Infectious neuropathies

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Purpose of review
Infectious neuropathies are heterogeneous neuropathies with multiple causes. They still represent an important world health burden and some of them have no current available therapy.

Recent findings
Leprosy incidence has decreased by 50% during the last years, but leprosy-related neuropathies still cause severe disability. The pure neuritic leprosy is a diagnostic challenge that may require nerve biopsy or nerve aspiration cytology. The treatment itself may lead to a 'reversal reaction', which further causes injuries to the nerve. HCV-related neuropathies may be related or not to the presence of cryoglobulins. The absence of vasculitis, the most frequent form is a peripheral sensory neuropathy involving small nerve fibers, and more accurately diagnosed by pain-related evoked potentials. HIV-related neuropathy has become the major neurological complication of HIV infection. Both HIV-induced neuropathy and antiretroviral toxic neuropathy are clinically indistinguishable. The existence of an isolated chronic polyneuropathy due to *Borrelia burgdorferi* remains highly controversial. Lastly, an active infectious ganglioneuritis caused by varicella zoster virus, producing shingles, is the most frequent infectious neuropathy in the world and may cause various neurological complications. Zoster sine herpete remains frequently undiagnosed.

Summary
Recent data have improved our knowledge and diagnostic tools of infectious neuropathies. Treatment of the injured nerves is not yet available, and prevention and rapid diagnosis remain the main priorities for the clinician.

Keywords
Borrelia burgdorferi infection, hepatitis C virus, HIV infection, leprosy, peripheral neuropathy, varicella zoster virus

INTRODUCTION

Although the endoneural compartment is protected by the blood–nerve barrier, some microorganisms succeed in producing neuropathies, either by a direct invasion of the nerve, or by inducing an inflammatory or immune-mediated reaction leading to a nerve injury. In addition, some drugs used against the causal infectious agent may also be neurotoxic and induce peripheral neuropathies. As our therapeutic tools to repair injured nerves are very limited or absent, a rapid diagnosis and an early treatment of these infectious neuropathies are of the utmost importance to prevent chronic pain, deformities and severe disability.

LEPROSY-RELATED NEUROPATHIES

Leprosy is a chronic granulomatous infection, principally affecting the skin and peripheral nerves. The infectious agent is an obligatory intracellular organism, *Mycobacterium leprae*. The nasal mucosa is the preferential site of entry and exit of the bacillus, but the oral mucosa may be a secondary site of transmission and infection [1]. Worldwide, the detection of new cases is decreasing, from about 515 000 in 2003 to 244 796 in 2009 [2]. In spite of this decreasing prevalence, leprosy remains an important health problem in countries such as India, Brazil, Nepal and central Africa.

Leprosy can be classified into three major clinical subtypes based on the extent of host immune response: lepromatous (multibacillar) in the case of a predominant humoral response, tuberculoid (paucibacillar) in the case of a predominant cell-mediated immunity and borderline (in-between).

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KEY POINTS

- Although the prevalence of leprosy is significantly decreasing, pure neuritic forms still occur and diagnosis may require nerve biopsy or fine needle aspiration cytology.
- HCV-related neuropathies are not always associated with cryoglobulinemia, and pain-related evoked potentials are more sensitive than standard nerve conduction velocity measurements.
- Peripheral neuropathy has become the major neurological complication of HIV infection.
- Varicella zoster reactivation (shingles) is the most frequent cause of infectious (ganglio)neuritis with a lifetime risk estimated to be 10–20%. ZSH is a diagnostic challenge and is likely underdiagnosed.

Nerve involvement in leprosy affects sensory, motor and autonomic fibers. Sensory loss is the earliest and most frequent modality. Granulomatous inflammation of peripheral nerves causes palpable enlargement, which is most often painful. Enlarged nerves can be damaged because of entrapment within fibro-osseous tunnels [3,4].

The posterior tibial nerve is the most commonly affected, causing anesthesia on the soles of the feet, followed by the ulnar, median, lateral popliteal and facial nerves. In a consecutive series of 100 leprosy patients, the facial nerve was involved in 17 [5]. Small dermal nerves can be affected leading to loss of sweating and a glove and stocking sensory loss. The effect of the disease on nerves leads to disability and deformity because of loss of motor function and impaired sensation favoring trauma and secondary infections.

The presence of a skin lesion overlying a major nerve trunk is associated with a significant increase in risk of impairment in that nerve. However, a pure neuritic leprosy (PNL) does exist and affects peripheral nerve trunks in the absence of cutaneous signs. About 4–10% of patients with leprosy could have a pure neural involvement [6,7]. In such cases, nerve biopsy examination is an important diagnostic procedure for detecting the presence of acid-fast bacilli (AFB) within the nerve. However, nerves do not always contain AFB and may only show relatively unspecific morphological alterations.

