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REVIEW

Infectious diseases causing autonomic dysfunction

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Abstract

Objectives To review infectious diseases that may cause autonomic dysfunction.

Methods Review of published papers indexed in medline/embase.

Results Autonomic dysfunction has been reported in retrovirus (human immunodeficiency virus (HIV), human T-lymphotropic virus), herpes viruses, flavivirus, enterovirus 71 and lyssavirus infections. Autonomic dysfunction is relatively common in HIV-infected patients and heart rate variability is reduced even in early stages of infection. Orthostatic hypotension, urinary dysfunction and hypohidrosis have been described in tropical spastic paraparesis patients. Varicella zoster reactivation from autonomic ganglia may be involved in visceral disease and chronic intestinal pseudo-obstruction. Autonomic and peripheral nervous system dysfunction may happen in acute tick-borne encephalitis virus infections. Hydrophobia, hypersalivation, dyspnea, photophobia, and piloerection are frequently observed in human rabies. Autonomic dysfunction and vagal denervation is common in Chagas disease. Neuronal depopulation occurs mainly in chagasic heart disease and myenteric plexus, and megacolon, megaesophagus and cardiomyopathy are common complications in the chronic stage of Chagas disease. Parasympathetic autonomic dysfunction precedes left ventricle systolic dysfunction in Chagas disease. A high prevalence of subclinical autonomic neuropathy in leprosy patients has been reported, and autonomic nerve dysfunction may be an early manifestation of the disease. Autonomic dysfunction features in leprosy include anhidrosis, impaired sweating function, localised alopecia ,and reduced heart rate variability. Urinary retention and intestinal pseudo-obstruction have been described in Lyme disease. Diphtheritic polyneuropathy, tetanus and botulism are examples of bacterial infections releasing toxins that affect the autonomic nervous system.

Conclusions Autonomic dysfunction may be responsible for additional morbidity in some infectious diseases.

Keywords Autonomic dysfunction · Chagas disease · Flavivirus · Infectious diseases · Retroviruses

Introduction

Although less frequent compared to inflammatory and immune-mediated disorders, infectious diseases may also affect the autonomic nervous system. There are several pathogenic mechanisms that explain why infections can induce autonomic dysfunction, including the direct invasion of the central nervous system, the involvement of the peripheral autonomic system, and a toxin-mediated-effect. Immune-mediated mechanisms occurring during the para- or post-stage of an infection is a well-known trigger in acute transverse myelitis and Guillain–Barre syndrome, and also in some acute autonomic neuropathies (Table 1) [1].

Dysfunction of autonomic nervous system can occur as a complication of acute meningitis or meningoencephalitis, and diffuse brain edema and medulla oblongata impairment may affect the main autonomic centers [2]. However, several specific pathogens can compromise the autonomic nervous system in the context of a specific systemic infection not related to a meningo-encephalitic process (Table 2).

The objective of this paper is to review the pathogens that can affect the autonomic nervous system, particularly the cardiovascular autonomic system, of which Chagas disease is a good example. In addition, a review of the most

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Table 1 Main aetiologies of autonomic neuropathies

Acute autonomic neuropathies
Immune-mediated autonomic neuropathy
Auto-immune ganglionopaties
Guillain–Barre syndrome
Pandysautonomias of unknown origin
Paraneoplastic autonomic neuropathy
Infectious diseases: botulism
Drug- and toxin-related autonomic neuropathies
Chronic autonomic neuropathies
Metabolic causes: diabetes, uremia
Amyloidosis
Degenerative diseases: multiple system atrophy/Shy Drager
Immune-mediated disorders/connective tissue disease
Infectious diseases: HIV, lepra, Chagas disease
Others
Syringomyelia/syringobulbia
Spinal cord injury
Surgery: vagotomy

common infectious diseases that may cause autonomic dysfunction will be presented.

Medline and Embase searches were conducted using the terms "autonomic dysfunction", "autonomic nervous system", and "infectious diseases" or "virus infection", "Chagas disease", "flavivirus", "herpes viruses", "Lyme", "bacterial infections", among others. Papers about specific infections causing autonomic nervous system impairment were reviewed, and the reference lists from research and review articles were also examined. English, Spanish, Portuguese and Japanese language journals were included in the search. A critical appraisal of the literature was performed.

Table 2 Main infectious causes of autonomic dysfunction

Virus
HIV
HTLV-1
Herpes viruses
Tick-borne encephalitis virus
West Nile virus
Rabies virus
Enterovirus 71
Bacteria
Borrelia burdorgferi
Mycobacterium lepra
Corynebacterium diphteriae
Clostridium tetani
Clostridium botulinum
Parasite
Trypanosoma cruzi (Chagas disease)
Prion
Fatal familial insomnia

Human immunodeficiency virus (HIV)

Approximately 37 million people are living with HIV, with 70% of reported cases occurring in Africa, mostly in the Sub-Saharan region. Autonomic dysfunction is relatively common in HIV-infected patients. Frequent autonomic symptoms include orthostatic intolerance, secretomotor and gastrointestinal dysfunction, and male sexual dysfunction, and blunted blood pressure response to sustained handgrip has also been described [3, 4].

Symptomatic autonomic neuropathy in HIV-infected people has been associated with increased morbidity [5]. Before the era of highly active antiretroviral therapy, autonomic dysfunction was associated with longer duration of the disease and uncontrolled HIV viremia. However, virologically suppressed HIV patients on combined antiretroviral therapy still present autonomic dysfunction symptoms.

In a case–control study, 48 HIV-positive patients and 22 HIV-negative controls responded the 169-item Autonomic Symptom Profile which evaluates 11 domains of autonomic function; in addition, autonomic dysfunction was assessed by standardized tests for cardiovagal, adrenergic and sudomotor functions [3]. HIV patients on stable combined antiretroviral therapy reported higher frequency of autonomic symptoms in comparison with HIV-negative controls, particularly in urinary, sleep, gastroparesis, secremotor, and pupillomotor domains, and in male sexual dysfunction. Moderate autonomic neuropathy, as defined by a Composite Autonomic Scoring Scale between 4 and 6, was detected in 24% of patients.

Heart rate variability (HRV) spectral analysis is a sensitive method to assess cardiovascular autonomic function and to evaluate fluctuations in autonomic tone. HRV analysis allows the differential analysis of sympathetic and parasympathetic components. HRV in the high-frequency range is an index of parasympathetic activity, whereas HRV in the low-frequency range is considered to be the result of a predominantly sympathetic activity. The low- to high-frequency ratio of heart rate is a parameter of sympathovagal balance. Using this methodology, HRV has been shown to be reduced in HIV-infected individuals even in the early stages of infection [6]. Studies using HRV analysis have shown that the occurrence and natural course of cardiac autonomic nerve dysfunction is also linked with HIV disease progression [7].

