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INFECTIOUS NEUROPATHIES

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ABSTRACT

Infectious neuropathies are an important morbidity worldwide. These can be caused by viruses (HIV, HTLV, HBV, HCV, VZV) or bacteria (M. leprae, Borrelia Burgdorferi, Corinebacterium diphteriae). HIV infection, already pandemic, is at the origin of many and various peripheral neuropathies. Also, HTLV can produce various neuropathies, but it is more limitedly spread. Postzosterian neuralgia is a fiercely complication, sometimes hard to treat of herpes zoster produced by varicella-zoster virus (VZV). Neurologic involvement of Lyme disease is quite controversial, but it is after all a reality. Leper and diphtheria are associated with a lower standard of living, but still present. A special mention should be done regarding the possibility of occurrence of peripheral neuropathies as a consequence of the use of some of the antibiotics used to treat some infections, even if these infections have no neural tropism.

Keywords: neuropathy, infection, virus, bacteria, leper, borreliosis, diphtheria

INTRODUCTION

Infectious neuropathies are an important cause of morbidity, with a worldwide distribution. Many infectious agents can cause direct or indirect lesions in peripheral nerves (Table 1).

TABLE 1. *Main infectious agents involved in peripheral neuropathies*

Viruses	• HIV1 and 2 • HTLV 1 and 2 • HBV • HCV • Varicella-Zoster Virus (VZV)
Bacteria	• Mycobacterium leprae • Borrelia Burgdorferi • Corinebacterium diphteriae

Leper produces a variety of neurologic lesions which are going to be described in the following and is found in some geographical areas (Africa, South America, Asia). HIV infection is already pandemic and produces many peripheral neuropathies. HTLV is responsible for the HTLV1 associated myelopathy or the tropical spastic paraparesis and may cause inflammatory myelopathy. Peripheral neuropathies may be found in patients with hepatitis viruses (HBV, HCV). Diphtheria neuropathy continues to be present in the underdeveloped countries. Lyme disease is a very frequent zoonosis in the northern hemisphere caused by Borrelia Burgdorferi which is transmitted by Ixodes ricinus thick. Postzosterian neuralgia is a fiercely complication, sometimes hard to treat of herpes zoster produced by varicella-zoster virus (VZV). A special mention should be done regarding the possibility of occurrence of peripheral neuropathies as a consequence of the use of some of the antibiotics used to treat some infections, even if these infections have no neural tropism (1).

HIV ASSOCIATED NEUROPATHIES

HIV infection produces many neuopthies that may appear at different timepoints in the evolution of the disease, depending on the immune suppression stage. When HIV infection is present, other viruses, like the cytomegalic virus (CMV) may produce neuropathies. Antiretroviral therapies may also produce peripheral neuropathies.

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Demyelinating inflammatory polyneuropathy

This entity appears more frequently at the seroconversion time in HIV 1 infected patients which usually are not immune suppressed. Clinical manifestations are similar to those of Guillain-Barré syndrome. Sensory alterations like paresthesia may precede the installation of motor deficits in the limbs (symmetrical) associated with lack of reflexes. The maximum of the symptomatology is reached in the 4th week of evolution. Sometimes, the respiratory muscles may be involved, and in these cases, the patients may need respiratory support.

Cerebrospinal fluid (CSF) exam may show slight increase of the number of leukocytes with mononucleates (20-50/mm^3), increased proteins (usually as high as 250 mg/dl), polyclonal gammaglobulinemia

Demyelination is proved by low neural conduction speed or high distal latencies Sometimes, electrophysiological studies may show complete blockage of the neurologic conduction.

The mechanism of this neuropathy seems to be, as in the case of Guillain-Barré syndrome, autoimmune.

Treatment: generally, the inflammatory demyelinating neuropathy is self-limited, but recovery takes usually more than in the case of Guillain-Barré syndrome. Plasmapheresis may be required when the evolution is severe. Corticotherapy may be beneficial in these patients, but must be used with caution in those with immunosuppression. Intravenous immune globulins have been also used in combination with plasmapheresis, but the results are not conclusive yet (2).

Distal sensitive polyneuropathy

This type of peripheral neuropathy is the most frequent, occurring in 35% of the patients and in an additional 20% of the patients being asymptomatic. It occurs mainly in the immunosuppression phase in patients with high viral loads.

Clinically, it is characterized by symmetrical parhestesias, painful at the beginning, initially in the lower limbs. The patients describe frequently a burning sensation in the soles, that may be worsened by wearing socks and shoes, making thus difficult these patients mobilization. Gradually the painful parhestesias involve the lower limbs up to the knees, when there can also be present symptoms in upper limbs. Hyporeflexia of the lower limbs is almost a rule. Ataxia may be present. Muscular force is usually preserved.