Antunes *et al.* [8▪] compared 144 nerve biopsies from leprosy patients with 196 biopsies from patients with nonleprosy peripheral neuropathies. In the first group, 109 of 144 were AFB negative, and 71/124 were *M. leprae* DNA negative by PCR. Thus, only 35 PNL cases were unequivocally diagnosed by the presence of AFB in either Schwann cells or macrophages. In addition, 28 of 92 AFB-negative samples had a positive PCR test. The diagnosis of the remainder group relied on the presence of serum anti-phenolic glycolipid 1 antibodies and a high suspicion based on clinical and epidemiological dataset. Mononuclear infiltrates and perineurial fibrosis were more frequently observed in AFB-negative, clinically suspected PNL than in nonleprosy neuropathies. Together, both anomalies correctly detected 100% of the former, and 0% of the latter. It should be noted that seven nerve samples were normal in the PNL group, indicating that the lesions may be focal and segmental [9].

As nerve biopsy is an invasive procedure and may lead to neural deficit, fine needle aspiration cytology of an affected nerve could be a valuable and less invasive procedure for the diagnosis of pure neuritic form. Smears from five suspected cases revealed nerve fiber infiltration by chronic inflammatory cells in all cases, presence of epithelioid cell granulomas in three cases and AFB in two cases [10].

During or after the multidrug treatment (rifampicin, dapsone and clofazimine), a so-called 'reversal reaction' may occur leading to an acute, painful and disabling neuritis. This type of reaction is most frequent in the multibacillar lepromatous form, and should be treated early with oral corticosteroids [3]. Some authors recommend to combine the multidrug therapy with 60 mg prednisone, with a gradual tapering over 5 months, to prevent further neurological damage [11].

HEPATITIS C VIRUS-RELATED NEUROPATHIES

Chronic infection with hepatitis C virus (HCV) is a growing global health issue affecting an estimated 170 million people [12▪▪]. This infection is a leading cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma, but has been also associated with numerous extrahepatic manifestations. The most frequent is cryoglobulinemia, present in up to 50% of HCV-infected patients and inducing symptomatic diseases in nearly 15% of cases. Cryoglobulins are cold-precipitable immunoglobulins, which, following vascular deposition, elicit inflammation and occlusion of small-sized and medium-sized blood vessels. Up to 95% of type II and type III cryoglobulins (called 'mixed cryoglobulins') are associated with chronic HCV or HIV infections [13].

In patients with HCV-associated cryoglobulins, the involvement of the peripheral nerves ranges from 26 to 86% in function of the clinical/electrophysiological protocols for neuropathy ascertainment [12▪▪]. In the case of acute sensorimotor mononeuropathy multiplex, pathological features

are indicative of ischaemic nerve changes as a consequence of small-sized or medium-sized vasculitis. Moderate polyneuropathies are characterized by lymphocytic perivascular infiltrates only [14]. In patients without cryoglobulins, immune complexes or HCV-induced autoimmune mechanisms may play a pathogenic role in inducing vascular and perivascular inflammation [15].

Sensory neuropathy represents the most prevalent form in HCV-infected patients. Variants include large-fiber sensory neuropathy characterized by sensory loss, paresthesias and numbness, and small-fiber sensory neuropathy, a painful condition characterized by burning feet, tingling and thermoalgic hypoesthesia. Unusual forms include pure motor polyneuropathies, autonomic neuropathies and demyelinating features. Demyelinating neuropathy may develop in HCV-infected patients unrelated to antiviral therapy, may meet the criteria for chronic inflammatory demyelinating polyneuropathy, and respond to intravenous immunoglobulins [16].

In a series of 46 cryoglobulins-negative, HCV-infected patients, Yoon *et al.* [17] observed a prevalence of peripheral sensory neuropathy of 43.5% (20/46), without correlation with the duration of the disease, current viral load, virus subtype or interferon treatment. Pain-related evoked potentials were more sensitive than standard nerve conduction velocity measurements. The most frequently reported symptoms were paresthesias (39%), of which 50% were reported as painful numbness (23.9%), nocturnal cramps in the lower limbs (11%), allodynia (8.7%) and burning feet (6.5%). The most frequent neurological deficits were increased vibration perception threshold (19.6%), loss of ankle deep tendon reflex (15.2%), decreased sensation to pin-prick (10.9%), distal paresis (8.7%) and temperature perception deficits (4.3%). A positive correlation between clinical symptoms and deficit scores on one hand and pain-related evoked potentials on the other was observed.

