NEUROPATIE INFETTIVE

Dott.ssa Marina Padroni

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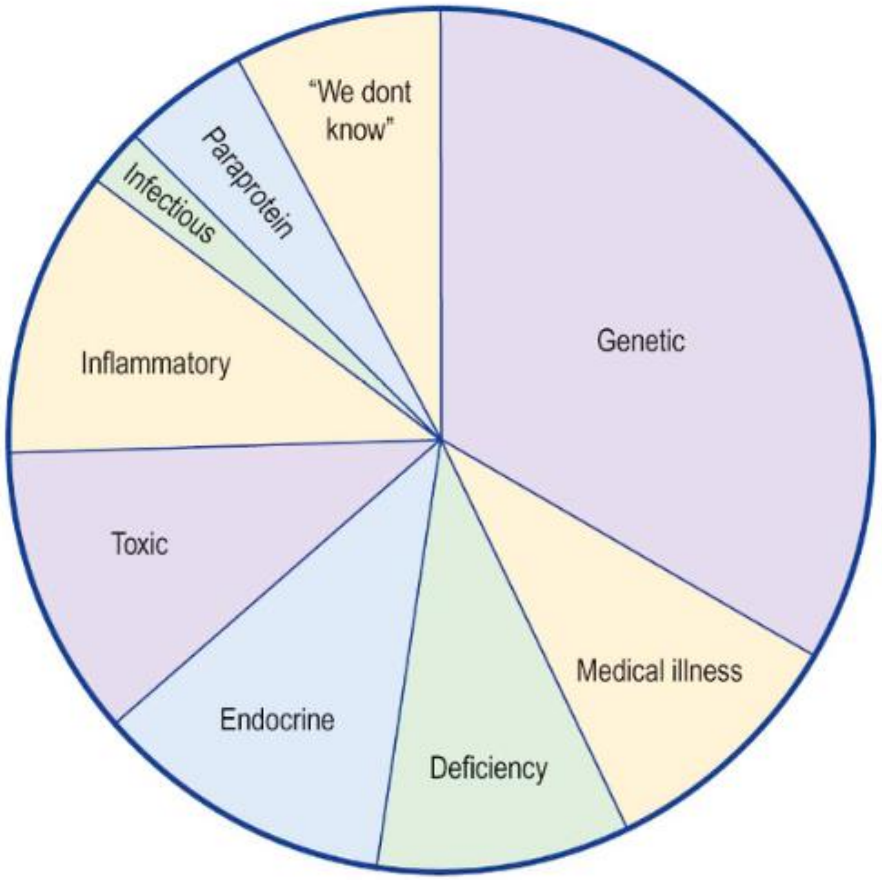


Overview of polyneuropathy

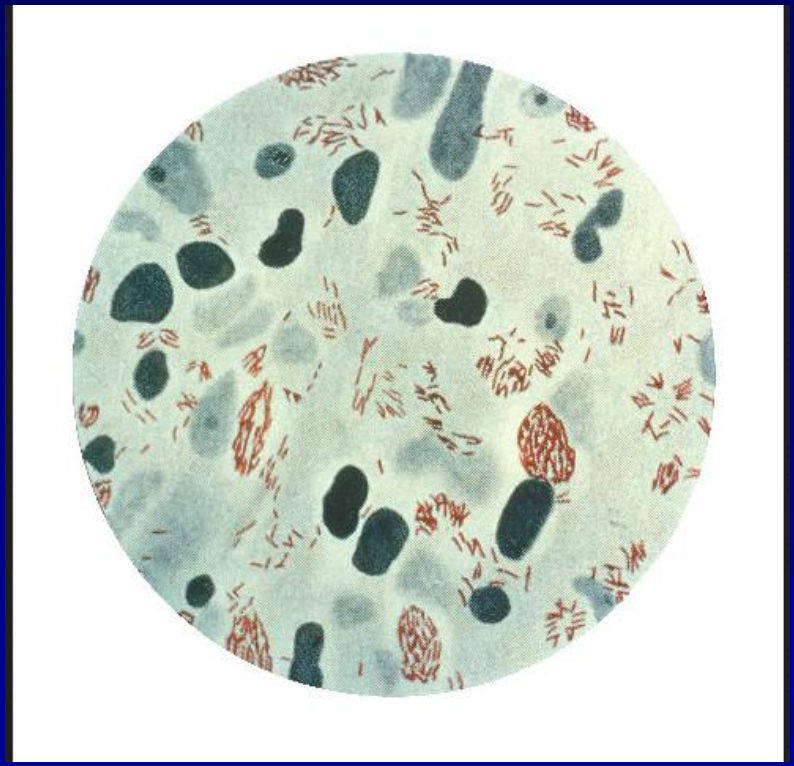
CURRENT OPINION

Infectious neuropathies

Christian J.M. Sindic

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

Mycobacterium Leprae



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.

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 cellmediated immunity,
- borderline (in-between).

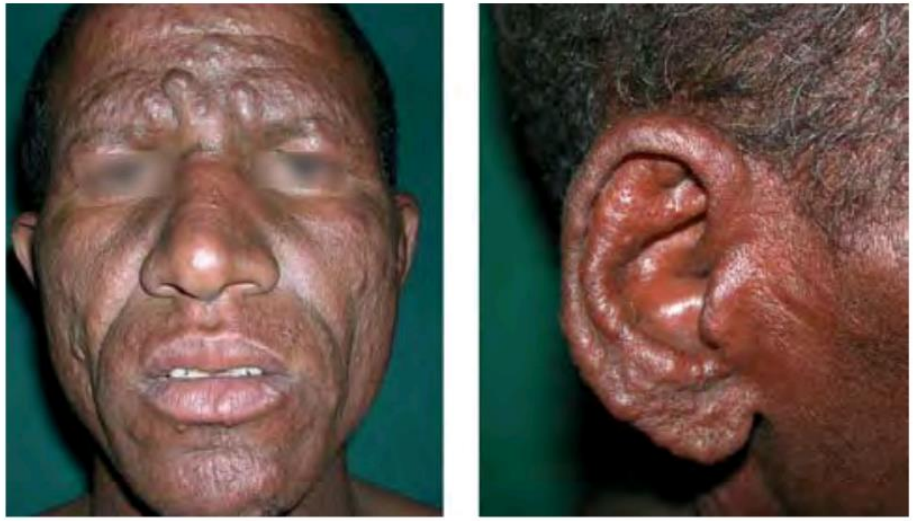


Figura 13 - Lebbra lepromatosa: lesioni nodulari della regione frontale, associate a infiltrazioni diffuse del volto e lesioni nodulari del padiglione auricolare particolarmente evidenti a livello dell'elice

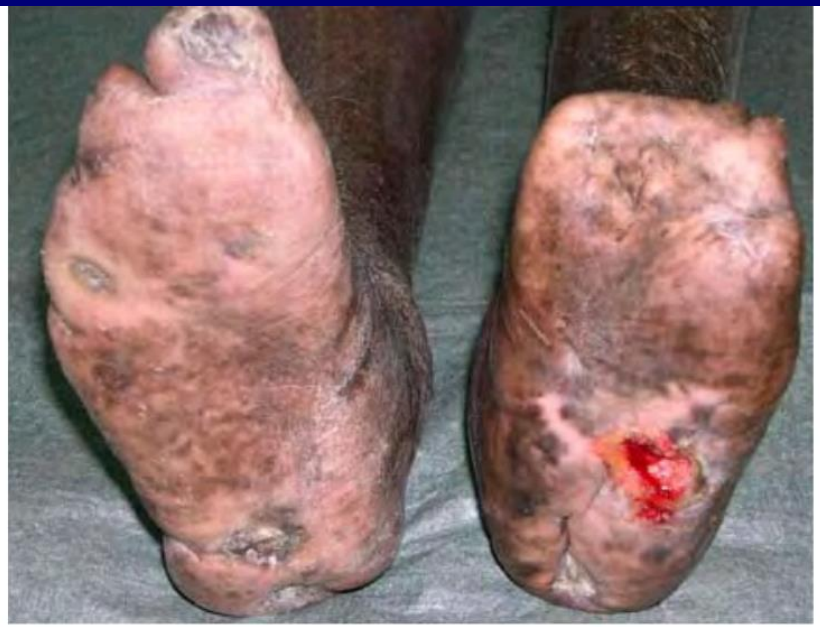


Figura 20 - Complicanze neurologiche nei pazienti affetti da lebbra: deformazione completa dei piedi con scomparsa dell'arcata plantare, lesioni ulcerative e riassorbimento delle falangi