CSF exam may show non-specific modifications common to all patients with HIV infections: slight increase of leukocytes, with mononucleates and slight increase of proteins.

Electrophysiological studies show the reduction of the amplitude or the absence of the potentials in sural nerve. Conduction speeds of the sensitive and motor nerves are usually not affected. Nervous biopsy shows axonal degenerescence. The presence of an inflammatory infiltrate with activated macrophages is responsible for the production of this type of neuropathy.

Multiplex mononeuritis

Appears in patients usually asymptomatic by this moment, with HIV1 infection, with CD4 lymphocytes over 200/microliter.

Clinically, the patients show the sudden installation of a sensitive or motor deficit in one or more nerves territory. The symmetrical character of the manifestations are the facts that differentiates it from the other neuropathies described here.

The evolution is usually self limited in the early phases of the infection or more severe in patients with severe immune suppression.

CSF exam may indicate non-specific modifications: slight increase of leukocytes and increased proteins. One case with crioglobulinemia was reported.

Treatment: in mild forms usually no treatment is necessary as they resolve spontaneously. Sometimes plasmapheresis and/or intravenous immune globulins may be of use. Corticotheraphy should be used with caution. Ganciclovir treatment could be useful in patients with proved CMV concomitant infection.

Progressive poliradiculopathy

Appears in patients with advanced immune suppression.

Initially, the patients accuse parhestesias in lower limbs extremities and sometimes in the territory of cauda equina. These manifestations are followed by rapid installation of a non-reflexive progressive

paraparesis and an ascendent loss of sensory. Upper limbs are usually spared. Frequently CMV infection is present as retinitis, colitis, esophagitis.

CSF exam is characteristic: a marked increase of the number of PMN leukocytes, increased proteins and low glucose. CMV can be cultured or evidenced by PCR in 60% of the patients.

Electrophysiological studies may differentiate between progressive poliradiculopathy and demyelinating polineuropthy.

Treatment of these neuropthies, strongly associated with CMV infection consists mainly in the administrations of intravenous ganciclovir or foscarnet.

HTLV NEUROPATHY

HTLV 1 and HTLV 2 infections were the first ones in which neurologic lesions have been described (1). The entity described since 1956 (3) was associated with HTLV infections in 1985 and received the name of HTLV associated myelopathy (HAM) or tropical spastic paraparesis (TSP).

HAM is more frequent in woman and affects less than 2% of the infected patients. It becomes clinically manifest between 4 months and 30 years from the moment of the infection (median 3.3 years) (4). Risk factors that permit the development of this neuropathy are not completely understood. There is a clear association with the level of viral load (5). Some IL10 and IL28B polymorphism are also incriminated in the production of HAM (5).

Clinically, the disease is characterized by the installation of a motor deficit slowly progressing in both lower limbs, accompanied by spasticity, hyperreflexia, clonus and lumbar pain. Other manifestations include nicturia, urinary incontinence, impotence, paresthesia, loss of vibratory sensitivity in the lower limbs. Upper limbs are not affected. The disease is more prominent in patients with HTLV1 infection (1). Usually it appears in the 4th decade of life (2).

The diagnostic criteria have been established by a panel of WHO (Table 2).

Cerebral and spinal MRI may be normal or may show cervical medular atrophy or white substance lesions in the subcortical and periventricular areas. CSF exam may show mild increase of leukocytes and increase of proteins. Virus presence in CSF may be documented by PCR.

TABLE 2. *HAM diagnostic (WHO)*

Diagnostic criteria
Age and sex Usually sporadic in adults, sometimes familial. Sometimes in childhood. More frequent in females.
Debut Usually insidious.
Frequent neurologic manifestations Chronic spastic paraparesis Motor def cit in lower limbs, more important proximal Neurologic def cits in urinary bladder Neurosensitive manifestations – paresthesia Low lumbar pain with irradiation in lower limbs Vibratory sensibility alteration Hyperref exia in lower limbs + Babinski sign Hiperref exia in upper limbs
Rare neurologic manifestations Cerebelous involvement, optic atrophy, deafness, cranial nerves involvement, nystagmus, seizures, cognitive impairment. Muscular atrophy, fasciculations, meningitis, encephalopathy
Non-neurologic systemic manifestations Pulmonary alveolitis, Sjogren syndrome, arthropaties, vasculitis, crioglobulinemia, lymphoma
Laboratory diagnostic HTLV1 serology CSF leukocytes increase Lobulated lymphocites in blood or CSF Mild/moderate increase of proteins in CSF

Antiviral treatment did not prove its efficiency in HAM. Corticotherapy may slow the progression of the disease, reduces the functional impotence and improves the pain (1,2). Beta interferon treatment is still under evaluation but may be efficient (6).