It is not clear the mechanism by which HIV infection affects the autonomic nervous system; however, it is thought that the damage of autonomic fibers may occur early in the course of infection, and pathological studies of jejuna mucosa in HIV patients support this hypothesis [8].

Human T-lymphotropic virus type-1 virus (HTLV-1)

Human T-lymphotropic virus type-1 is a human type C retrovirus that causes HTLV-1-associated myelopathy (HAM), also called tropical spastic paraparesis (TSP). Approximately 20 million people worldwide are infected with HTLV-1. Endemic areas are Japan, Middle East, Sub-Saharan Africa, Caribbean region, Central and South America, and Melanesia [9]. HTLV-1 can be transmitted via sexual intercourse, breastfeeding, blood transfusion and transplantation of contaminated organs. HAM patients present with a slowly progressive spastic paraparesis, sphincter and sexual dysfunction, back pain and lower limb paresthesias [10, 11].

Autonomic dysfunction features including orthostatic hypotension, urinary dysfunction and hypohidrosis have been described in HAM-TSP patients, although its prevalence may be underestimated. Cardiovascular dysautonomia predominantly affects the sympathetic nervous system [12], and induces changes in normal circadian rhythms of heart rate and blood pressure [13, 14] and abnormal nocturnal variation in blood pressure [12]. In a case–control study performed in Japan, circadian rhythms of blood pressure and heart rate were evaluated in 23 HAM/TSP patients and 23 controls [13]. HTLV-1-infected patients had significantly lower blood pressure amplitudes and lower 24-h mean systolic and diastolic readings in the non-invasive monitoring tests as compared to the control group. HRV is also affected in HAM/TSP. Reduced parasympathetic tone with no heart rate variation with both deep inspiration/expiration and Valsalva has been seen in elderly HTLV-1-infected patients [14].

HAM/TSP is associated with chronic inflammation in the spinal cord, including perivascular lymphocytic cuffing and mild parenchymal lymphocytic infiltrates, and thoracic spine segments are more frequently affected. As sympathetic afferents pass through the *nucleus intermedio-lateralis* in thoracic T1–T4 segments, HAM/TSP thoracic chronic damage leads to cardiovascular autonomic dysfunction.

In a case–control study, 19 HAM/TSP patients and 29 normal subjects were evaluated [15]. Power spectral analysis of R–R interval variability of the 24-h Holter electrocardiogram was performed, and the low to high frequency ratio was used as a marker of sympathetic activity. The low to high frequency ratio was significantly lower in HAM/TSP patients as compared to the control group, and in around 90% of HAM/TSP patients who had orthostatic hypotension. The low to high frequency ratio was also significantly lower in HAM/TSP patients who had spinal cord atrophy.

Herpes viruses

The family of herpes viruses include herpes simplex virus type 1 (HSV1) and 2 (HSV2), varicella zoster virus (VZV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Herpes virus infections are very common, and the viruses usually remain latent for the entire life of the host after initial infection.

Varicella zoster virus and Herpes simplex viruses

Varicella zoster virus is the etiological agent of varicella (chickenpox) and zoster (shingles), and remains latent in neurons of cranial nerve ganglia, dorsal root ganglia and the autonomic ganglia along the entire neuroaxis. HSV1 and HSV2 infect the epithelial cells of the oral or genital mucosa, followed by the infection of peripheral nervous system and establish mainly a latent infection in dorsal root ganglia, the cranial nerve ganglia (HSV1) and sacral ganglia (HSV2) [16].

Necropsy studies have confirmed the presence of Alpha herpesvirus DNA in human thoracic sympathetic ganglia by means of polymerase chain reaction (PCR) techniques [17]. In a pathological study, VZV DNA was found in all subjects and in the 65% of 117 thoracic sympathetic ganglia obtained from 15 subjects, whereas HSV1 DNA was found in only 4% of samples. PCR-based studies have also revealed the presence of VZV and herpes virus DNA in human nodose and celiac ganglia of the autonomic nervous system [18].

Neurological complications associated with VZV reactivation may occur in the absence of rash [19]. VZV can reactivate in dorsal root ganglia and thoracic sympathetic ganglia, and may be followed up by transaxonal spread targeting organs and causing visceral disease [17]. The thoracic sympathetic ganglia supply postganglionic fibers to viscera, and also to blood vessels, skin, heart, gastrointestinal tract, and bladder as well as viscera such as liver, spleen, lung, and kidneys. Case reports of VZV-hepatitis and gastritis in bone marrow transplant recipients have been described [17].

Nevertheless, the spread of herpes viruses beyond the sensory nervous system and the new resulting broader spectrum of the disease are not well understood [20]. Stress has been associated with exacerbation of clinical symptoms and recurrences in both human and animal models. Herpes viruses can replicate and establish latency in sensory and

autonomic neurons that are highly responsive to stress hormones [21]. Autonomic neurons seem to be more responsive to epinephrine and corticosterone than sensory neurons, and the autonomic nervous system may play an important role in herpes pathogenesis [21].

Rodent models have been helpful in describing the involvement of the enteric nervous system following herpes infection. A mouse model of genital herpes showed that HSV infection-associated lethality was correlated with severe faecal and urinary retention, and that HSV spread via the dorsal root ganglia to the autonomic ganglia of the enteric nervous system in the colon [20]. The spread of the virus to enteric nervous system caused neutrophil-mediated neuronal damage leading to the loss of intestinal peristalsis and the development of toxic megacolon. In a rat model of HSV1 intragastric inoculation, the virus established a latent infection in the rat myenteric ganglia which led to gut dysmotility [22]. In another rodent model-based study, adenosine-mediated enteric neuromuscular function was also impaired during enteric infection by HSV1 [23].

In humans, VZV can also infect enteric neurons and establish latency in ganglia of the enteric nervous system [24]. Some cases of chronic intestinal idiopathic pseudo-obstruction have been associated with herpes virus infections. Gastrointestinal impairment, recurrent episodes of nausea and vomiting associated with abdominal pain, and acute colonic pseudo-obstruction episodes have been reported following VZV infection [25]. Intestinal aganglionosis after generalized varicella-zoster virus infection has been described in a 3-year-old girl with acute lymphoblastic leukemia who developed an ileus. Histopathological analysis of small intestine demonstrated a nearly complete neural loss, and myenteric and submucous enteric ganglia were nearly completely absent owing to virus infection [26].