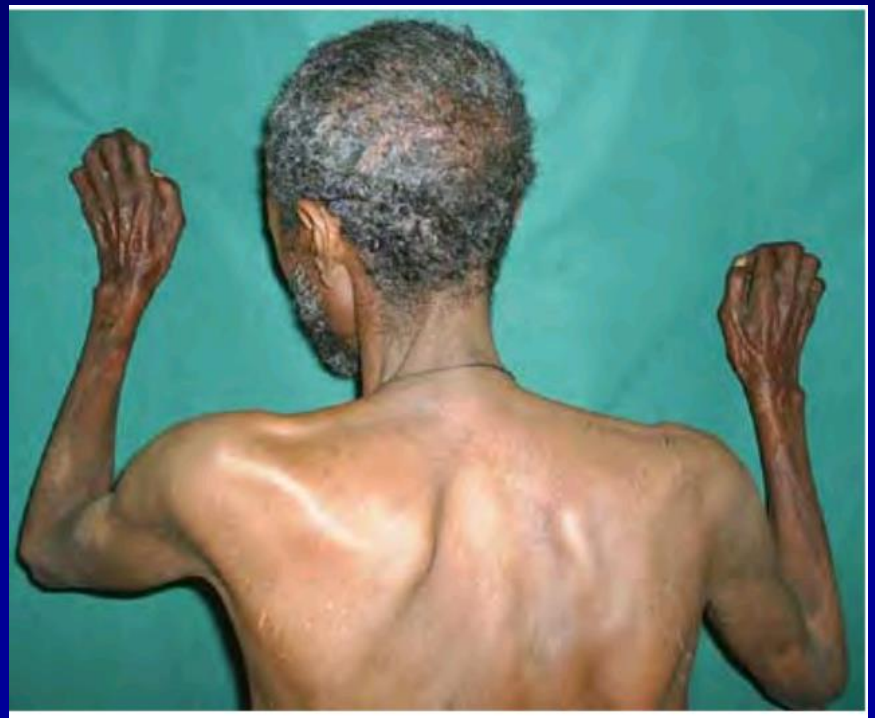


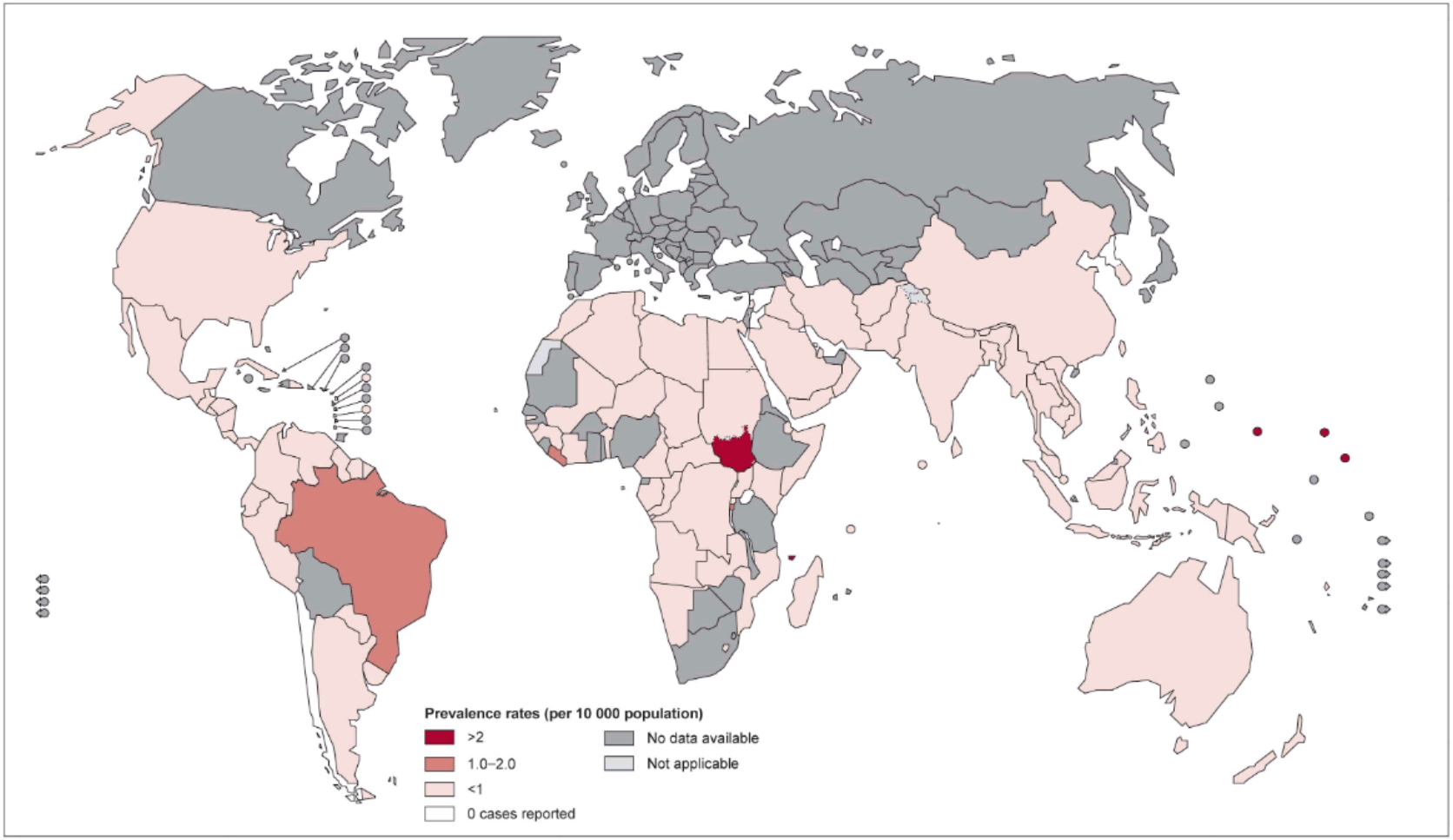
Figura 49 - Lebbra neuritica: mani ad artiglio per paralisi dei nervi ulnari e mediani

- Based on official data from Ministries of Health in endemic countries, the global annual detection of leprosy has shown a declining trend since 2001. New case detection was 407,791 in 2004 but had fallen to 228,474 by 2010, and to 219,075 in 2011 - a reduction of over 46%.

- During 2010, the number of new cases detected continued to decline in all regions except the Eastern Mediterranean. More new cases were detected in this region than in earlier years owing to increased coverage of leprosy control services, along with the the provision of better services in southern Sudan.

- The proportion of cases with MB leprosy among new cases ranged in the African Region from 61.72% in the Democratic Republic of the Congo to 99.21% in Kenya; in the Region of the Americas, from 40.88% in Brazil to 83.06% in Cuba; in the South-East Asia Region from 42.33% in Bangladesh to 80.96% in Indonesia; in the Eastern Mediterranean Region, from 61.95% in Yemen to 88.38% in Egypt; and in the Western Pacific Region, the proportions ranged from 29.67% in Kiribati to 93.92% in the Philippines.

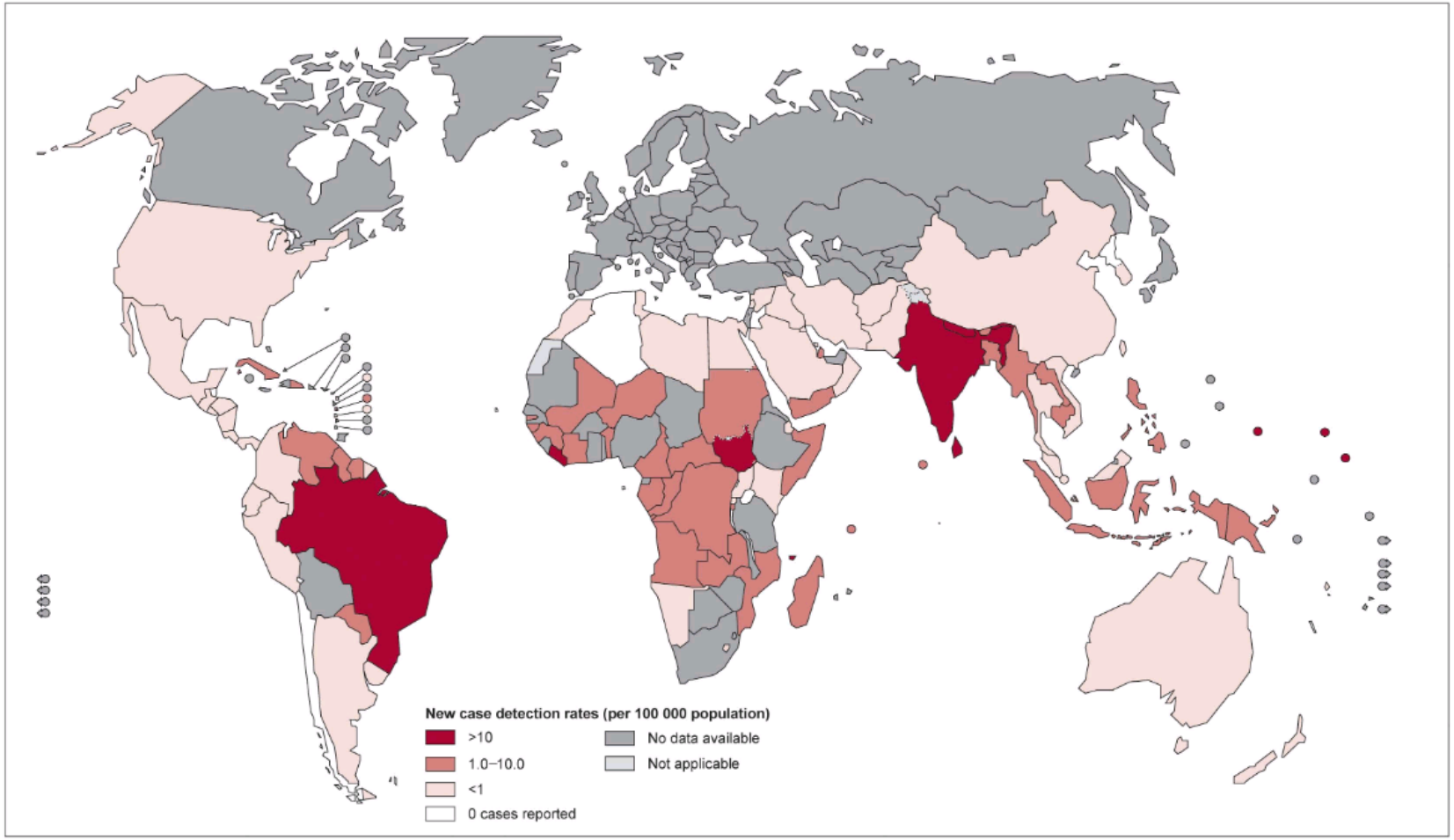
Leprosy prevalence rates, data reported to WHO as of January 2012



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Leprosy new case detection rates, data reported to WHO as of January 2012



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

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.

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.

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. 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. 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 perineural 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

246 *Mem Inst Oswaldo Cruz*, Rio de Janeiro, Vol. *107*(2): 246-253, March 2012

Histopathological examination of nerve samples from pure neural leprosy patients: obtaining maximum information to improve diagnostic efficiency

Sérgio Luiz Gomes Antunes[1]/+, Leila Chimelli[2], Márcia Rodrigues Jardim[1], Robson Teixeira Vital[1], José Augusto da Costa Nery[1], Suzana Corte-Real[3], Mariana Andréa Vilas Boas Hacker[1], Euzenir Nunes Sarno[1]

ELSEVIER SAUNDERS

NEUROLOGIC CLINICS

Neurol Clin 25 (2007) 115–137

Infectious Neuropathies

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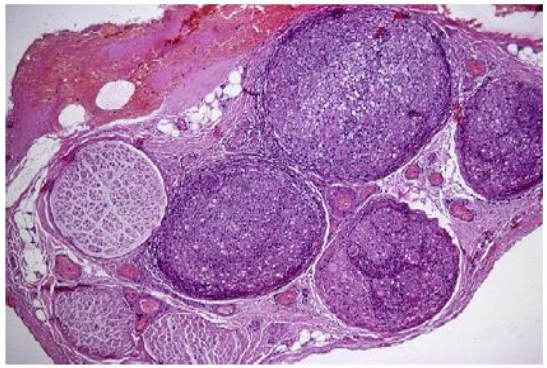


Fig. 4. Superficial peroneal nerve biopsy of a patient who has mononeuritis multiplex resulting from borderline-lepromatous leprous neuropathy. Note the important inflammatory infiltration that spares one fascicle, in keeping with the pattern of sensory loss observed in leprosy (hematoxylin-eosin staining).