The disease evolution is variable from patient to patient, but has a progressive character in all affected patients resulting in invalidity.

HBV INFECTION NEUROPATHY

The case published in 2013 by Yimammshowed one more time that HBV infection may be associated with Guillain-Barré syndrome (7). Guillain-Barré syndrome is a rare complication of HBV infection with only 20 cases described by now (8). A multiplex mononeuropthy of non-vasculitic origin was described in a patient with HBV infection (9), but the causal association is not very clear.

Poliarteritis nodosa is an extrahepatic manifestation of HBV infection (2). This entity mey produce peripheral neuropathy in 60% of the affected patients. The neuropathy in poliarteritis nodosa may manifest as multiplex mononeuritis, distal pol-

yneuropathy, cutaneous neuropathy and can interest either sensitive or motor nerves.

Clinically is an asymmetric sensitive or motor neuropathy caused by ischemia and necrosis of the nerves following the vasculitis phenomenon (10).

HCV INFECTION NEUROPATHY

Approximatively 50% (46-54) of the patients with HCV infection have circulating crioglobulins, but the majority of them do not have clinical manifestations (11). The periferic neuropathies are manifestations of the crioglobulinemia. The mechanism of the crioglobulinemic neuropathies is not clear, but there are many hypothesis: the interference of vasa nervorum by crioglobulin deposits or ischemia by vasculitis. An immune mechanism by demyelination was also proposed (12). The neuropathy appears mostly in type II and III crioglobulinemia (11).

The crioglobulinemic neuropathy involves mainly sensitive nerves, with only 5% of the cases affecting just the motor branches (11).

There have been described cases of peripheral neuropathy in patients without crioglobulinemia (13,14), iand HCV was identified in the nerves of these patients by PCR, raising the suspicion of a possible direct injury of the nerves by HCV (15).

VZV INFECTION NEUROPATHY

VZV primo infection causes varicella, after which the virus localizes in the sensitive ganglia where it can persist in a latent form through biologic mechanisms that have not been elucidated yet. Virus reactivation from these ganglia produces herpes zoster.

Clinical manifestations area those of a peripheral mononeuropathy, usually sensitive (given the mentioned localization), but in some cases motor involvement can also be present by the affection of the anterior corn cells. The typical exanthema with dermatomeric disposition makes the clinical diagnosis easy usually.

Postzosterian neuralgia is a complication of herpes zoster, sometimes hard to manage. Rare in young persons, it appears in 25-50% of patients over 50 years old and lasts in 50% of these cases over one month. It can be continuous or intermittent. It is more severe during the night and at temperature changes, sometimes being incapacitating (2).

A particular form of herpes zoster is Ramsay-Hunt syndrome that appears by affection of the geniculate ganglia. It can appear even in the absence of an exanthema. Classically it has tipical rash before the ear or in the mouth, ipsilateral palsy, dizziness, ipsilateral hearing loss, headache, tinnitus, pain, ataxia, fever, cervical adenopathy.

In 0.03% of the patients Guillain-Barré syndrome may be present.

The treatment with acyclovir must be started in the first 72 hours in order to have an effect (16). After 72 hours it may be started only if eruptive elements continue to appear. Acyclovir treatment shortens the evolution and leads to a more rapid resolution of the pain (16), its benefits showing mostly in patients over 50 years old.

The postzosterian neuralgia frequently involve tricyclic antidepressants, gabapentine and pregabaline. Local treatment with capsaicine may pe effective in mild forms. Sometimes we have to use even opiates in order to control the pain. In some cases cryotherapy or surgery may be necessary.

LEPER NEUROPATHY

Leper is one of the most frequent cause of peripheral neuropathy. Mycobacterium leprae is an intracellular parasite with tropism for macrophage and Schwann cells of the peripheral nerves. Once entered the Schwann cells it multiplies slowly, determining a response from T lymphocytes, which produces in time, besides the direct action of the bacteria, progressive lesions in the peripheral nerves.

Leper transmission is done through direct contact with the secretions or skin of the infected patients, respiratory or cutaneous and the incubation is 10-20 years. Factors like insufficient nutrition, low hygienic conditions, crowds are necessary in order for leper to occur.