HIV-RELATED NEUROPATHIES

Peripheral neuropathy has become the major neurological complication of HIV infection in the developed world [18]. Distal sensory neuropathies are the most frequent and have two different causes resulting in similar signs and symptoms, a primary HIV-induced neuropathy on one hand and an antiretroviral toxic neuropathy on the other. The most neurotoxic antiretroviral drugs are dideoxynucleoside reverse transcriptase inhibitors (e.g. didanosine, zalcitabine and stavudine), which likely inhibit mitochondrial γ DNA polymerase with subsequent mitochondrial dysfunction. The use of these drugs has become uncommon in the developed world but remains in resource-limited settings because of low cost.

In both cases, the main symptom is a neuropathic pain defined as burning or aching sensations in the feet, paresthesia, allodynia and hyperalgesia, beginning in the toes and soles of the feet. As a rule, the pain is worst at night or after walking. The hands and arms are generally spared, suggesting that both neuropathies are length-dependent phenomena. Neurological signs consist of absent or reduced ankle deep tendon reflexes, and loss of pinprick, temperature or vibratory sensations in the lower limbs. The only tool to distinguish between a primary HIV-neuropathy and a drug-induced neuropathy is the history of a recent neuropathic onset after initiation of a neurotoxic antiretroviral drug. Incidence of symptomatic antiretroviral toxic neuropathy peaks within 3 months, and patients who tolerate the first year of treatment with stavudine seem unlikely to be affected thereafter [19].

Nerve conduction studies with electromyography are useful for excluding other conditions but may be normal in both HIV-induced neuropathy and antiretroviral toxic neuropathy, as both conditions usually involve small nerve fibers. However, it is imperative to rule out other causes of painful sensory neuropathy such as diabetes, nutritional deficiency, ethanol abuse and other neurotoxic drugs. It should be noted that hepatitis C seropositivity is not a risk factor for sensory neuropathy among patients with HIV [20].

The pathological changes are characterized mainly by axonal degeneration in a distal-to-proximal distribution, with predominant loss of small myelinated and unmyelinated fibers. Activated macrophages and lymphocytes infiltrate the dorsal root ganglia, but the precise mechanisms of neuronal injury remain elusive [21▪▪].

In a series of 1539 HIV-infected patients enrolled in the CNS HIV Anti-Retroviral Therapy Effects Research study from six US academic medical centers [22], 881 (57.2%) had at least one clinical sign of sensory neuropathy. Among them, neuropathic pain was the most frequent symptom, occurring in 61%. In comparison with patients without sensory neuropathy, those with one or more signs of neuropathy were significantly older, had a lower CD4 nadir, had received antiretroviral neurotoxic drugs in the past and were more frequently on combination antiretroviral therapy (cART). Seropositivity for HCV was not a risk factor. Thus, those patients who had started cART after their CD4 cell counts fell below 350/μl were significantly more likely to have a sensory neuropathy than were those

who started cART before this level of immunosuppression.

Prevalence of, and risk factors for peripheral neuropathy in HIV patients, have been studied in a large prospective cohort of 2141 patients enrolled in cART by the AIDS Clinical Trials Group [23]. This study differentiated asymptomatic peripheral neuropathy (defined as at least mild loss of vibration sensation in both great toes or absent/hypoactive ankle reflexes bilaterally) from symptomatic peripheral neuropathy (the same signs and numbness, paresthesia, burning sensation, stabbing pain). At 3 years, the rate of asymptomatic neuropathy was 32.1%, and the rate of symptomatic neuropathy was 8.6%, in spite of the fact that 87% of these patients had less than 400 copies/ml of HIV-1 RNA, and that 70.3% had a CD4 cell count greater than 350/μl. Associations with higher odds of peripheral neuropathy included older age, neurotoxic antiretroviral therapy and diabetes mellitus. Recovery was less likely in older patients after discontinuation of neurotoxic agents. Signs of peripheral neuropathy remained despite virologic and immunologic control of the disease, but asymptomatic forms were far more frequent than symptomatic ones [23].

HIV-infected patients may also develop Bell's facial palsy, whether unilateral or bilateral, most often around the time of primary HIV infection and seroconversion. Recovery is similar to that in patients who are not infected with HIV.

BORRELIA BURGDORFERI-RELATED NEUROPATHIES

Infection of the nervous system with *Borrelia burgdorferi* usually presents as a painful asymmetric meningo-radiculitis with a frequent associated facial palsy. Pleocytosis in cerebrospinal fluid (CSF) and intrathecal synthesis of *B. burgdorferi* antibodies are always observed. In a very early stage, an isolated neuritis close to the tick bite area is theoretically possible; a concomitant seroconversion and the absence of CSF pleocytosis are required for this diagnosis [24]. An early, antibiotic-responsive demyelinating neuropathy has also been reported [25].

More rarely, a chronic peripheral neuropathy may occur in conjunction with a chronic skin disorder, acrodermatitis chronica atrophicans. In such a case, a high level of serum *B. burgdorferi* antibodies is the rule, but with normal CSF findings.