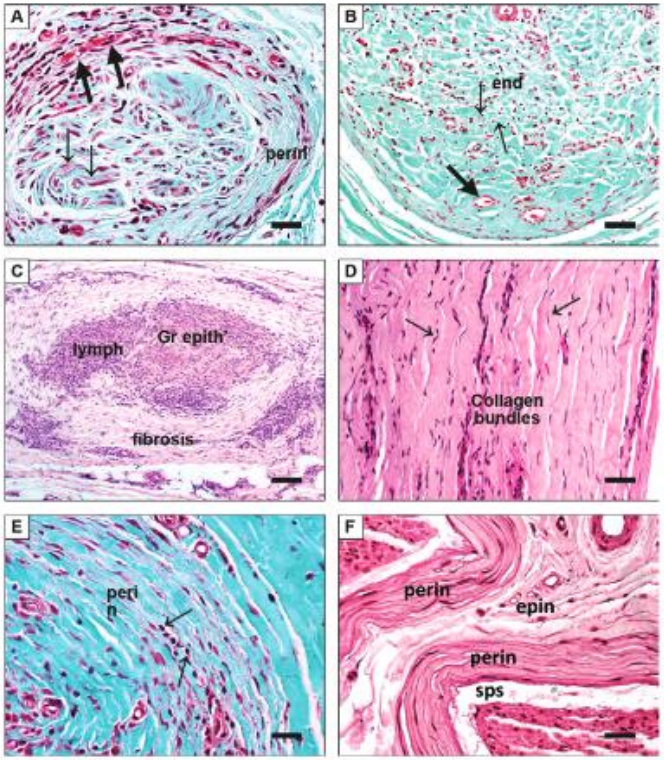


Fig. 1 A: one nerve fascicle showing perineurial enlargement (perin) and mononuclear inflammatory infiltrate partially surrounding perineurial microvessels (arrows). Small myelinated fibres (thin arrows) can be seen in the endoneurium (end) compartment. Gomori's trichrome. Bar = 40 µm; B: one nerve fascicle showing sparse mononuclear cells (thin arrows) spread throughout the endoneurium. Absence of myelinated fibres and presence of angiogenic vessels with thickened walls (thick arrows). Gomori's trichrome. Bar = 40 µm; C: one nerve fascicle showing an epithelioid granuloma (gr epith) surrounded by a collar of lymphocytes (lymph). Endoneurial fibrosis erasing the perineurial, endoneurial and epineurial boundaries can also be seen. Haematoxylin-eosin (H&E) staining. Bar = 80 µm; D: one nerve fascicle showing longitudinally-arranged parallel bundles of collagen fibres aligned with endoneurial fibroblasts (arrows) characterizing endoneurial fibrosis. H&E staining. Bar = 20 µm; E: one nerve fascicle showing perineurium and mononuclear inflammatory infiltrate among the perineurial layers (arrows). Gomori's trichrome. Bar = 20 µm; F: partial view of two nerve fascicles and intervening epineurium (epin) showing thickened perineurium and enlargement of subperineurial space (sps) with irregular microfibrillar material within. H&E. Bar = 20 µm.

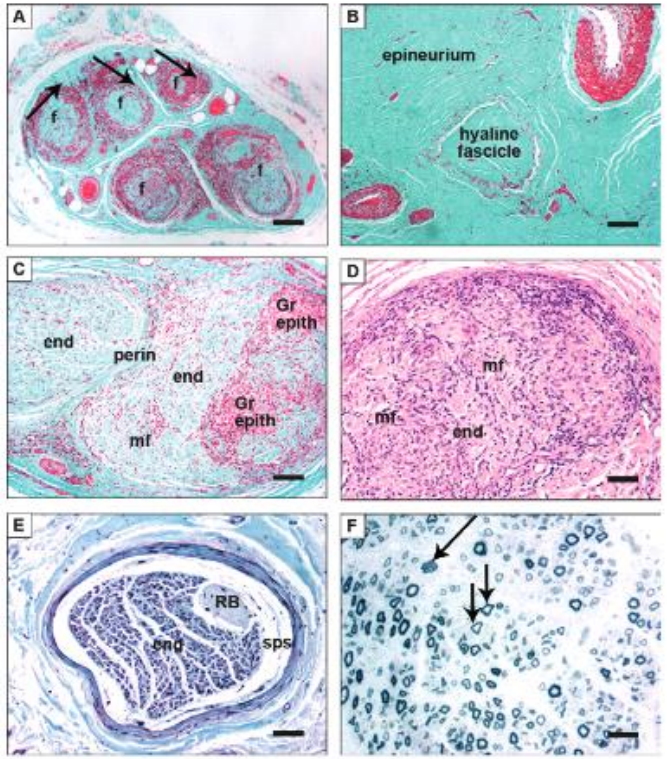


Fig. 2 A: cross section of a peripheral nerve showing five fascicles (f) with mononuclear inflammatory infiltrate surrounding a fibrotic endoneurial compartment (arrows) devoid of nerve fibres. Gomori's trichrome. Bar = 200 µm; B: a fibrotic nerve fascicle showing a hyaline aspect and no fibre. The epineurium is also densely fibrotic. Gomori's trichrome. Bar = 80 µm; C: two nerve fascicles divided by a perineurial septa (perin) show the absence of myelinated nerve fibres and an irregularly spreading focus of epithelioid granulomas (gr epith) in the endoneurium (end). Microfasciculation (mf) can be seen in the lower left quadrant of the same fascicle. Gomori's trichrome. Bar = 80 µm; D: one nerve fascicle showing mf in the end. mf are nest-like, round structures surrounded by perineurial cells containing nuclei and pink-stained material. Haematoxylin-eosin staining. Bar = 40 µm; E: one nerve fascicle showing enlargement of subperineurial space (sps) and microfibrillar material within. A Renaut body (RB) can be seen in the endoneurium. Gomori's trichrome. Bar = 40 µm; F: partial view of endoneurium showing a reduced number of large and small myelinated fibres, sprouting regenerating nerve fibres (long arrows) and few remyelinated fibres with a relatively thin myelin sheath (short arrows). Toluidine-blue staining. Bar = 20 µm.

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.

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.

Some authors recommend to combine the multidrug therapy with 60mg prednisone, with a gradual tapering over 5 months, to prevent further neurological damage

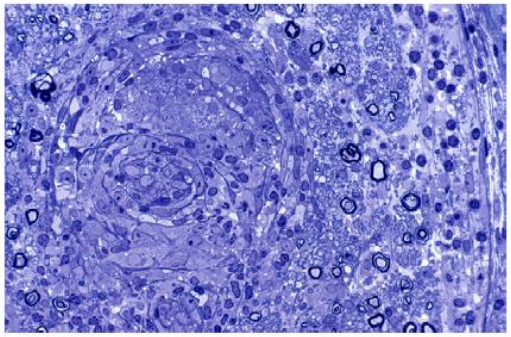
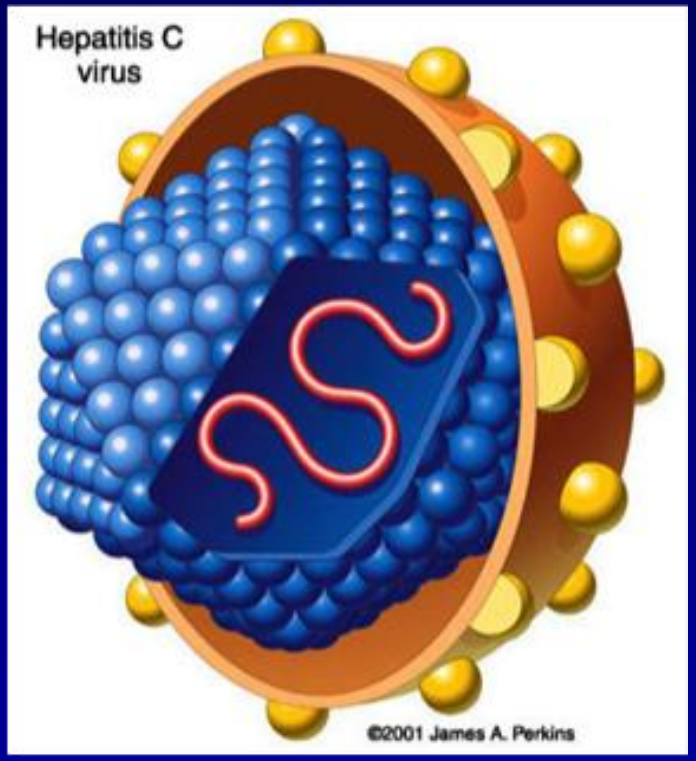
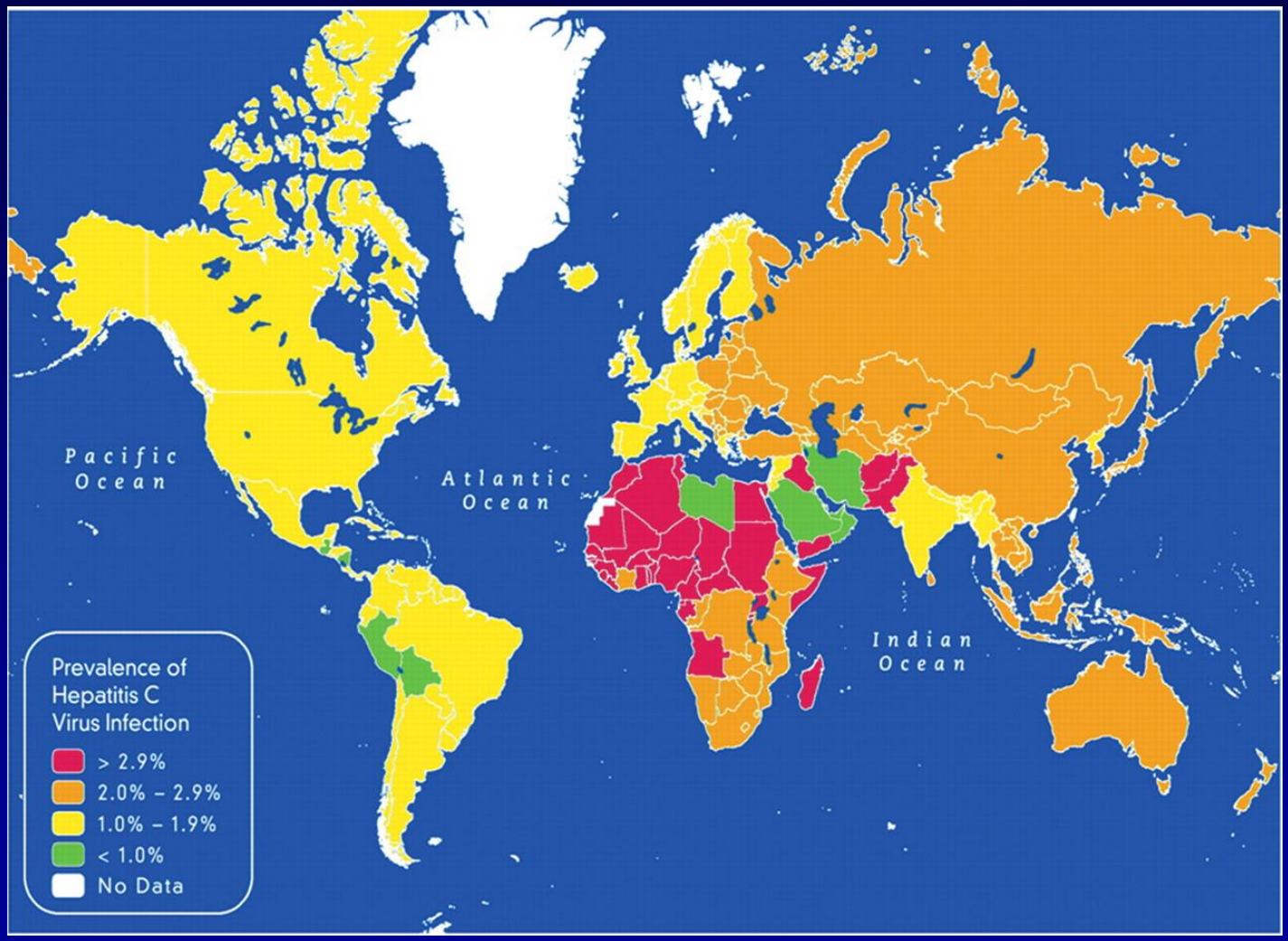


Fig. 5. Superficial peroneal nerve biopsy. Multifocal neuropathy in a patient treated for lepromatous leprosy for several months. Upgrade reversal reaction showing formation of a granuloma inside a nerve fascicle. Epon-embedded specimen (thionin blue staining).