Epstein–Barr virus

(EBV is the etiological agent of infectious mononucleosis which affects mainly children and young adults. Reactivation may happen in immunocompromised subjects. Acute EBV infection is associated with neurologic complications including meningitis, encephalitis, cerebellitis, myelitis, and radiculopathy in 0.5–7.5% of patients. Peripheral nervous system involvement may cause radiculitis, Guillain–Barre syndrome, plexopathy, mononeuritis multiplex, and autonomic neuropathy [27, 28].

The involvement of the autonomic nervous system in EBV infection has occasionally been described. Acute pandysautonomia, orthostatic syncope and paresthesias [29], and also acute cerebellar ataxia and orthostatic hypotension [30] following EBV infection, have been reported. The presence of high titers of serum EBV antibodies suggests that pandysautonomia is related to EBV infection [29]. Acute autonomic neuropathy initially presenting with blurred vision, orthostatic intolerance, constipation and paresthesias has been reported in a case of acute central nervous system infection which was confirmed by positive EBV DNA and serology in the CSF [27].

Autonomic dysfunction and intestinal pseudo-obstruction symptoms following glandular fever has also been reported. A rare case of acute pharyngitis and abdominal ileus associated with EBV infection was followed by prolonged intestinal pseudo-obstruction and pandysautonomia [31]. Pathological analysis of appendix and a rectal biopsy showed an absence of ganglion cells in the appendix and hypoganglionosis in the rectum, with mononucleate inflammatory infiltrate in close contact with the myenteric plexus [31].

Cytomegalovirus

Cases of Guillain–Barre syndrome preceded by cytomegalovirus infection have been described in the literature. Although relatively uncommon, acute autonomic and sensory-motor neuropathy following cytomegalovirus infection can happen [32]. Orthostatic hypotension and distal paresthesias and muscle weakness and neurogenic atonic bladder were noted [32]. Subacute autonomic and sensory neuropathy following cytomegalovirus infection may cause sympathetic nerve dysfunction, and orthostatic hypotension and abnormal cold pressor test were observed [33]. Dysfunction of postganglionic autonomic nerves with a decrease in the accumulation of (123)I meta-iodobenzylguanidine on myocardial scintigraphy was also noted [33].

Tick-borne encephalitis virus (TBEV)

Tick-borne encephalitis virus is a flavivirus endemic in Central and Eastern Europe and Asia that causes tick-borne encephalitis, an emerging zoonosis transmitted by ticks. The more severe cases of TBEV meningoencephalomyelitis are associated with a poliomyelitis-like syndrome causing acute flaccid paralysis.

Autonomic and peripheral nervous system dysfunction have been described in acute tick-borne encephalitis. In a case–control study, 14 patients with acute tick-borne virus encephalitis, 17 diabetic patients and 30 healthy controls were evaluated [34]. Time and frequency domain parameters of HRV at rest and deep respiration were assessed. Sympathovagal unbalance with increased sympathetic activation and a significantly elevated minimal heart rate was noted.

Sphingosine-1-phosphate seems to be increased in plasma and cerebrospinal fluid of patients with tick-borne virus encephalitis [35], and this fact has been proposed be the cause for the predominant sympathetic innervations in TBEV-infected patients.

Reduced HRV and gastrointestinal symptoms, including vomiting, postprandial abdominal pain, reduced bowel motility and constipation, have also been described [36]. In a study of 656 patients with TBEV infection, impaired bowel function was reported to occur in around 13.5% of patients with TBEV meningoencephalitis [37]. In a murine experimental model, intravenous inoculation with TBEV resulted in intestinal distension, paresis and death, and immunohistochemical techniques showed TBEV antigens in the enteric plexus [38]. Pathological studies are lacking in humans.

West Nile virus (WNV)

West Nile virus is a mosquito-borne RNA flavivirus that has caused outbreaks in Europe (Romania and Russia), Africa, and Middle East, and in the last decade in the United States, Canada, and Mexico, among other countries. WNV may cause high fever, malaise, headache and retro-orbital pain, joint and muscle pain, and a maculopapular rash.

Severe neurological complications have been reported following the New York outbreak in 1999, including encephalitis, meningitis, poliomyelitis, myeloradiculitis and nerve root involvement [39]. Anterior horns of the spinal cord are affected in WNV poliomyelitis; however, inflammatory changes may also affect the adjacent white matter. The involvement of sympathetic ganglia neurons has been hypothesized to be the cause of the signs of autonomic instability detected in some patients [39]. Reported symptoms included hypotension, labile vital signs and potentially lethal cardiac arrhythmias [40–42].

In rodents, WNV can infect neurons that control cardiac and gastrointestinal function and cause autonomic dysfunction. Autonomic symptoms, decreased HRV and stomach and intestine distension, have been described in an experimental animal model of hamster infected with WNV. Autonomic function, as measured by HRV, was suppressed [43]. Histhopathological studies showed that brain-stem and myenteric plexus neurons, and also cells in sinoatrial and atrioventricular nodes, were infected by WNV. However, autonomic deficit has not been found to be the cause of death in WVN animal models of neurological disease [44]. Extrapolation of these pathological findings to humans should be made with caution.

Rabies

Rabies virus is a RNA Lyssavirus transmitted to humans by contact with saliva from infected animals. Each year, thousands of people die in developing countries due to rabies. Rabies is a viral zoonosis that persists in wildlife reservoirs, although dogs are the most common vectors.

The classic furious or encephalitic rabies is characterized by behavioral changes, agitation, a fluctuating level of consciousness, aerophobia and inspiratory spasms, hydrophobia and prominent autonomic dysfunction. In a study of 104 human rabies cases in Bali, the prevalence of signs and symptoms of autonomic dysfunction was: hydrophobia (93%), hypersalivation (88%), dyspnea (74%), photophobia (30%), and piloerection (5%). Of these cases, 78% had furious rabies and only 21% had paralytic rabies [45].

Rabies associated with bat rabies virus variants may present with atypical clinical features, such as focal brain-stem signs, myoclonus and Horner's syndrome [46]. Dysautonomia may also be the cause of death in some patients [47].

