features* of DSP at sural nerve 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 [29]. 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 correlate with neuropathic pain scores [30]. 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 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 transcription reverse 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 *macrophages activation* in the induction of sensory neurons 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 [31]. Another study demonstrates the association between large mitochondrial deletions and sural nerve amplitude and intra-epidermal nerve fiber density in HIV-DSP patients, suggesting a role of these mutations in the pathogenesis of neuropathy [32]. Since pain is the major symptom in patients with HIV-DSP, symptomatic pain management is the main target of current treatment. *Treatments* include the use of different classes of drugs: non-steroidal 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 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 5 months [33]. *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 [34]. As shown in a placebo-controlled trial performed by Abrams and colleagues, smoked *cannabis* produced a significant reduction of pain in DSP [35]. 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 [36]. 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. Rare 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 also been reported [37]. 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 7 cases, concluding that the absence of pleocytosis in AIDP patients does not exclude HIV infection [38]. Like in non-HIV patients, *pathological examination* of peripheral nerve in CIDP cases shows segmental degeneration

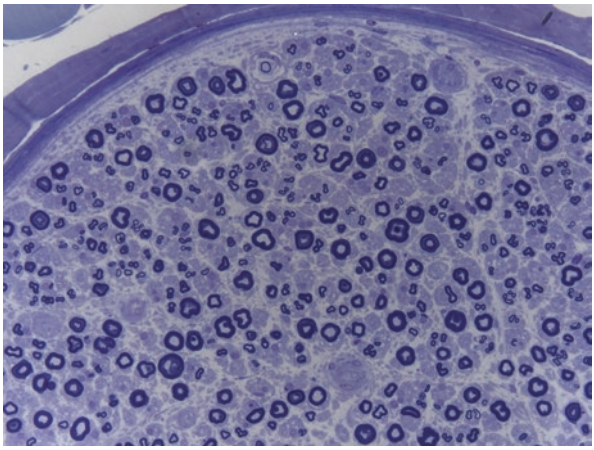

Fig. 19.2 Sural nerve fascicles showing asymmetric loss of myelinated fibers in a patient with cryoglobulinemic neuropathy and HCV infection (toluidine blue, original magnification ×50)

and onion bulb formation, infiltration of mononuclear cell of nerve fascicles, and endoneurial edema (Fig. 19.2). *Treatment* of AIDP includes IVIG and plasmapheresis. Clinical signs of CIDP 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 [38].

19.3.3 Mononeuropathy Multiplex (MM)

MM, characterized by asymmetrical sensorimotor involvement of single nerves, is a rare complication occurring in early and late stages of HIV infection. The initial asymmetrical involvement of peripheral nerves may progress, during the evolution of the disease, in a clinical picture simulating a distal symmetrical neuropathy. If it occurs 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 occur only in 0.3–1.0% of patients with AIDS either as isolated process involving peripheral nerves or as a manifestation of a systemic disease. In post-cART era, vasculitis of PNS may present as distal symmetrical polyneuropathy [39]. *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 predominantly 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 lympho-monocytes cell infiltration of nerve fascicles and the presence of cytomegalic cells filled with CMV particles.

19.3.4 Progressive Polyradiculopathy (PLP)

Progressive lumbosacral polyradiculopathy (PLP) starting with back and leg pain and evolving into paraparesis and sensory and sphincter dysfunction has been frequently observed in HIV-infected subjects pre-cART era [40]. PLP usually occurs in 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 [23]. The diagnosis includes *CSF* examination with polymerase chain reaction amplification to detect viral agents, mycobacterial and cryptococcus antigen. 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 [41]. 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 [42]. This syndrome may affect 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 symmetrical 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 [43]. In these patients, chronic HCV infection and *immune reconstitution inflammatory syndrome (IRIS)* are the principal differential diagnosis to be considered. *Treatment* of DILS consist mainly in *cART* but *steroids* may also be added when organ infiltration persist.