HCV



Global prevalence of chronic hepatitis C virus infection



Francisco M. Averhoff et al. Clin Infect Dis. 2012;55:S10-S15

Clinical Infectious Diseases

Chronic infection with hepatitis C virus (HCV) is a growing global health issue affecting an estimated 170 million people. 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.

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. 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.

In patients without cryoglobulins, immune complexes or HCV-induced autoimmune mechanisms may play a pathogenic role in inducing vascular and perivascular inflammation.

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.

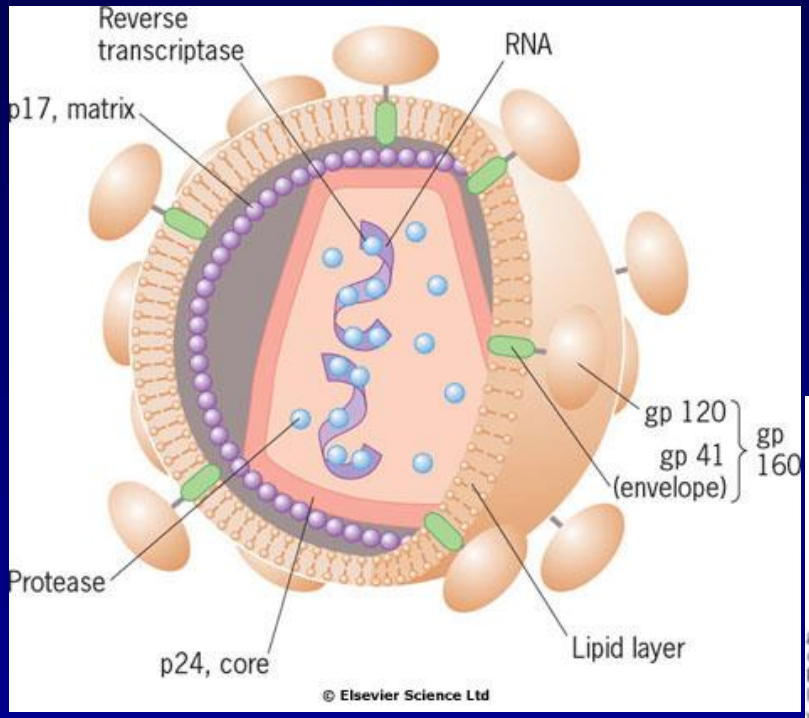
J Neurol. 2011 Jan;258(1):80-8. doi: 10.1007/s00415-010-5686-1. Epub 2010 Aug 4.

Sensory neuropathy in patients with cryoglobulin negative hepatitis-C infection.

Yoon MS[1], Obermann M, Dockweiler C, Assert R, Canbay A, Haag S, Gerken G, Diener HC, Katsarava Z.

In a series of 46 cryoglobulins-negative, HCV infected patients, Yoon et al. 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%).

HIV


Reverse transcriptase
RNA
p17, matrix
gp 120
gp 41 (envelope)
gp 160
Protease
p24, core
Lipid layer
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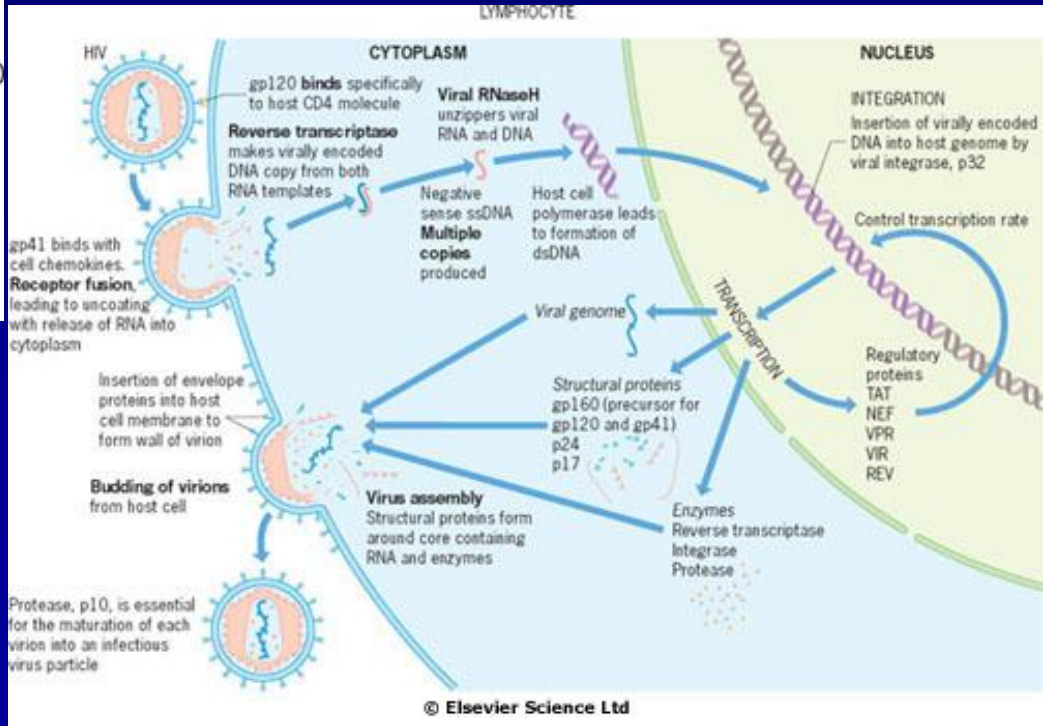
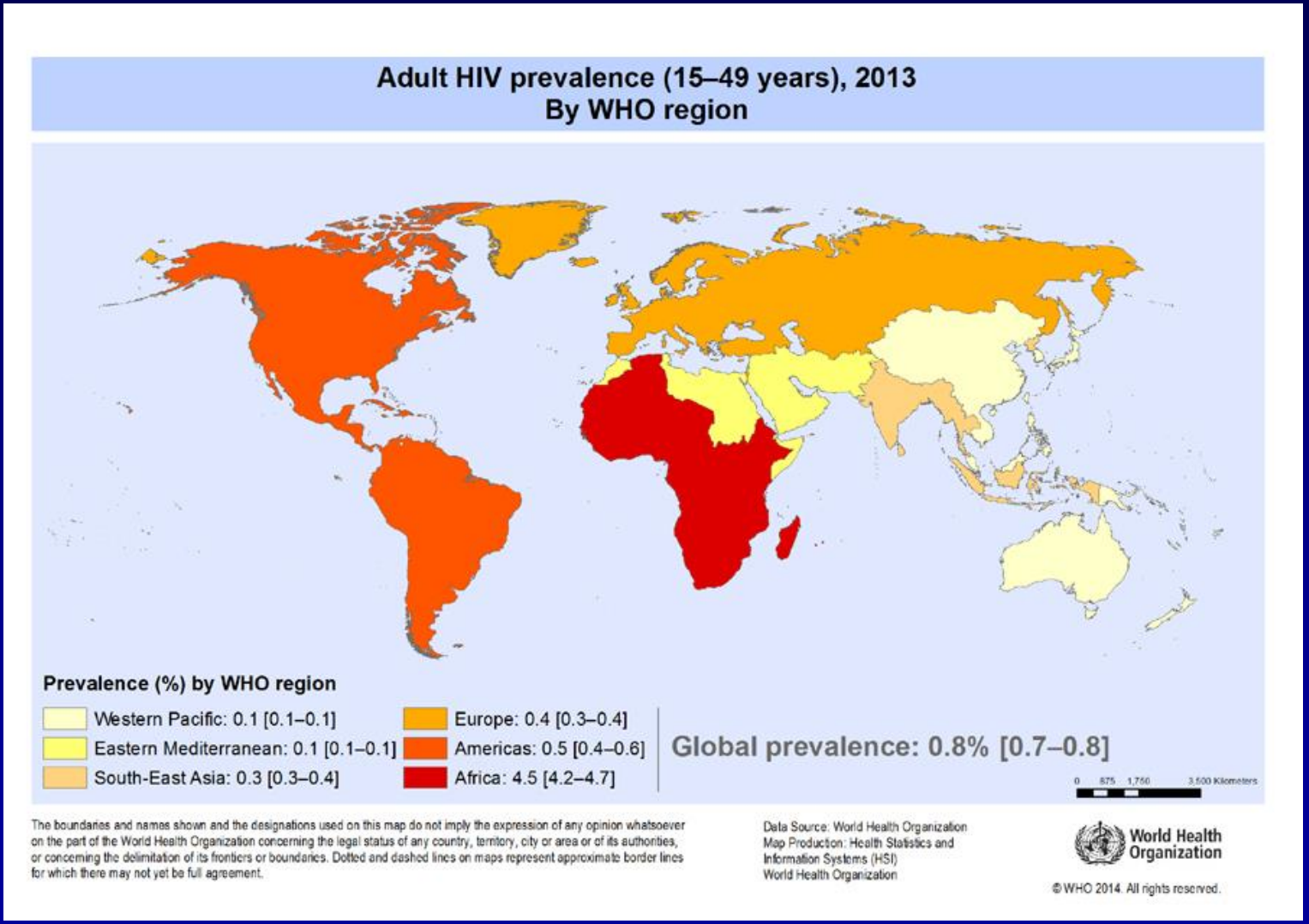

LYMPHOCYTE
HIV
CYTOPLASM
NUCLEUS
gp120 binds specifically to host CD4 molecule
Reverse transcriptase makes virally encoded DNA copy from both RNA templates
Viral RNaseH unzippers viral RNA and DNA
Negative sense ssDNA Multiple copies produced
Host cell polymerase leads to formation of dsDNA
INTEGRATION
Insertion of virally encoded DNA into host genome by viral integrase, p32
Control transcription rate
gp41 binds with cell chemokines. Receptor fusion, leading to uncoating with release of RNA into cytoplasm
Viral genome
TRANSCRIPTION
Regulatory proteins TAT NEF VPR VIR REV
Insertion of envelope proteins into host cell membrane to form wall of virion
Structural proteins gp160 (precursor for gp120 and gp41) p24 p17
Budding of virions from host cell
Virus assembly
Structural proteins form around core containing RNA and enzymes
Enzymes Reverse transcriptase Integrase Protease
Protease, p10, is essential for the maturation of each virion into an infectious virus particle
© Elsevier Science Ltd

- Globally, 35.0 million people were living with HIV at the end of 2013. An estimated 0.8% of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults living with HIV and accounting for nearly 71% of the people living with HIV worldwide.