Post-mortem studies have shown ganglionitis in autonomic ganglia, and immunohistochemical demonstration of rabies virus antigen in the hippocampus, medulla, tongue, cerebellum, autonomic ganglia, muscle spindles and skeletal muscles in the tongue. The involvement of the brain-stem in rabies encephalitis, as demonstrated by magnetic resonance imaging and necropsy studies, may explain the profound autonomic dysfunction observed in these cases [46].

Enterovirus 71 and other virus

Enterovirus 71 is an emerging polio-like enterovirus that has caused numerous outbreaks in South-east Asian countries. Enterovirus 71 may cause a hand-foot-mouth disease/herpangina. Neurological complications associated with enterovirus 71 infection include encephalitis, cerebellitis, transverse myelitis, poliomyelitis-like syndrome and autonomic dysfunction. In a study of 48 children from Singapur, autonomic dysfunction was reported in 1 of 36 children (2.8%) with neurological manifestations [48]. The patient presented with mydriasis, widespread loss of sweating, and bladder dysfunction during the acute infection.

Reactivation of human polyoma John Cunningham (JC) virus infection in the central nervous system can cause a condition called progressive multifocal leukoencephalopathy. Recently, it has been hypothesized that JC virus can also infect the enteric glia of the myenteric plexuses, and JC virus particles have been detected in

patients with chronic idiopathic pseudo-obstruction [49]. Further confirmatory studies are needed to identify the pathological role of JC virus in enteric neuropathy.

Chagas disease

American trypanosomiasis, also called Chagas disease, is a parasitary infection caused by *Trypanosome cruzi*, and transmitted by the bite of *Triatominae* bugs. The disease is endemic in 21 Latin American countries and has spread from northern Argentina, Brazil, Bolivia and Caribbean region to Mexico and southern Texas [50]. Between 8 and 14 million are infected by *T. cruzi* in the Americas, and annually around 40 000 acute cases and 10 000 deaths are reported. Chagasic patients can now be found in non-endemic areas as thousands of people from endemic regions have emigrated in the last couple of decades to Europe, North America and Australia [51]. Non-vector transmission may occur through infected organ transplantation, transfusion of infected blood, and mother-to-child (congenital) infection. Oral outbreaks have been reported in the Amazon basin.

Acute Chagas disease usually occurs in infancy and childhood, and most cases are asymptomatic, although severe cases of encephalitis and myocarditis may occur. Initial infection is followed by a latent asymptomatic stage called the indeterminate form of Chagas disease that may last years. At least one-third of Chagas disease patients will develop a chronic chagasic cardiomyopathy, and around 15% a digestive chronic form (megaesophagus, megacolon or both) or mixed cardio-digestive forms [52, 53]. Symptoms of chronic Chagas disease are summarized in Table 3.

Diffuse damage of the autonomic nervous system, mainly the parasympathetic branch, is one of the hallmarks in Chagas disease, and affects the heart and digestive tracts. Several pathogenic mechanisms have been proposed to explain the appearance and progression of chagasic chronic forms: denervation of autonomic nervous system with dysautonomia, impairment of microcirculation, parasite-dependent tissue damage due to persistence of the parasite, and immune-mediated injury [53]. Today, it is accepted that persistence of the parasite is one of the most important mechanisms involved in chronic chagasic myocardiopathy progression. However, for the purpose of this article, we will focus mainly on the autonomic denervation pathogenic mechanism.

Chagasic chronic digestive form

All gastrointestinal segments can be affected in the chronic chagasic digestive form, although the esophagus and the descending and sigmoid colon and rectum are the most commonly affected. The destruction of myenteric plexus of the esophagus by *T. cruzi* causes chagasic megaesophagus, and as a consequence functional changes occur including motor dyskinesia, hypercontractility and achalasia of lower esophageal sphincter. Denervation of the colon segments cause megacolon, and complications of chagasic megacolon include severe constipation, fecaloma, sigmoid volvulus and even perforation [54] (Figs. 1, 2).

Table 3 Symptoms/signs associated with chronic Chagas disease

Chronic cardiomyopathy
Palpitations/arrhythmias
Fatigue/dyspneia/heart failure
Syncope/conduction blocks
Sudden death
Peripheral embolism and stroke
Megaesophagus
Dysphagia
Regurgitation
Retrosternal chest pain
Gastric/duodenal involvement
Dyspepsia and pyrosis
Epigastric pain
Megacolon
Chronic constipation
Diarrhea

The human enteric nervous system is constituted by the myenteric and submucosal plexus. Enteric glial cells and neuronal cell bodies lie in these ganglionated nerve networks. The myenteric plexus is located between the longitudinal and circular muscle layer (Auerbach), and extends from upper esophageal to internal anal sphincter. In addition, the submucosa of humans contains two ganglionate submucosal plexus (the internal is called Meissner's plexus, whereas the external is called Schabadasch's plexus) which is restricted to the small and large intestines. Most human submucosal neurons are cholinergic, whereas human myenteric neurons are either nitrergic or cholinergic [55].

During the acute stage of Chagas disease, direct parasite invasion of the muscle tissue of the heart and digestive system occurs. Lymphocytic infiltrates, ganglionitis, and degenerative neuronal lesions are seen in these organs. In Chagas disease, a massive myenteric neuron loss has been observed, whereas submucosal neuron loss is moderate. Nevertheless, it is thought than neuron loss alone does not completely explain the loss of motility, and other cells such as interstitial Cajal cells and smooth muscle cells may be affected. Changes of calibre in chagasic megacolon may also influence motility [55].