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 occurs in three countries: Brazil, India, and Indonesia [44]; however, it is a worldwide problem since new cases have also been reported in travellers 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 classified 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) [45]. 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, 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 fit better with patients' clinical condition and prognosis. The suspect of ML infection is established when *multifocal neuropathy* is associated with hypo-pigmented, hypoesthetic or reddish *skin lesions*, even if some patients may present signs of neuropathy in the absence of the characteristic skin lesions. Indeed, 3 to 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 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, can be damaged [46]. Typically, in the course of ML infection nerves are enlarged and painful on palpation and electrophysiological examination shows axonal changes. The use of imaging techniques as *nerve sonography* and MRI may be useful in the diagnosis. Analyzing high-resolution sonography, Visser and coll. showed that the epineurium of the ulnar nerve is often strikingly thickened in these patients, especially in those with ulnar involvement [47]. Symmetric *polyneuropathy* is rarely reported in leprosy while regional *autonomic* dysfunctions are frequently observed. Although the diagnosis of leprosy is mainly clinical, *nerve biopsy* can be helpful, especially in atypical cases or in patients

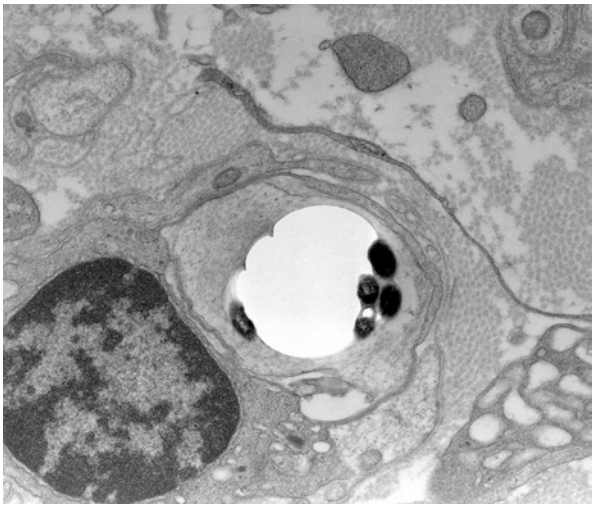

Fig. 19.3 Electron micrograph of sural nerve biopsy in pure neuritic form of leprosy showing a Schwann cell containing *Mycobacterium leprae* particles (original magnification ×12000)

with pure neuritic forms, not only as diagnostic procedure but also in personalizing therapy [48]. The definite diagnosis is based on skin smear or biopsy demonstrating granulomatous inflammation or foamy macrophages with acid-fast bacilli (Fig. 19.3).

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 affect humans as incidental hosts. 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 [49]. Subacute painful *meningoradiculitis*, which consists in painful migrant burning radiculitis, peripheral motor deficit, and *CSF* inflammation, alone or in combination, are the prevalent manifestation of early neuroborreliosis. Motor damage consists frequently of bilateral and asymmetrical peripheral facial nerve palsy. More rarely, third or fourth cranial nerve involvement is present, sometimes only observed at MRI [49]. Isolated or concomitant limb paresis often bilateral, asymmetrical, 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 course of Lyme borreliosis and confirmed by sural nerve findings of small lymphocytic infiltration around endoneurial vessels, perineurial fibrosis, and Wallerian degeneration [50]. However, nerve involvement in the absence of radicular symptoms or CSF inflammation has been rarely described [49]. *Brachial neuritis*, *Guillain-Barré*, and *CIDP*-like syndrome have also been reported [51, 52]. 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 biopsies* 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 detected [49]. Biopsy of sural nerve shows a prevalent axonal damage with perivascular infiltration [53, 54]. The acute neurological involvement in course of borreliosis presents usually with a benign course, but antibiotics as penicillin, cephalosporin, ceftriaxone, or oral doxycycline accelerates clinical recovery and prevents the development of new neurological deficit. Also chronic symptoms frequently improve 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 the idea that the pathogenesis of this condition, known as "*chronic arthropod-borne neuropathy*" could be linked to toxins, immunological, autoimmune, or psychological illness rather than the infectious agent [49].

19.6 *COVID-19* Pandemic and PNS Involvement

The new coronavirus disease-19 (COVID-19) pandemic, caused by *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)* infection, started in December 2019 and rapidly spread all over the world. Since the beginning of the pandemic, many cases of patients with neurological symptoms and diseases have been described in patients affected with COVID-19. Furthermore, an increasing number of studies describing the involvement of the peripheral nervous system (PNS) in COVID-19 have been reported in the literature.

19.6.1 Critical Illness Polyneuropathy

The prolonged *Intensive Care Unit* (ICU) stay caused by severe respiratory impairment, characteristic of COVID-19, exposes the patients to the risk of care-related PNS complications as critical illness polyneuropathy (*CIP*). According to the different studies CIP affects 30–50% of severely critically ill patients and represents the most frequent form of acute neuropathy in ICU [55]. Several studies reported CIP