Classificazione CDC dell'infezione da HIV

- A = asintomatico o poliadenopatia o malattia acuta durante seroconversione
- B = condizioni cliniche HIV correlate (vedi)
- C = condizioni cliniche proprie dell'AIDS
  - 1 CD 4 > 500 / mm^3
  - 2 CD 4 200-499
  - 3 CD 4 < 200

Classificazione CDC dell'infezione da HIV
B- condizioni cliniche HIV correlate

- Candidiasi orofaringea
- Sintomi generali
- Leucoplachia villosa orale
- Zoster di più di 1 dermatomero
- Porpora trombocitopenica
- Listeriosi
- Malattia infiammatoria pelvica (ascesso tubo-ovarico)
- Neuropatia periferica

Classificazione CDC dell'infezione da HIV
C- condizioni cliniche di AIDS

- Candidiasi (bronchi, polmone, esofago)
- carcinoma cervicale invasivo
- criptococcosi extrapolmonare
- criptosporidiosi cronica
- retinite CMV
- Encefalopatia HIV
- Ulcere croniche o bronchite, polmonite, esofagite da HSV
- Kaposi
- linfoma immunoblastico
- linfoma cerebrale

Classificazione CDC dell'infezione da HIV
C- condizioni cliniche di AIDS

- Mycobacterium avium complex disseminato
- Mycobacterium tb
- PCP
- Leucoencefalopatia multifocale progressiva
- Toxoplasmosi cerebrale
- Sepsi ricorrente da Salmonella
- Polmoniti ricorrenti
- Cachessia HIV

Distal sensory neuropathies

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 g 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

	HIV-associated differential diagnosis
Sensory polyneuropathy	
Symmetrical painful distal sensory polyneuropathy	Distal sensory polyneuropathy, antiretroviral toxic neuropathy, diffuse infiltrative lymphocytosis syndrome
Symmetrical non-painful distal sensory polyneuropathy	Asymptomatic distal sensory polyneuropathy
Sensorimotor polyneuropathy	
Symmetrical motor-predominant polyradiculoneuropathy	Acute inflammatory demyelinating polyneuropathy*, diffuse infiltrative lymphocytosis syndrome, chronic inflammatory demyelinating polyneuropathy, vasculitis
Symmetrical distal sensorimotor polyneuropathy	Advanced distal sensory polyneuropathy
Lumbosacral radiculopathy†	Tuberculosis‡, diffuse infiltrative lymphocytosis syndrome, cytomegalovirus, herpes simplex virus types 1 and 2, varicella zoster virus, lymphoma
Brachial radiculopathy†	Lymphoma, immune-mediated
Asymmetrical sensory or sensorimotor polyneuropathy	Segmental acute or chronic inflammatory demyelinating polyneuropathy, lymphoma, diffuse infiltrative lymphocytosis syndrome, vasculitis
Motor polyneuropathy	
Symmetrical motor polyradiculoneuropathy	Acute or chronic inflammatory demyelinating polyneuropathy
Lower-motor-neuron syndromes	Diffuse lower-motor-neuron syndromes, pure motor lumbosacral polyradiculopathy, brachial diplegia
Mononeuropathy	
Cranial mononeuropathy	HIV seroconversion, lymphoma, diffuse infiltrative lymphocytosis syndrome, vasculitis, varicella zoster virus, herpes simplex virus type 1, chronic meningitis (tuberculous, syphilitic, cryptococcal)
Other	Entrapment

*Also described as immune reconstitution inflammatory syndrome. †Also reported with involvement of the respective plexus—ie, lumbosacral radiculoplexopathy and brachial radiculoplexopathy. ‡We have noted cases of immune reconstitution inflammatory syndrome in our practice, but they have not been reported.

Table 1: **Clinicoanatomical presentations of peripheral nervous system manifestations of HIV infection**

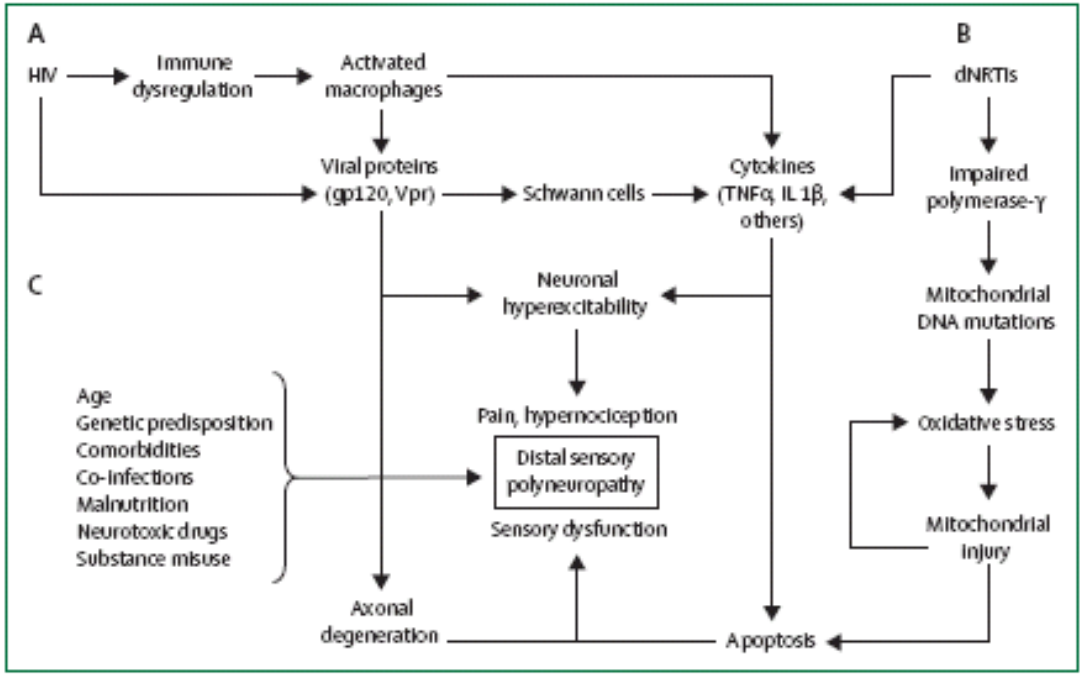


Figure 2: Pathogenesis of distal sensory polyneuropathy

(A) HIV-infected macrophages resident in or infiltrating the dorsal root ganglion become activated and release proinflammatory and pronociceptive cytokines—eg, TNFα and IL1β.[27] Activated macrophages provide a source of viral surface gp120, which, when bound to chemokine receptors on Schwann cells, initiates an inflammatory cascade leading to cytokine-mediated neuronal apoptosis and axonal degeneration.[23,28] Macrophages might also provide a source of other viral proteins acting in a similar manner.[30] By acting directly on axons, gp120 induces further axonal degeneration independently of inflammatory intermediaries.[29] Binding of gp120, Vpr, and possibly other viral proteins to neuronal chemokine receptors results in neuronal hyperexcitability and painful symptoms.[24,31] (B) dNRTIs inhibit mitochondrial polymerase-γ, the enzyme that catalyses replication and repair of mitochondrial DNA, resulting in accumulation of mitochondrial DNA mutations, defective respiratory chain subunits, impaired oxidative phosphorylation, and oxidative stress, driving apoptotic processes in distal axons.[32] In the dorsal root ganglion, dNRTIs are associated with upregulation of chemokines and chemokine receptors, contributing to the inflammatory background.[32] (C) The final phenotype of distal sensory polyneuropathy is characterised by pain and nerve dysfunction, to which other host and comorbid factors can contribute synergistically. dNRTIs=dideoxynucleoside reverse transcriptase inhibitors. Gp120=glycoprotein 120. TNFα=tumour necrosis factor α. IL1β=interleukin 1β. Vpr=viral protein R.

Panel 1: Drugs that can cause neuropathy

- Antiretrovirals
  - Stavudine
  - Didanosine
  - Protease inhibitors
- Antimicrobials
  - Isoniazid
  - Ethambutol
  - Metronidazole
  - Chloramphenicol
  - Dapsone
  - Amphotericin B
- Antineoplastics
  - Cisplatin
  - Vincristine
  - Vinblastine
- Others
  - Phenytoin
  - Corticosteroids
  - Herbal drugs (might contain neurotoxic contaminants)

Panel 2: Causes of sensory neuropathies in the general population

- Metabolic disorders
  - Diabetes or prediabetes
  - Metabolic syndrome
  - Disorders of thyroid function
  - Renal failure
- Nutritional deficiencies
  - Vitamin B12
  - Thiamine
  - Vitamin B6*
- Paraproteinaemic syndromes
- Paraneoplastic syndromes
- Sjögren's syndrome
- Toxic neuropathies—eg, alcohol
- Hepatitis C
- Coeliac disease
- Inherited neuropathies

*In the context of isoniazid treatment. Chronic pyridoxine supplementation in excess of 2 g per day might be neurotoxic.

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.

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.

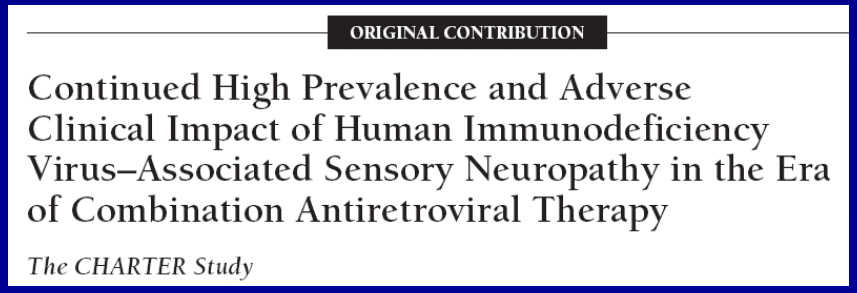
	Mechanism of action	Randomised controlled trial	Efficacy	Comments
Antidepressants				
Amitriptyline	Central inhibition	Shlay et al[59]	Not superior to comparator*	Titration might be necessary to optimise response
Anticonvulsants				
Gabapentin	Calcium channel stabilisation	Hahn et al[57]	Not superior to placebo†	High doses might be needed; drowsiness can occur
Lamotrigine	Sodium channel stabilisation	Simpson et al[60]	Superior to placebo for secondary outcomes in participants receiving dNRTIs	Slow titration reduces incidence of rash
Pregabalin	Calcium channel stabilisation	Simpson et al[61]	Not superior to placebo‡	Swelling of legs
Topical agents				
Capsaicin patch	Desensitisation by activation of TRPV1 receptors	Simpson et al[62] Clifford et al[63]	Superior to low-concentration comparator Superior to low-concentration comparator in secondary analyses	Expensive
Disease-modifying agents				
Recombinant human NGF	Neuroprotective and neuroregenerative	McArthur et al[64]	Superior to placebo	Not currently available
Acetyl-L-carnitine	Easing of fatty acid transport into mitochondria	Youle et al[65]	Superior to placebo in assessable study population only (non-ITT)	Available as a nutritional supplement
Other				
Cannabis	Modulation of pain signals	Ellis et al[66]	Smoked cannabis superior to smoked inactive cannabis	Legal and regulatory issues limit access; smoking-related health issues

Additionally, mexilitine, capsaicin cream, prosaptide, and peptide T have been trialled, all with negative results (systematically reviewed in Phillips et al[58]). Trials of lidocaine patch, memantine, and nimodipine were excluded from the same review because of issues with their methods. dNRTIs=dideoxynucleoside reverse transcriptase inhibitors. ITT=intention to treat. *The comparator group comprised participants receiving placebo and those receiving placebo plus acupuncture or control acupuncture. †Significant reductions in pain and sleep scores during 4 weeks were noted in the gabapentin but not in the placebo group. ‡Greater improvement in pain scores for the pregabalin group at some timepoints. Participants in the pregabalin group with prominent pinprick hyperalgesia had greater improvement in pain scores during the study than did those receiving placebo.