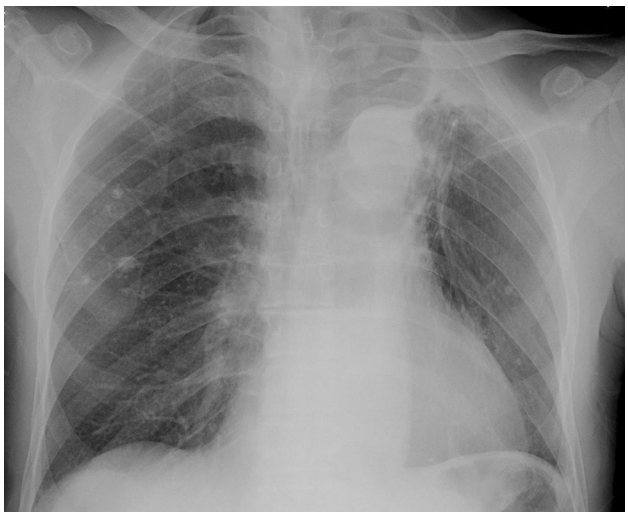

Fig. 1 Chest X-ray. Chagas disease chronic cardiomyopathy

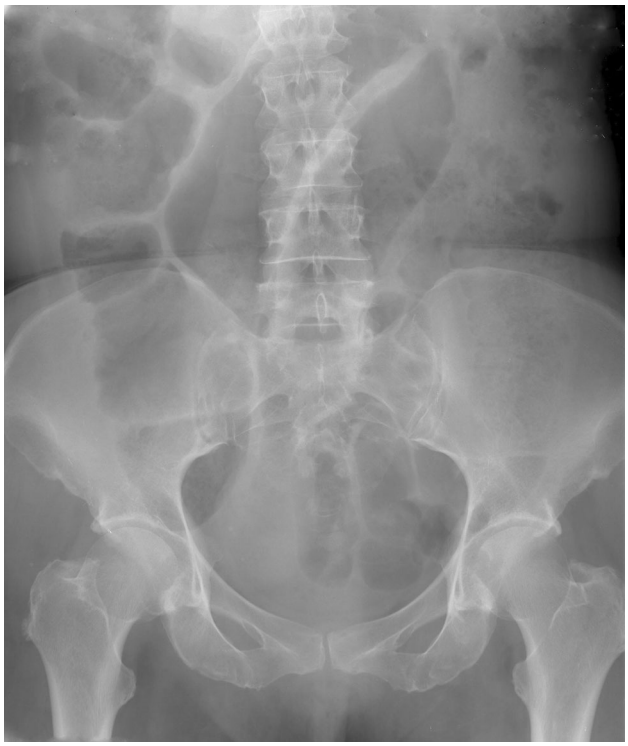

Fig. 2 Abdomen X-ray. Megacolon in chronic Chagas disease

Although the pathogenesis is not fully understood, it is accepted that the protozoa affects the muscle cells of the digestive tract, and that the enteric nerve plexuses are destroyed due to local inflammatory and immune-mediated mechanisms. The destruction of the neurons of the enteric nervous system causes a severe peristaltic dysfunction. Neuronal involvement seems to be selective, and neurons involved in smooth muscle relaxation producing nitric oxide and the vasoactive intestinal peptide are spared. Vasoactive intestinal peptide/nitric oxide neurons are a minority in healthy myenteric plexus and only a few myenteric neurons survive in chagasic megacolon; however, vasoactive intestinal peptide/nitric oxid neurons are a majority in a normal submucosal plexus and most submucosal neurons survive. There is also a decrease in the number of interstitial Cajal's cells which play a major role in digestive tube motility modulation. Reduction in Cajal's cells is common in chagasic megaesophagus and megacolon. Fibrosis in the smooth muscle and myenteric plexuses and lymphocytic infiltrates at submucosal and myenteric plexus and smooth muscle layer are other pathological findings observed in the chronic digestive form [54, 55].

Chagasic cardiomyopathy

Electrocardiogram abnormalities are common early signs in chagasic cardiomyopathy, and include right bundle branch block, left anterior hemiblock and ventricular extrasystoles. Chagasic chronic cardiomyopathy and progressive myocarditis are associated with complex cardiac arrhythmias, conduction disorders, left ventricle dysfunction, progressive heart failure, segmental wall abnormalities and ventricular aneurysms, peripheral thromboembolim and stroke, and can finally lead to sudden death [50]. Chagas disease is a common cause of cardioembolic stroke in endemic areas, and stroke may also be the first manifestation of Chagas disease [56]. Stroke can also occur in asymptomatic *T. cruzi*-infected patients.

Pathological studies in Chagas disease have shown parasympathetic denervation both in animal models and human necropsy specimens, with neuronal damage occurring during the acute phase of the infection [57, 58]. In the 1950s, Koberle described the first pathological studies concerning ganglionic damage and depopulation in subepicardial intramural parasympathetic neuronal cells of the heart [58]. Neuronal loss in chagasic heart disease seems to occur mainly during the acute infection. Direct parasitism of neurons, degeneration caused by periganglionic inflammation and anti-neuronal immune-mediated reactions are thought to be important pathogenic mechanisms [59]. In addition to the damage to the autonomic nervous system causing neuronal depopulation, the acute inflammatory process also affects the sinus and atrioventricular nodes and the bundle of Hiss, causing secondary cardiac autonomic dysfunction [60].

Functional autonomic nervous system studies have demonstrated impaired parasympathetic heart rate regulation in adult chagasic patients. They are deprived of the tonic inhibitory mechanism exerted by the parasympathetic system by means of the vagal nerve on the sinus node and cannot respond with rapid bradycardia or tachycardia to transient changes in blood pressure or venous return [53].

Studies performed by means of head-up and -down tilt testing, hand grip techniques, the Valsalva maneuver, facial immersion techniques, and spectral analysis of 24-h Holter recording among other tests showed that the parasympathetic function failed in chagasic chronic cardiomyopathy patients [53]. Parasympathetic dysfunction in chagasic cardiomyopathy is characterized by blunting of normal heart rate and blood pressure responses to several stimuli ,including Valsalva maneuver, deep breathing and orthostatism [61].

Vagal impairment can be detected in all forms of Chagas disease, including the indeterminate form and before and independently of left ventricular dysfunction. Several studies with I-123 metaiodobenzylguanidine also detected sympathetic dysfunction in chagasic patients with the indeterminate form and without left ventricular systolic dysfunction [62, 63]. However, not all studies detected impaired vagal heart modulation in early forms of Chagas disease. A meta-analysis of seven studies that evaluated the autonomic heart modulation using the R–R interval variation during the Valsalva maneuver, including 396 chagasic patients without cardiopathy, concluded that chagasic patients had reduced Valsalva ratio values compared to healthy controls, indicating early vagal dysfunction. The negative findings in some studies could have been linked to small sample size [64].

T. cruzi-infected children also show early signs of autonomic dysfunction during the indeterminate phase of the infection. In a matched case–controlled study of Peruvian children infected by *T. cruzi* and healthy controls, infected *T. cruzi* children had blunted autonomic responses to the Valsalva maneuver, the cold pressor test and the orthostatic test [65].