The existence of an isolated chronic polyneuropathy related to *B. Burgdorferi* remains highly controversial and is not supported by the current data. A positive IgG serology does not imply a causal relationship with a chronic polyneuropathy, especially in endemic areas, and a chronic infection with *B. burgdorferi* results in seropositivity in almost 100% of cases. Detection of *B. burgdorferi* antibodies only with western blot techniques and not with ELISA, and detection of *B. burgdorferi* IgM antibodies without simultaneous detection of *B. burgdorferi* IgG antibodies should be considered as seronegativity. Patients who attribute their isolated subjective symptoms to chronic *B. burgdorferi* infection on a doubtful basis should be offered a thorough and systematic diagnostic approach for other neurological or rheumatologic disorders and psychological support. A tentative antibiotic treatment longer than 4 weeks is not recommended [26▪].

VARICELLA ZOSTER VIRUS-RELATED NEUROPATHIES

Varicella zoster virus (VZV) causes chickenpox (varicella), becomes latent in the cranial nerve and dorsal root ganglia, and may reactivate anywhere on the body several decades later. The lifetime risk of herpes zoster (shingles) is estimated to be 10–20%. Shingles is characterized by unilateral radicular pain and a vesicular rash that is generally limited to one to three contiguous dermatomes. During and after this reactivation phase, VZV can cause additional neurological complications. The most frequent one is postherpetic neuralgia, a neuropathic pain syndrome that persists more than 3 months after the dermatomal rash has healed. Other acute neurological complications affect either the peripheral nervous system (cranial neuropathies, motor radiculopathies of the arm or the leg, bladder and bowel dysfunction) or the central nervous system (meningitis, myelitis and vasculitic encephalitis). The same neurological complications may be observed in zoster sine herpete (ZSH), which is defined by the absence of antecedent vesicular rash. ZSH remains a diagnostic challenge in clinical practice [27▪▪].

The most common site of zoster is the chest, followed by the ophthalmologic distribution of the trigeminal nerve. The latter may be complicated by zoster keratitis and ophthalmoplegia of the third, sixth and less frequently of the fourth cranial nerve.

Ramsay Hunt syndrome is characterized by peripheral facial weakness and a rash in the external auditory canal, the tympanic membrane (zoster oticus) and/or the anterior two-thirds of the tongue or hard palate. Compared with idiopathic facial palsy (Bell's palsy), Ramsay Hunt syndrome is often characterized by a more severe palsy and by an incomplete recovery. Of note, Ramsay Hunt syndrome has been associated with spinal trigeminal nucleus and tract involvement on MRI [28].

Whether, some cases of Bell's palsy are in fact due to VZV reactivation without rash (ZSH) remains controversial and unproven.

Zoster in the cervical or lumbar nerve distribution may be followed by lower motor neuron-type weakness in the respective dermatomas. However, in the absence of rash and disc herniation or other compressive causes, a painful sciatica, cruralgia or any other radicular pain should push the clinician to perform an analysis of the CSF including VZV DNA PCR, and detection of intrathecal synthesis of anti-VZV antibodies [29]. The ability of VZV to reactivate from some dermatomes with rash and from other dermatomes without rash has been reported [30]. In the case of chronic active VZV infection as demonstrated by CSF analysis, intravenous treatment with acyclovir may be required.

HERPES SIMPLEX VIRUS-RELATED NEUROPATHIES

In comparison with VZV, neuropathies related to reactivation of herpes simplex virus (HSV) are very rare, and have been only reported in some patients with frequent herpes labialis and trigeminal neuropathy. In a recently reported case, brain MRI showed a focal lesion in the spinal trigeminal nucleus and tract, without CSF abnormalities. Transaxonal spread of HSV from the Gasser's ganglion along the trigeminal nerve, to the spinal nucleus, was therefore considered as the cause of the sensory trigeminal neuropathy concomitant to herpes labialis [31]. Vestibular neuritis could also be caused by the reactivation of a latent HSV-1 infection, as HSV-1 DNA has been detected on autopsy by PCR in the human vestibular ganglia [32,33]. However, additional data are needed to confirm this hypothesis.

CONCLUSION

Viral, bacillary and spirochetal infectious agents may cause neuropathies either by a direct invasion of the nerves, or by inflammatory and immune-mediated reactions within the nerves. These neuropathies may be concomitant to the early phase of the infection or to a chronic infection or to a delayed reactivation after a latency phase of many years. Most of these neuropathies involve small nerve fibers, and neuropathic pain is often a severe and long-lasting complication. Nerve biopsies, neurophysiological studies, serum (auto) antibodies, CSF analysis and specific PCR in body fluids or in biopsy tissue may be required for establishing a robust diagnosis, and then a specific and early treatment. Nerve lesions are at best partially reversible, and no repair treatments are available so far.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 589–590).

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