***Table 3*: Investigated treatments for painful distal sensory polyneuropathy**

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

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, 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/ml were significantly more likely to have a sensory neuropathy than were those who started cART before this level of immunosuppression.


ORIGINAL CONTRIBUTION

Continued High Prevalence and Adverse Clinical Impact of Human Immunodeficiency Virus–Associated Sensory Neuropathy in the Era of Combination Antiretroviral Therapy

The CHARTER Study

AIDS. 2011 Apr 24;25(7):919-28. doi: 10.1097/QAD.0b013e328345889d.

Peripheral neuropathy in HIV: prevalence and risk factors.

Evans SR[1], Ellis RJ, Chen H, Yeh TM, Lee AJ, Schifitto G, Wu K, Bosch RJ, McArthur JC, Simpson DM, Clifford DB.

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.

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/ml.

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.

Symmetrical sensorimotor polyneuropathies

GBS

In HIV-infected people, the disorder is thought to occur more frequently in the context of a preserved rather than a depleted CD4 cell count, or as an HIV seroconversion illness.. However, in a small retrospective series, four of ten patients had fewer than 200 CD4 cells per µL and features of AIDS. Although rare cases have occurred in patients with fewer than 50 CD4 cells per µL, a demyelinating polyneuropathy with profound immunosuppression would suggest cytomegalovirus infection, and should be treated accordingly.

CSF fi ndings in HIV-associated acute inflammatory demyelinating polyneuropathy are similar to those noted in patients who are not infected with HIV; however, pleocytosis can occur, which should alert the clinician to underlying HIV infection. CSF protein concentrations are often raised, with fewer than 10 cells per µL, but up to 50 cells per µL is acceptable for diagnosis in the context of HIV. Neurophysiological findings of delayed or absent F-wave responses early on or prolonged distal latencies, or both, and slowed conduction velocities in the later stages, are similar to those noted in patients with acute infl ammatory demyelinating polyneuropathy who do not have HIV infection.

Patients typically respond to treatment and might recover spontaneously. Treatment does not differ on the basis of HIV serostatus, and includes use of plasmapheresis and intravenous immunoglobulin

GBS or similar syndromes occurring within 2 months of initiation of cART and associated with features of immune reconstitution inflammatory syndrome have also been reported

Diffuse infiltrative lymphocytosis syndrome

Nerve involvement in diffuse infiltrative lymphocytosis syndrome most often manifests as an acute or subacute painful sensorimotor polyneuropathy. In most instances, the neuropathy is distal and symmetrical; however, in a third of patients the neuropathy might be focal at onset and progress to a multifocal and then symmetrical neuropathy. Less often, the neuropathy in diff use infiltrative lymphocytosis syndrome can be painful, distal, symmetrical, and purely sensory.

Diff use infiltrative lymphocytosis syndrome was first described in HIV-infected patients presenting to rheumatological services with so-called sicca symptoms and parotidomegaly reminiscent of Sjogren's syndrome.

Diagnostic criteria include bilateral salivary gland involvement, xerostomia of greater than 6 months' duration, and histological confi rmation of salivary or lacrimal gland CD8 lymphocytic infi ltration. Not all patients with diff use infiltrative lymphocytosis syndrome have sicca symptom or parotidomegaly, but characteristically they have a circulating CD8 hyperlymphocytosis

(more than 1000 cells per μL), although the syndrome has been reported in patients with lower cell counts. Widespread CD8 lymphocyte infiltration of lymph nodes, viscera, and, less frequently, peripheral nerves is noted.

In the pre-cART era, diff use infi trative lymphocytosis syndrome was reported in 3–8% of HIV-infected patients, although this might have been an underestimate.

The prevalence of diffuse infi trative lymphocytosis syndrome has decreased since the introduction of cART, and patients on cART seem to have less extraglandular involvement, particularly of the lungs, than do those not on cART.

The range of neuropathies in diff use infi ltrative lymphocytosis syndrome is poorly defi ned, and thus diagnosis should be considered in HIV-infected patients presenting with painful neuropathies.

In diffuse infiltrative lymphocytosis syndrome, CD4 cell counts are typically preserved.

Neurophysiological studies most often show axonal changes. Substantially increased protein concentrations and mild lymphocytic pleocytosis might be noted in the CSF. Nerve biopsies show dense perivascular CD8 infiltration in the epineurium and endoneurium without fibrinoid necrosis, which is in keeping with a nonnecrotising vasculitis. That diff use infiltrative lymphocytosis syndrome is a host response to HIV infection has been postulated, with proliferation of MHC-restricted, antigen-driven oligoclonal CD29–CD8 T cells, which infiltrate tissues and suppress viral replication.

The neuropathy usually responds well to cART (if treatmentnaive) or prednisone, or both, and some patients recover completely

HIV-associated neuromuscular weakness syndrome

This is a subacute progressive weakness that is associated with hyperlactataemia and stavudine exposure and presents as a severe, symmetrical, predominantly motor axonopathy with prominent leg involvement. Associated systemic features include nausea, vomiting, weight loss, and hepatomegaly.

Stavudine doses were not noted in early descriptions, but the syndrome has not been reported since the standard daily dose was lowered from 80 mg to 60 mg. Neuromuscular weakness syndrome can be fatal, but most patients recover after stavudine discontinuation.

CIDP

CIDP differs from the acute disorder in that it has a more insidious progression (more than 8 weeks) and might relapse and remit. It frequently presents as a symmetrical,

mainly motor neuropathy in which both proximal and distal weakness are more prominent than are sensory findings, but can also evolve asymmetrically. Tendon reflexes are reduced or absent. Sensory complaints include dysaesthesiae or deep limb pain. Occasionally

involvement of the proximal root is predominant, in which case the disorder might be confused with a myopathy if the patient has no detectable sensory signs or symptoms.

CIDP is probably more common than the acute form. It can occur in early HIV infection, but more frequently occurs in moderately advanced disease.

Neurophysiological tests might confirm demyelinating features such as those described for the acute disorder, but could show only subtle slowing of proximal conduction—eg, delayed F-wave responses or even mixed demyelinating and axonal features.

Protein concentrations in the CSF are generally raised, with less than 50 cells per μL. CSF

analysis is useful in exclusion of infective or neoplastic causes, especially when patients have fewer than 200 CD4 cells per μL. Importantly, lymphoma and diff use infiltrative lymphocytosis syndrome neuropathy can mimic CIDP.

Treatment includes plasma exchange, intravenous immunoglobulin, or corticosteroids, and patients often have excellent responses. Initiation of cART is very important.

Other distal axonal sensorimotor polyneuropathies

In the pre-cART era, patients with advanced immunodeficiency, cachexia, and distal sensorimotor painful polyneuropathies were reported. Such cases are still noted in settings with high disease burden before initiation of cART, and probably represent a severe form of distal sensory polyneuropathy. Electrodiagnostic and pathological studies show motor and sensory axonopathy. Treatment with cART and other supportive measures should be initiated.

Painful immune-mediated vasculitic and inflammatory neuropathies can initially manifest as mononeuritis multiplex, but progress to symmetrical (or asymmetrical) polyneuropathies before clinical presentation. In low-income countries, a nerve biopsy to secure a diagnosis of vasculitis might be difficult. A trial of immunomodulation with corticosteroids or intravenous immunuglobulin could be therapeutic provided that the patient has no contraindications and is not substantially immunosuppressed. Initiation of cART is important to consider because immune dysregulation can contribute to pathogenesis.

Asymmetrical sensorimotor polyneuropathies

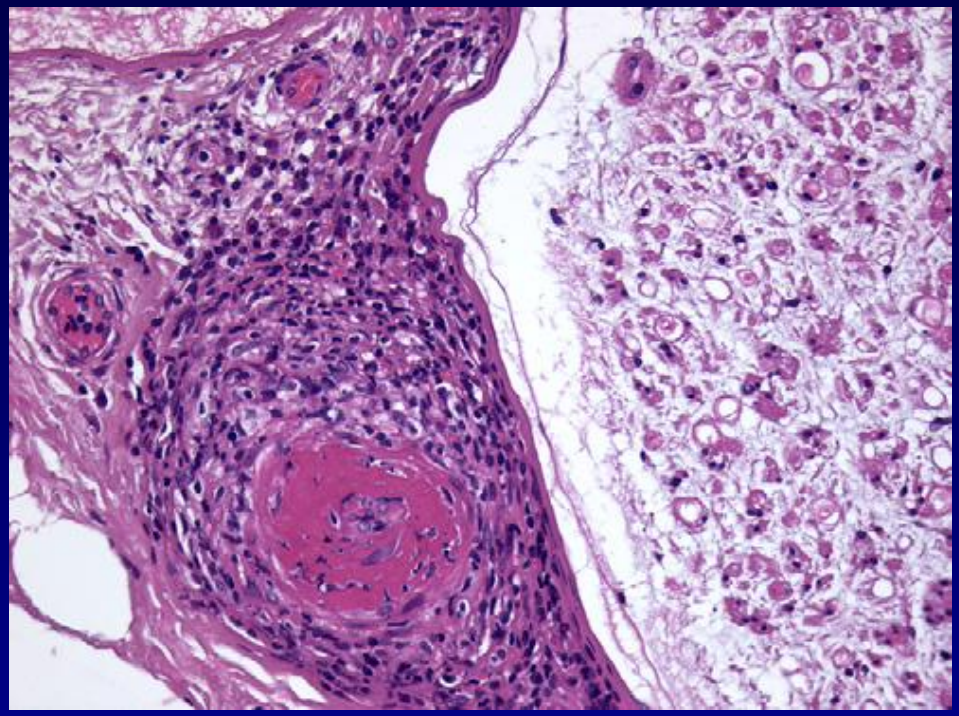
- **Atypical (segmental) variants of acute and chronic inflammatory demyelinating polyneuropathies**

- **Others**

Infiltrative or vasculitic neuropathies can manifest from onset as asymmetrical sensorimotor neuropathies or begin with the acute involvement of single nerves (including cranial nerves) in the pattern of mononeuritis multiplex. A painful asymmetrical or symmetrical polyneuropathy with focal onset, preservation of deep tendon jerks in unaffected nerve territories, and electrodiagnostic features of multifocal axonopathy in a patient with preserved immune function suggests immune-mediated pathogenesis. Joints and skin might be implicated in vasculitic neuropathies.