However, the role of autonomic dysfunction in the pathogenesis of chagasic cardiomyopathy is still not well understood. After the pioneer studies by Koberle that showed severe intramural neuronal depopulation, it was thought that autonomic dysfunction could be the cause of the progression of chagasic cardiomyopathy (this was called the "neurogenic hypothesis" of chronic Chagas disease) [57]. While parasympathetic denervation has been proven to be an important factor in the genesis of megaesophagus and megacolon, its role in the development and progression of chronic cardiomyopathy is less clear. Indeed, today, it is accepted that progressive contractile alteration depends mainly on the ongoing inflammatory process and fibrosis of the myocardium [59]. An imbalance to sympathetic autonomic function causing catecholamine-induced cardiomyopathy has not been demonstrated.

The role of immune-mediated mechanisms in the progression of the disease needs further elucidation. Left ventricle dysfunction has also been correlated with the presence of functionally-active antibodies against cardiac muscarinic M2 and adrenergic B1 receptors [66].

Autonomic dysfunction can also affect metabolism, and increased adiponectin levels have been found in chagasic heart disease patients. The levels of adiponectin have been associated with the high-frequency component of HRV and inversely associated with the lower-frequency component [67]. Adipose tissue is mainly innervated by the sympathetic nervous system, and a peripheral impairment of the sympathetic system may lead to reduction of activity in adipose tissue and increase the secretion of adiponectin. The link between metabolic pathways and autonomic dysfunction in Chagas disease also needs further confirmatory studies.

Leprosy

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. According to the World Health Organization, more than 210,000 new cases of leprosy were detected in 2015. India accounted for 60%, Brazil 13% and Indonesia for 8% of reported new cases [68]. Leprosy subtypes and clinical presentation depends of a complex interaction between bacilli and the host immune response. Classical forms are tuberculoid, lepromatous, borderline, and indeterminate leprosy.

Mycobacterium leprae can damage both myelinated and unmyelinated nerve fibers causing extensive inflammation, axonal atrophy and fibrosis, and increase in nerve size and thickness. As a consequence, motor, sensory and autonomic symptoms may occur. Small fiber involvement is common in the initial stages of the infection, whereas large diameter myelinated fibers may be involved later [69]. Thin unmyelinated autonomic fibers and post-ganglionic autonomic fibers containing unmyelinated small fibers may be damaged first, then small myelinated fibers and finally large myelinated fibers [70]. The most frequent presentation of leprosy is mononeuritis, and nerves in the upper limbs (ulnar, median, posterior auricular, superficial radial nerves) are commonly involved [69]. In lower limbs, leprosy may more frequently cause a predominantly axonal polyneuropathy which may be severe [71]. Anaesthetic patches can be found on the trunk and extremities, and anesthesia following glove and stocking distribution has been found in different combinations, and peripheral nerves can be enlarged. Sensory loss and motor paralysis may result in significant morbidity and disability.

Leprosy neuropathy can present as isolated mononeuritis, mononeuritis multiplex and polyneuritis. Pure neuritic leprosy and small fiber polyneuropathy can occur in the absence of anesthetic skin lesions. Autonomic dysfunction, including anhidrosis, impaired sweating function, localised alopecia and reduced HRV, has been reported in leprosy althoughthe real prevalence of autonomic dysfunction is

unknown. In a Brazilian study which included 76 patients, vasomotor reflex was impaired in at least one finger in more than 40% of patients [72].

Subclinical autonomic neuropathy in leprosy patients is common, and autonomic nerve dysfunction is an early manifestation of the disease [73]. Nerve damage can happen from the very beginning of infection, and multibacillary leprosy is more susceptible to nerve damage [74].

Autonomic neuropathy and damage of vascular autonomic inervation of the skin and the loss in vascular tone may result in impairment of capillary blood flow and may delay ulcer healing [75]. Loss of sweating over distal parts of the upper and lower limbs and heat intolerance have been described following treatment in lepromatous leprosy [75]. The starch-iodine test has been used to detect the absence of areas of sweating.

Sympathetic skin response and heart rate R–R interval variation have been evaluated in several studies which were mostly performed in Turkey. In one of these studies, 37 lepromatous leprosy patients and 35 age-matched healthy subjects were included [73]. Orthostatic tests, the Valsalva ratio, R–R interval variation during at rest and deep breathing, and sympathetic skin response latency and amplitude from both palms were analyzed. Mean values of R–R interval variation in leprosy patients at rest and during deep breathing were significantly lower compared with controls. The mean latency of sympathetic skin response in the leprosy group was also significantly prolonged. In another case–control study from Turkey, 10 patients with borderline lepromatous leprosy and 19 patients with lepromatous leprosy were compared with 30 healthy volunteers. No sympathetic skin responses were recorded in 80% of cases, and the R–R interval variations of the leprosy patients were reduced during both resting and deep forced hyperventilation [71].

Head-up tilt testing can provide helpful information about orthostatic abnormalities in leprosy. In another Turkish study, mean values of the "30/15" head-up tilt test were found to be significantly lower compared with controls. Patients who had clinical evidence of autonomic neuropathy had lower scores than patients without overt autonomic dysfunction [76].

As autonomic nerve damage may happen before clinical manifestations of leprosy become apparent [70, 73], it has been proposed that early detection of asymptomatic autonomic neuropathy could be valuable in identifying those leprosy patients at high risk of developing symptoms [76].

Lyme disease

Lyme disease is a tick-borne zoonosis caused by the spirochete *Borrelia burgdorferi*. Disseminated disease may occur after initial infection and involve musculoskeletal, cardiovascular and central nervous systems. Neuroborreliosis may affect 15% of infected subjects, and cranial neuritis, meningoencephalitis and meningoradiculitis are frequent clinical manifestations [77]. Lyme disease and neuroborreliosis should be included in the differential diagnosis in endemic areas, as many patients may not have a previous history of chronic erythema migrans or may not recall being bitten by ticks.

Autonomic dysfunction may happen in neuroborreliosis, although cases of neuroborreliosis primarily affecting the autonomic nervous system are rare. Chronic intestinal pseudo-obstruction presenting with abdominal pain, severe constipation and urine retention has been described [78–80]. CSF analysis may reveal intrathecal synthesis of anti-Borrelia IgM and IgG and lymphocytosis [80]. Gastrointestinal function significantly improved in some patients following antibiotherapy, and this fact suggests a reversible autonomic neuropathy [79, 80]. Urinary bladder detrusor dysfunction [81] and acute urinary retention associated with Lyme myelitis [82] are other rare forms of presentation. Pathological studies have shown evidence of lymphoplasmocellular infiltrates in the autonomic ganglia resulting in sympathetic denervation in lower extremities [83].