in COVID-19 affected patients. Among 12 patients affected with COVID-19 and suspected critical illness syndrome, Cabanes-Martinez et al. identified by nerve conduction studies (NCS) and electromyography (EMG) 4 patients with CIP [56]. All the patients suffered from a severe acute respiratory syndrome with long ICU stays (more than 12 days) and presented general weakness and difficulty to wean from the ventilator, which are typical manifestations of CIP or *critical illness myopathy* (CIM). The authors were not able to find any distinctive clinical and electrophysiological features of CIP between ICU patients affected by SARS-CoV-2 infection and ICU patients not affected by SARS-CoV-2 infection. NCS and EMG studies play an essential role in the diagnosis of the patients with general weakness in ICU in order to distinguish the predominance of PNS or muscular involvement and to identify the axonal or demyelinating pattern of nerve involvement. The lack of extensive studies in CIP patients is partly due to the severity and infectious risk of COVID-19 patients in ICU, which make it difficult to perform appropriate neurophysiological studies in large numbers of patients. Furthermore in exceptional situations as a pandemic the medical resources may be limited. The prospective study of Frithiof et al. [57] included 111 patients, 11 of whom developed CIN or critical illness myopathy (CIM). Subjects with CIN/CIM presented more severe disease, longer ICU stay and underwent invasive ventilation for more than 2 weeks. In particular, CIN was more frequent among COVID-19 patients compared with a non-COVID-19 cohort. The authors emphasize the importance of serum biomarkers such as *neurofilament light chain (NfL)* and *glial fibrillary acidic protein (GFAP)* whose levels were higher in the CIN/CIM group. These data support the role of NfL and GFAP levels in diagnosing and predicting axonal damage in CIN.

19.6.2 Guillain Barré Syndrome (GBS)

Almost every known variant of GBS has been described in the course of COVID-19, but the most frequently reported is the classic sensory-motor demyelinating form.

The first series of patients with GBS after SARS-CoV-2 infection was reported by Toscano et al. Subsequently, many case reports and cases series of GBS syndrome in ongoing COVID-19 have been described so far, but the direct influence of SARS-CoV-2 infection in the development of GBS is still debated. Case series of Northern Italy and Spain reported an increased incidence of GBS during COVID outbreak [58–60] supporting a possible role of SARS-CoV-2 infection in pathogenesis of GBS. The interesting study of Keddie et al. examined, in the first 6 months of SARS-CoV-2 pandemic in the UK, the epidemiological data of cases with confirmed COVID-19, the incidence of hospitalized patients with GBS and a large cohort of the GBS cases presenting with and without COVID-19 [61]. Finally the authors, also using a proteomic approach, found no association between GBS and COVID-19. Following the systematic review of Adalawi et al., most cases GBS in COVID-19 are sensorimotor demyelinating subtype with frequent facial palsy [62]. *Anti-ganglioside antibodies* were analyzed in a small number of cases of GBS/COVID-19 and in the majority of cases resulted negative, in the positive ones the

antibodies were directed against different gangliosides, mainly GM1, GD1a, GD1b, and GM2. The latency between infection and onset of neurologic symptoms, as well as the absence of SARS-CoV-2 detected by PCR in CSF, suggest a *post-infectious*, rather than a direct infectious mechanism. Uncini et al. examined the clinical and neurophysiological features of 24 patients with acute inflammatory demyelinating polyneuropathy (AIDP) and COVID-19 compared with 48 control AIDP without SARS-CoV-2 infection [63]. In COVID-AIDP patients, the authors frequently found increased dCMAP durations and absent F waves. These findings may be partially due to muscle fiber conduction slowing for the *hyperinflammatory state* of COVID-19, involving also the skeletal muscle, as in CIM.

19.6.3 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

A clinical worsening of rare cases of CIDP may occur during COVID-19 [64, 65]. Although a causal association between SARS-CoV-2 and exacerbations in CIDP has been not previously reported, it has been assumed that SARS-CoV-2 infection may trigger a proinflammatory state that may be able to amplify autoimmune processes as CIDP.

19.6.4 Nerve Injuries

The guidelines for acute respiratory treatment of COVID-19 recommend a prolonged prone position of patients, who are therefore exposed to peripheral nerve injuries involving in the majority of cases the upper limbs. General anesthesia and malpositioning increase the risk of nerve injury. In an Italian experience, 7 cases of compression injuries of 135 patients who underwent invasive ventilation in prone positioning have been observed [66]. According also with other studies, the most frequent sites of injuries are the ulnar nerve, radial nerve, sciatic nerve, brachial plexus, and median nerve [67]. In conclusion, peripheral nerve injuries following prone position are common in severe COVID-19 and the patients require greater care in positioning due to increased susceptibility to nerve compressions.

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.
- The SARS-CoV-2 pandemic exposes patients to increased risk of neuropathy, in particular critical illness neuropathies and compression neuropathies.

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