In people coinfected with HIV and hepatitis C virus, cryoglobulinaemic vasculitis is a possible diagnosis. Nerve biopsies might show infl ammatory infiltrates or vasculitis. Prednisone significantly improves pain within a few weeks, and immune restoration with cART might be an important adjunctive therapy.

In patients with advanced immunodefi ciency (fewer than 50 CD4 cells per μL), cytomegalovirus infection or lymphomatous infi ltration of nerves and roots might present as mononeuritis multiplex rapidly progressing to an asymmetrical axonal or, less often, demyelinating neuropathy (even if the results of analyses of the CSF are normal).



HIV multifocal neuropathy. Necrotizing arteritis of an epineural artery of the superficial peroneal nerve biopsy sample. Note axonal degeneration of the nerve fibers of the neighboring fascicle (hematoxylin-eosin staining).

Signs confined to leg

Lumbosacral radiculopathy presents with rapidly progressive weakness of both legs. Symptoms of urinary retention or incontinence are usually but not invariably present. Although clinical overlap is apparent between this phenotype and that of an evolving ascending polyradiculopathy, we discuss presentations confi ned to the lumbosacral nerve roots (or plexus). Different causes have been identified, dependent on the degree of immune dysfunction.

Cases of subacute motor lumbosacral radiculopathy (without implication of the urinary sphincter) that developed during several weeks were previously reported in immunocompetent patients as an early manifestation of HIV infection; these patients recovered spontaneously after several weeks and respond to steroids.

An unusual presentation of painful, weak legs, which was thought to be due to lumbar canal lipomatosis resulting from indanivir-associated central fat redistribution, has been reported; the syndrome resolved when indanivir was withdrawn.

A CD8-infiltrative lumbosacral radiculopathy (so-called focal diffuse infiltrative lymphocytosis syndrome) was described. The patient recovered on cART.

In regions where co-infection with HIV and *M tuberculosis* is prevalent, variations of lumbosacral radiculopathy caused by tuberculous meningitis can occur in patients who are moderately or severely immunocompromised. The development of lumbosacral radiculopathy during tuberculosis treatment (assuming that treatment is adequate and the infectious organism drug sensitive) might be the result of delayed adhesive arachnoiditis, but could be a lumbosacral radiculopathy–immune reconstitution inflammatory syndrome that is responsive to corticosteroids

Patients with paradoxical tuberculosis immune reconstitution inflammatory syndrome present with lumbosacral radiculopathy somewhat frequently and within weeks of initiation of cART, especially those with low CD4 cell counts.

An asymmetrical chronic lumbosacral radiculopathy due to Epstein-Barr virus- associated neurolymphomatosis has been reported in a moderately immunocompromised patient.

Lumbosacral polyradiculitis has been described (with or without HIV infection) as a result of reactivation of herpes simplex virus type 2 in the sacral dorsal root ganglia after genital herpes, and can progress to acute ascending necrotising myelitis

Visualisation of the nerve roots with a gadolinium MRI will exclude compressive lesions.

A case of syphilitic lumbosacral radiopathy has been reported

In patients with fewer than 50 CD4 cells per μL, cytomegalovirus infection can cause a rapidly progressive flaccid paralysis, often with sphincter involvement, due to inflammatory necrosis of the caudal roots. This disorder can be intensely painful. Electromyography shows acute motor axonal loss. The CSF frequently shows polymorph predominance, raised protein concentrations and low glucose concentrations; however, it might be normal. Cytomegalovirus can be detected in the CSF via PCR. Not delay empirical treatment in suspected cases because early treatment can result in excellent neurological recover → cART and intravenous ganciclovir

Signs confined to arms

Brachial plexus neuritis, with the typical acute onset of pain in the shoulder girdle followed by atrophy and weakness, has been described as an HIV seroconversion illness.

Pronounced neurological recovery with cART was noted in two patients

Pure motor syndromes

HIV-associated lower-motor-neuron syndromes seem more frequently reported than are amyotrophic lateral sclerosis or similar disorders. A review of patients in whom lower motor neurons were affected and who were described between 1988 and 2005 included nine patients with generalised involvement (CD4 cell counts ranged from 44/μL to 540/μL) and 11 with segmental involvement, in whom the weakness, atrophy, and fasciculations were confi ned either to the legs or arms (2/μL–560/μL). Segmental implication of the upper limbs was noted in seven of 11 patients. These patients might improve on cART.

Brachial amyotrophic diplegia that developed during 4 months was described in an HIV-infected man who had begun cART 4–6 weeks previously. His MRI showed signal hyperintensities in the region of the anterior cord grey matter, not unlike features described in polio-like syndromes. Although enterovirus in particular can cause acute flaccid paralysis, it has not yet been reported in association with HIV infection

Mononeuropathies

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.

Patients with several cranial neuropathies, including cases of bilateral optic neuropathies, who are infected with either HIV-1 or HIV-2 can improve after cART initiation..
Cranial mononeuropathies in patients who are substantially immunocompromised are frequently the result of meningeal infection or lymphomatosis. Tuberculous meningitis, which has a predilection for the basal cisterns, can produce cranial neuropathies

Reactivation of dormant varicella zoster virus in the dorsal root ganglia can occur (most frequently in trigeminal neuropathy or thoracic radiculopathy). Generally, zoster vesicles are present in the corresponding dermatome, but can be absent. Associated weakness in the affected myotome and myelopathy can accompany reactivation of varicella zoster virus. Treatment with aciclovir is indicated in HIV-infected patients. Ramsay-Hunt syndrome, consisting of facial palsy, vertigo, deafness, and vesicles in the ear or palate, should not be missed. Cases of monocular visual loss due to rapidly necrotising varicella zoster virus retinopathy being misdiagnosed and treated as inflammatory optic neuritis have been reported rarely; recognition that such patients are severely immunocompromised would have helped with early recognition

Entrapment neuropathies of the lateral cutaneous nerve of the thigh, common peroneal, median, and ulnar nerves are noted in hospital inpatients with advanced HIV disease.

Systemic disease—eg, diabetes mellitus, thyroid disease—can predispose to entrapment neuropathies, but whether a similar susceptibility is conferred by HIV infection is unknown.. Pressure care in ill patients would prevent these complications.

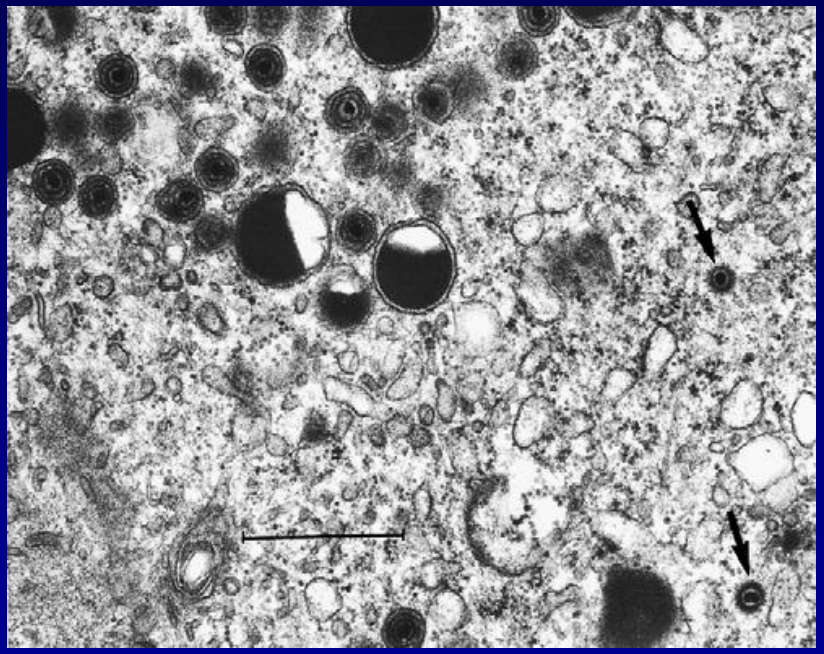
Cases of chronic inflammatory demyelinating poly neuropathy sometimes initially present as peroneal mononeuropathies

Autonomic neuropathies

Disabling autonomic manifestations, including postural hypotension and syncopes, paroxysmal arterial hypertension, sphincter disturbances, abnormal pupil reaction to light, and abnormal sweating, are reported in patients who have HIV.
These autonomic manifestations occur in association with sensorimotor neuropathy, sometimes at each recurrence of a relapsing demyelinating neuropathy or as an isolated manifestation of HIV neuropathy

Simple therapeutic measures include stopping of potentially exacerbating drugs (eg, tricyclic antidepressants), supplementation with salt, use of fludrocortisone **…**

CMV



Electron micrograph of a nerve specimen from a patient who has CMV neuropathy. Viruses (arrows) are found in nuclei and cytoplasm of macrophages, Schwann cells, and endothelial cells in PNs (uranyl acetate and lead citrate staining). Bar, 1 mm.

Cytomegalovirus (CMV) neuropathy is a treatable neuropathy that occurs at a late stage of immunodepression . CMV infection represents the most common viral opportunistic infection in AIDS, affecting 15% to 35% of patients who have AIDS. Its most common clinical manifestation is retinitis, with vision loss that often is bilateral. Peripheral neuropathy often is associated with retinitis or with symptomatic CMV infection of other organs (colitis or pancreatitis). The diagnosis of CMV neuropathy should not be missed, because it is accessible to specific treatment by ganciclovir or foscarnet.

The different patterns of CMV neuropathy include:

(1) the polyradiculopathic pattern .Within a few days or weeks, patients develop a sensorimotor deficit of the lower spinal roots or a complete cauda equina syndrome with sphincter disturbances, often associated with signs of CNS involvement and general signs and symptoms;

(2) the multifocal pattern, which may include symptomatic lesions of spinal roots, nerve trunks, and sometimes cranial nerve involvement;

(3) both patterns of peripheral neuropathy, which may be associated in the same patient;

(4) severe CNS manifestations, including necrotic myelitis and encephalitis; and

(5) the CSF abnormalities that can be observed in this setting, which include high protein content, pleocytosis with polymorphonuclear leucocytes reaction, and decreased CSF glucose [but CSF that can remain normal.