Post-treatment Lyme disease syndrome is a controversial clinical picture characterized by chronic fatigue, musculoskeletal symptoms, and headache, pain and attention and memory problems following a proper antibiotic treatment for Lyme disease. There are overlapping symptoms between post-treatment Lyme disease syndrome and postural orthostatic tachycardia syndrome. Case studies have signaled that some patients with post-treatment Lyme disease syndrome may present with persistent symptoms of orthostatic intolerance consistent with postural orthostatic tachycardia syndrome [84].

Complex regional pain syndromes and reflex sympathetic dystrophy with regional sympathetic hyperactivity have also been reported in some patients with Lyme disease [85–88]. In some cases, specific IgG and IgM levels had a progressive rise [86]. Complex regional pain syndrome can be attributed to the release of pain-triggering molecules and the persistence of an inflammatory response. Although the pathogenesis is unclear in these rare cases associated with Lyme disease, it is thought that complex regional pain could be either immune-mediated or due to the persistence of spirochete infection in the tissues [85].

Diphtheria

Corynebacterium diphteriae is a Gram-positive bacillus that causes diphtheria, an infectious disease that is spread human to human by close contact through respiratory secretions and cutaneous lesions. Diphtheria is a biphasic illness, and the initial clinical picture is characterized by low-grade fever, sore throat, neck swelling with a classical bull neck appearance and ipsilateral palatal paralysis. There is a latency period between these first symptoms and the appearance of diphtheritic polyneuropathy. Classically, pharyngeal diphtheria leads to formation of pseudo-membranes in the pharynx (membranous tonsillitis). However, toxigenic *C. diphteriae* strains cause myocarditis and diphtheritic polyneuropathy. This neurological complication may happen in around 20% of patients, and can present as motor weakness and sensory symptoms, with progressive lower limb weakness and acute flaccid paralysis [89].

In the past, diphtheria was a major cause of morbidity and mortality in children, and, before the advent of vaccination, around 1 in 20 persons in temperate regions had diphtheria in their lifetime with a mortality rate of 5–10% [90]. The development of diphtheria toxoid vaccine led to a near-elimination of the disease in developed countries. However, in the 1990s, the fall of immunity in the adult population resulted in a return of the disease in Eastern Europe. Diphtheria resurgence happened mostly in the former USSR states, and epidemic outbreaks and also cases of diphtheritic polyneuropathy were reported in Russia [91] and Latvia [92]. Between 2007 and 2011, nearly 20 000 cases of diphtheria were reported by the World Health Organization, with 90% occurring in India [90, 93].

Only the *C. diphtheria* strains that harbor the tox bacteriophage gene cause polyneuropathy and cardiomyopathy. Diphtheritic polyneuropathy is mostly a demyelinating neuropathy, and nerve conduction studies usually detect prolonged distal motor latencies, slow conduction velocities, conduction blocks and prolonged F-response latencies [92].

Bulbar symptoms and bulbar palsy may happen around 3–6 weeks after initial infection, whereas polyneuropathy appears around 8 weeks later. Dysphonia and paraesthesias and numbness of the face and tongue may be the first initial symptoms. Signs of bulbar impairment include nasal or hoarse voice, dysphagia, excessive salivation, nasal regurgitation, and isolated palatal paralysis affecting the soft palate and posterior pharyngeal wall [93]. Oculomotor and ciliary paralysis can also be seen. A biphasic evolution of neurological symptoms is common, and bulbar dysfunction usually recovers during weeks 5-to-10, whereas worsening of motor muscle occurs at that time. Patients may present with descendent and symmetric quadriparesis or with acute flaccid paralysis.

Diphtheria can also be complicated by signs of autonomic dysfunction. Cardiac arrhythmias, tachycardia and hypotension are common, and in many cases are difficult to distinguish from symptoms related to diphtheritic myocarditis [92]. This fact may be difficult to interpret, as myocarditis may happen frequently and has been described in nearly two-thirds of patients with diphtheritic polyneuropathy [92]. Visual impairment, blurred vision from impaired accommodation, and an abnormal pupil reaction to light stimuli have also been reported. Bladder dysfunction, urine retention and urine catheterization may happen in one-third of cases. In a Russian study, xeroderma and hyperkeratosis were reported in 75% of patients, and hyperemia and hyperhidrosis of the face, neck and chest in 62% [92]. Autonomic function tests have demonstrated impairment of the parasympathetic vagal function [93], and abnormal R–R variation and heart rate reaction to Valsalva maneuver [94]. Normal sympathetic vasomotor and sudomotor functions were reported in one patient with diphtheritic neuropathy [95].

Tachycardia may be present in the absence of myocarditis, and cardiac vagal denervation was observed in half of the 10 patients with diphtheritic neuropathy [94]. The hypothesis of a parasympathetic dysfunction is also supported by pathological studies which showed lesions in the nodose ganglion of the vagus nerve [96].

Diphtheritic toxin can penetrate into the cells of Schwann and inhibit the synthesis of myelin basic protein and proteolipid [97]. Direct spread of toxin can provoke local toxic effects and early bulbar symptoms, whereas generalized demyelinizating polyneuropathy is thought to be caused by hematogenous dissemination [95].

Differential diagnosis includes Guillain–Barre syndrome which may also present with progressing motor, sensory and autonomic symptoms. However, in diphtheria, a higher prevalence of bulbar symptoms are usually detected at the beginning.

Main causes of death from diphtheria include myocarditis, cardiac arrhythmias associated with parasympathetic dysfunction of vagal nerve, and respiratory paralysis associated with laryngeal involvement [90].The use of diphtheria antitoxin reduces the fatality rate and should be given as soon as possible once diphtheria is diagnosed or even suspected.