Typical manifestations of leper are the cutaneous lesions that are hypo pigmented, infiltrating, erythematous with or without neurologic manifestations (hypoesthesia, motor deficit, autonomic dysfunction, peripheral nerves thickening – especially in the ulnar, median and posterior tibial nerve). Pure nevritic forms have been described too

in 5% of the patients, more frequently in India and Nepal (1,2). In these forms, only biopsy can be diagnostic.

The diagnostic is based on clinical exam and anamnesis, confirmed by cutaneous biopsy. Germs are visible in Ziehl Neelsen coloration and in direct smear from the cutaneous lesions. Serologic testing is yet insufficient developed.

Leper complications appear consecutively to the nervous involvement. These can be purely autonomous leading to cutaneous anydrosis; can affect sensitive nerves leading to wounds that do not heal or may affect motor nerves leading to palsies of the small nerves of the upper or lower limbs. Posterior tibial nerve is most frequently affected, followed by ulnar, median, lateral popliteal and facial.

Treatment is based on the use of dapsone, rifampin or clofazimine. The treatment duration is of 12-24 months depending on the number of germs identified in cutaneous biopsies.

LYME DISEASE NEUROPATHY

Neurologic manifestations in Lyme disease occur usually after weeks or months from a tick bite and can be sometimes the first manifestations of the disease. It is the case of the facial palsies or meningitis. Disseminated manifestations of the Lyme disease appear usually in a longer period of time, of more than a year.

Peripheral neuropathies may be divided in those caused by axonal lesions, those secondary to myelin deterioration and those caused by multifocal (vasculitis) lesions. The results of the antibiotic treatment suggest the direct involvement of the microbe in the neural lesions, and the anatomic-pathological studies show the role of the immune system, but the exact mechanism of the lesions remain to be elucidated. The presence of borrelia has not been proved in the peripheral nerves, but they have been found in the nerve's ganglia.

In the initial phases of the disease, cranial nerves involvement and radicular neuritis are common. Cranial nerves involvement usually manifests sudden. Any of the cranial nerves can be affected, but the most frequently involved is the facial nerve. Because this can be the first manifestation of the disease, in every patient with facial palsy, the diagnostic of Lyme disease must be sought, especially when there is bilateral involvement of the facial nerves. Nerves III, IV or VI may be also interested, resulting in visual impairment. Papilitis has also been described, through optic nerve involvement. Nerve VIII can also be affected.

Radicular neuritis are manifesting more frequently with pain in one or more dermatomes, being frequently underdiagnosed as being a part of a Lyme disease.

Bannwarth syndrome – painful radicular neuritis with variable motor deficiency, sometimes accompanied by facial palsy and CSF leukocytes increase can also be a manifestation of borreliosis.

Central nervous system involvement is also possible, with meningitis or encephalitis.

The diagnosis is based on the detection of the antibodies by the two methods (ELISA confirmed by Western Blot) in the blood.

CSF exam may show: slight or moderate increase of leukocytes and proteins in the CSF. Antiborrelia antibodies may be detected in CSF, but a negative test should not exclude neuroborreliosis. It is rare that Borrelia itself can be evidenced in CSF by PCR techniques, this fact reflecting probably the low number of germs at this level.

Treatment: for isolated facial palsy: doxycycline 100 mg bid 14-28 days. For any other neurologic manifestations of Lyme disease, Ceftriaxone is recommended in a dose of 2 g daily for 28 days.

THE DIPHTHERIA NEUROPATHY

Corinebactrerium diphtheria is not an invasive germ. It remains superficially on the lesions that he produces and induces by itself only a moderate inflammation. Its virulence is caused by the exotoxin that it produces. In nerves, the diphtheria toxin causes demyelination.

Up to 3 of 4 patients with severe diphtheria develop neurologic manifestations. The first to appear is palatine vale palsy, which causes nasal reflux of swallowed liquids. This is followed by other cranial nerves involvement, with oculomotor and accommodations deficits, facial palsy, laryngeal and glossopharyngeal nerve involvement that can lead to aspiration. Between 10 days and 3 months other peripheral neuritis may appear, especially a motor deficit visible initially in proximal muscular groups of the limbs and that extends distal and is accompanied by hyporeflexia.

Biopsies show myelin degenerescence and axonal degenerescence. Even though slow, the resolutions of these processes is usually the rule.

First line treatment consists of horse produced diphtheria antitoxin. Antibodies neutralize the toxin only before it enters the cell, so it is important to be administered as soon as possible. The antibiotic treatment is usually based on penicillin or erythromycin. Erythromycin is superior in eradicating the carrier state, and this is the main reason that it is the preferred choice in many clinicians (2).

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