Nerve lesions associated with endoneurial CMV infection in patients who have AIDS range from occasional, scattered, cytomegalic cells with minimal surrounding inflammation to large areas of necrosis. A prominent neutrophilic cell response often is associated with mixed, axonal and demyelinative,

HTLV 1

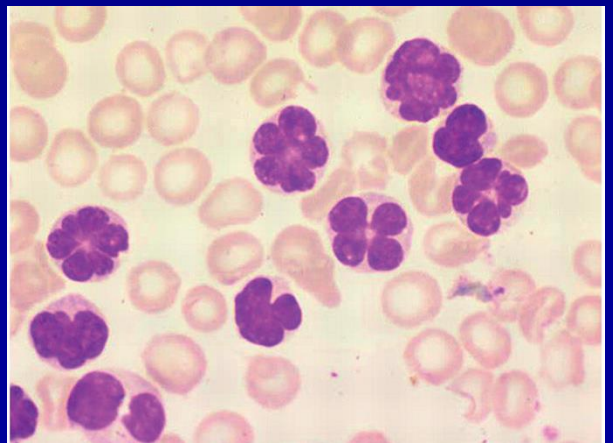
Although tropical myeloneuropathy primarily is a spinal cord disorder PN dysfunction has been noted in various studies. Roman and Roman noted absent ankle jerks in 28% of their patients from Colombia .Electrophysiologic evidence of PND has ranged from negligible to 32%.

PN involvement is characterized by mild sensorimotor, bilateral, deficit affecting distal lower limbs in association with sphincter disturbances and spinal cord involvement. In some patients, predominantly motor deficit and pyramidal tract involvement mimicks amyotrophic lateral sclerosis.

HTLV-1 infection also often is associated with sicca syndrome.

On nerve biopsy specimens, perineurial and perivascular inflammatory infiltrates with moderate axon loss and mixture of segmental demyelination and axonal degeneration can be observed , sometimes without inflammatory,infiltrates .

Demyelination and irregularity of the myelin sheath occur .



VZV

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.

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. 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 .

In the case of chronic active VZV infection as demonstrated by CSF analysis, intravenous treatment with acyclovir may be required.

Therapy: (Acyclovir), Valacyclovir or famcyclovir, Brivudin (in Europe) in immunocompetent

Acyclovir in immunocompromised

HSV 1 e HSV 2

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 .

Vestibular neuritis could also be caused by the reactivation of a latent HSV-1 infection,

As HSV-1 DNAhas been detected on autopsy by PCR in the human vestibular ganglia However, additional data are needed to confirm this hypothesis.

Therapy: Acyclovir

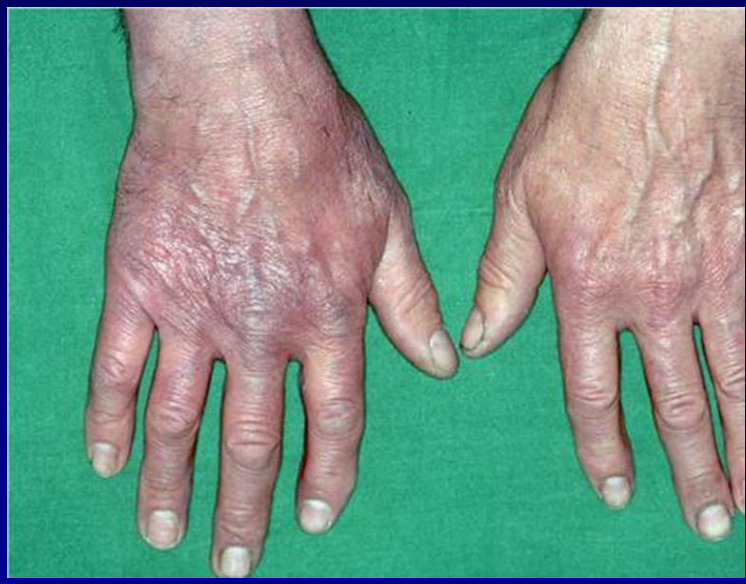
BORRELIA BURGDORFERI-RELATED NEUROPATHIES

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. An early, antibiotic-responsive demyelinating neuropathy has also been reported

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

Therapy: iv high dose penicillin, iv cephalosporins, oral doxycycline

Steroids are not recommended

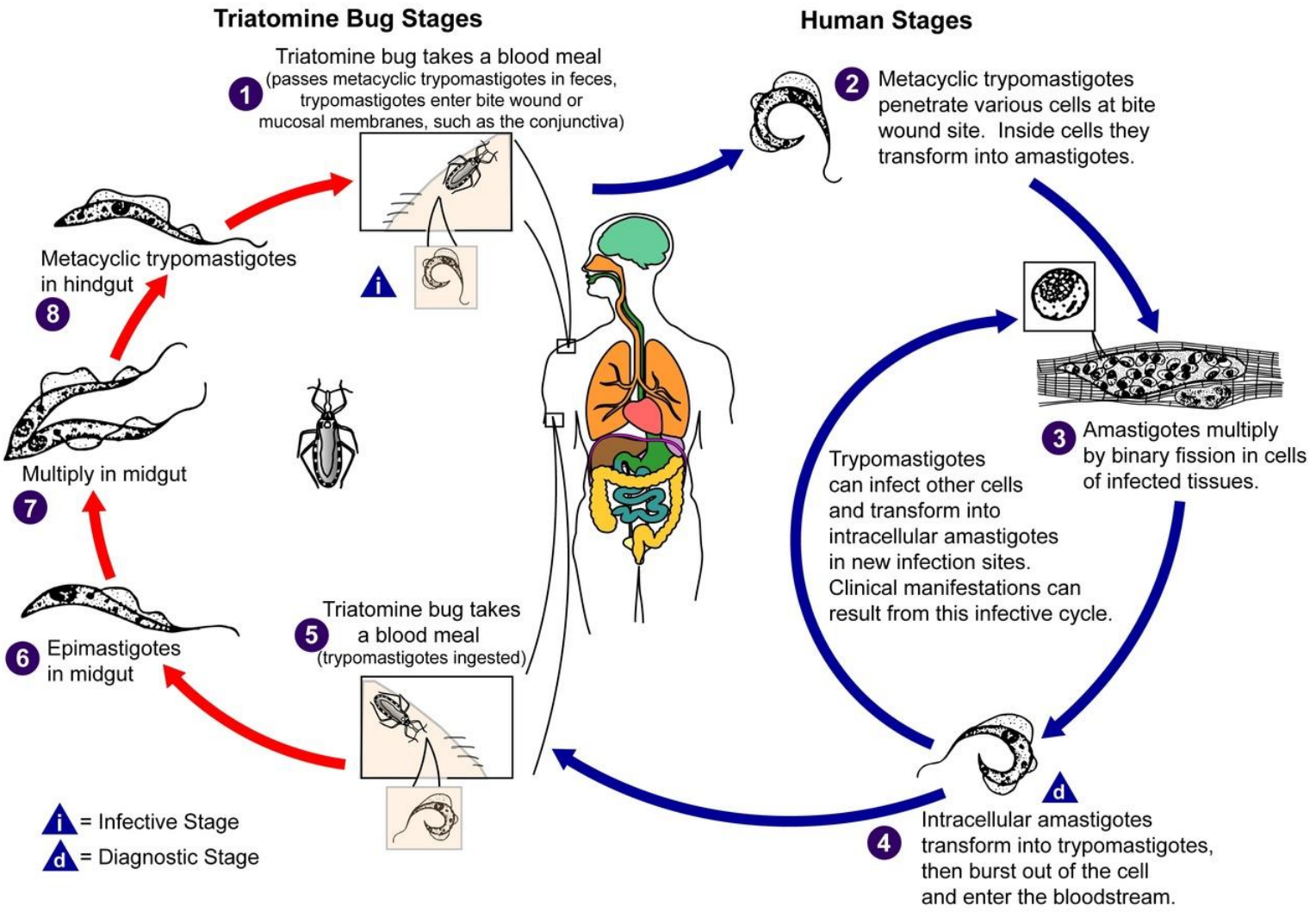
Chagas' disease

In Chagas' disease, infection is with the trypomastigote form of Trypanosoma cruzi by blood-sucking bugs of the Triatoma subfamily, Triatoma infestans. The metacyclic trypanosome in the bugs' feces penetrates minute skin abrasions, mucous membranes, or the conjunctiva. Other ways of transmission include congenital infection, laboratory accidents, organ transplantation, and blood transfusion. Chagas' disease is widespread in Latin America, where it affects several millions of people. After penetration in the host, the trypomastigote loses its flagellum, transforms into an amastigote, and multiplies in pseudocysts. Some amastigotes eventually may transform back into trypomastigotes and circulate in the blood.

Initial local multiplication of the parasite may result in local inflammation with heat, redness and swelling (chagoma), and enlargement of satellite lymph nodes. During this phase of active parasite multiplication, there is an intense interstitial inflammatory reaction with mononuclear cells. Later on, the parasite multiplication is suppressed by the cellular and humoral immune reaction of the host and becomes increasingly difficult to detect in the tissues. Ninety percent of the patients survive the acute phase but it is doubtful if the infection is ever eradicated. It usually remains asymptomatic throughout life in many of them, whereas others develop manifest symptoms after a period of years.

Trypanosomiasis, American (Chagas disease)

(Trypanosoma cruzi)



The neurologic manifestations are characterized mainly by the occurrence of the autonomic neuropathy at the chronic stage of the disease.

There is some regional differences in Chagas' disease because of the existence of different strains of T cruzi. The autonomic manifestations include cardiac and gastrointestinal involvement which are associated with inflammatory lesions of muscle and autonomic ganglia and nerves.

Peripheral neuropathy is not a prominent manifestation of Chagas' disease. It was recognized first in animal models . Although peripheral neuropathy seems common at a subclinical level in humans, especially on electrophysiologic examination at the acute and at the chronic phases of the disease the electromyogram abnormalities remain subtle.

Clinical neuropathy is uncommon , yet experimental models of Chagas' disease are useful

in understanding the pathophysiology of nerve and muscle lesions. In a series of investigations performed in the mouse model, the author has found that early localization of T cruzi occurred at the acute phase, associated with mild lesions. At the chronic stage of the disease, the amastigotes

are increasingly difficult to localize but immunostaining clearly shows the presence of T cruzi antigens in the nerve and muscle inflammatory infiltrates. Additionally, the author has been able to show that the endoneurial granulomas were the result of a delayed-type hypersensitivity

reaction . Nifurtimox and Benznidazole are used at the acute stage but are less active at the chronic stage. Only symptomatic treatment can be offered at the chronic stage

Peripheral neuropathies can result from several infective agents, ranging from viruses, especially retroviruses, to parasites and bacilli. Leprosy, which often is considered a disorder of the past, is still common in some geographic areas, especially in Africa, South America, and Asia. An increasing number of cases of neuropathies occurs in patients who have HIV or Lyme disease.

The important point is that all these neuropathies are treatable and often preventable


HOPE


"If you want to go fast,
go alone.
If you want to go far,
go together."
-African Proverb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