Tetanus

Tetanus is caused by a neutotoxin called tetanospasmin produced by the bacteria *Clostridium tetani*. The incidence of tetanus has significantly decreased in developed

Table 4 Autonomic nervous system dysfunction caused by infectious diseases

Disease	Etiological agent	Autonomic symptoms	Laboratorial findings
AIDS	HIV	Orthostatic intolerance/hypotension	Reduced heart rate variability
		Secretomotor and gastrointestinal dysfunction	Blunted blood pressure response to sustained handgrip
		Sexual/bladder/bowel dysfunction	
TSP	HTLV-1	Orthostatic hypotension, urinary dysfunction	Lower blood pressure amplitudes
		Hypohidrosis	Power spectral analysis of R–R interval variability: reduced low to high frequency ratio
Varicella	VZV	Gastrointestinal impairment, nausea and vomiting, abdominal pain and pseudo-obstruction episodes	
Mononucleosis	Epstein–Barr virus	Intestinal pseudo-obstruction and pandysautonomia	
		Orthostatic syncope	
CMV	Cytomegalovirus	Orthostatic hypotension, acute autonomic neuropathy	Abnormal cold pressor test
		Neurogenic atonic bladder	Decrease in accumulation of (123)I meta-iodobenzylguanidine on myocardial scintigraphy
TBE	TBEV	Vomiting, postprandial abdominal pain,	Decreased heart rate mobility
		Reduced bowel motility	
West Nile virus	West Nile virus	Stomach and intestine distension in murine model	Decreased heart rate variability
		Hypotension and cardiac arrhythmias in humans	
Rabies	Lyssavirus	Hypersalivation, dyspnea, piloerection	
Chagas	*Trypanosoma cruzi*	Dysphagia, constipation, palpitations Syncope, orthostatic hypotension, stroke	Hand grip, Valsalva manoeuvre, 24 h Holter, tilt test: blunted responses to heart rate and blood pressure
			Reduced Valsalva ratio values compared to healthy controls
Leprosy	*Mycobacterium leprae*	Anhidrosis, impaired sweating function	Reduced heart rate variability
		Localised alopecia	Prolonged sympathetic skin response
		Erectile dysfunction	Lower “30/15” head-up tilt test
Lyme	*Borrelia burdorgferi*	Urinary retention and intestinal pseudo-obstruction	
		Reflex sympathetic dystrophy/complex regional pain	
Diphtheria	*Corynebacterium diphteriae*	Cardiac arrhythmias, tachycardia and hypotension	Abnormal R–R variation to Valsalva maneuver
		Urine retention, xeroderma, hyperqueratosis	
Tetanus	*Clostridum tetani*	Tachycardia/bradycardia; hypertension/ hypotension	Extreme variations in heart rate and blood pressure
Botulism	*Clostridium botulinum*	Postural hypotension, constipation, hypohidrosis	Abnormal sudomotor function
		Mydriasis/xerophthalmia	Impaired HRV and blood pressure response to standing

Clinical features and laboratorial findings

AIDS acquired immunodeficiency syndrome, *CMV* cytomegalovirus, *HIV* human immunodeficiency virus, *HRV* heart rate variability, *HTLV-1* human T lymphotropic virus type 1, *TBEV* tick-borne encephalitis virus, *TBE* tick-borne encephalitis, *TSP* tropical spastic paraparesis, *VZV* varicella zoster virus

countries once vaccination programs covered most of the population. However, tetanus is still relatively frequent in developing countries with an estimated 700,000 cases per year [98]. Severe tetanus is characterized by rigidity, muscle spasms and autonomic dysfunction. Autonomic instability usually appears around the second week after symptom onset once the exotosin has reached the brain-stem. Tetanospasmin binds to motor neuron terminals and is transported from the periphery to cell neurons in the spinal cord and brain-stem by means of retrograde transport, and inhibits the release of gamma-aminobutyric acid, an inhibitory neurotransmitter [98].

Autonomic dysfunction because of severe tetanus has been reported in unvaccinated children [99]. Signs of autonomic dysfunction include tachycardia, hypertension, bradycardia and hypotension. The loss of inhibitory autonomic control results in labile high blood pressure, tachycardia and sweating, and less frequently brady-arrhythmias, persistent hypotension and even cardiac arrest [98].

Extreme variations in heart rate and blood pressure have been reported in severe tetanus, and autonomic crisis continue uninterrupted for weeks [98]. Magnesium sulfate is a useful drug to treat severe tetanus and autonomic dysfunction.

Debridement of necrotic tissue, antibiotherapy and the early administration of tetanus antitoxin are essential. However, in severe tetanus, sedation and supported invasive ventilation and neuromuscular blockade may be required. The best strategy to prevent catecholamine release is still waiting to be elucidated.

Botulism

Botulism is an intoxication caused by *Clostridium botulinum* toxin. Common forms of botulism are food-borne botulism (ingestion of toxin from home-canned food and fermented uncooked dishes), infantile botulism (colonization of children's digestive tract) and contamination of wounds with *C. botulinum*. Groups at risk are newborns, and also intravenous drug users. Botulism is characterized by a clinical picture of facial and bulbar motor weakness, ptosis, and ophthalmoplegia associated to a descendent paralysis, and autonomic involvement [100]. Pupils are usually dilated and poorly reactive to light stimuli and accommodation. Food-borne botulism usually starts with gastrointestinal symptoms.

Autonomic symptoms are common in botulism and include postural hypotension, constipation, hypohidrosis and dry mouth [101]. Pure autonomic failure has also been described in some cases, and the main signs were transient dysfunction of urinary bladder and gastrointestinal tract, and persisting anhidrosis of palms and soles as well as erectile dysfunction [102]. Sudomotor and cardiovascular reflex functions have been evaluated in a small series of five food-borne botulism patients by means of quantitative autonomic testing. Abnormal sudomotor function and marked impairment of HRV and blood pressure response to standing was observed [102]. The more prominent features were impaired baroreflex function, orthostatic hypotension, supine hypertension and high resting heart rate. In infant botulism, dysautonomia, as measured by HRV, may persist beyond the observable physical recovery [103]. In adults, long-lasting dysautonomia has also been reported [104].

Conclusions

The various autonomic disfunctions causd by infectious diseases and surveyed in this paper are summarized in Table 4.

Autonomic dysfunction may be responsible for additional morbidity in central and peripheral nervous system infections. However, the number of existing studies in the literature about autonomic dysfunction and infectious diseases is low ,and most papers are case reports, cases series or case–control studies with small sample size. In particular, there are no proper studies that have evaluated the differential impact of autonomic dysfunction in specific populations such as the elderly, children and pregnancy. In addition, the role of some common infections such as VZV, EBV, CMV or Lyme disease, which may have a less definitive cause-to-effect relationship to autonomic nervous system dysfunction, needs to be clarified. Only some studies evaluated cardiovascular function by means of objective measures of autonomic function such as heart rate variability. With the exception of Chagas disease, there is a general lack of pathological studies about the involvement of autonomic nervous system in infectious diseases. Early recognition of dysautonomic symptoms, such as orthostatic hypotension and cardiovascular dysfunction and bladder dysfunction, associated with specific infections are important as they may be adequately treated with specific therapy. Further research in this area is warranted.

Compliance with ethical standards

Conflict of interest The author have not conflicts of interest about this article.

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