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REVIEW ARTICLE

Cardiac Disorder in Chronic Hepatitis C

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Abstract

Chronic hepatitis C (CHC) has a high prevalence in the world. In addition to hepatic complications with cirrhosis in about 20% of patients and high risk for hepatocarcinoma, extrahepatic manifestations may also occur. Cardiac involvement in patients with CHC is associated with several factors, such as increased risk for coronary artery disease, primary cardiomyopathies, or hemodynamic and electrophysiological changes observed in liver cirrhosis. Furthermore, antiviral treatment may, in rare cases, causes cardiovascular adverse effects. Cardiac arrhythmias are the main form of clinical presentation, and, often, markers of poor prognosis in individuals with advanced liver disease. Although some mechanisms that justify these changes have already been reported, many questions remain unanswered, especially about the true involvement of the hepatitis C virus in the genesis of primary cardiac abnormalities, and the risk factors for cardiac-related complications of antiviral treatment.

Introduction

Chronic hepatitis C virus (HCV) infection affects more than 70 million people worldwide, accounting for about 1% of the global population.[1] In Brazil, the Ministry of Health estimates that 657,000 people are infected with HCV.[2] More than 70% of these infected individuals develop the chronic form of the disease, evolving with different degrees of liver conditions, and up to 20% develop advanced cirrhosis and 5% develop hepatocellular carcinoma.[3] The hepatic complications of hepatitis C account for about 400,000 deaths per year in the world.[1]

HCV infection can be considered a systemic disease and not simply restricted to the liver. Many forms of extrahepatic manifestations have been described, especially mixed cryoglobulinemia and other lymphoproliferative diseases. In addition, several authors have described a strong association of HCV with neurological, osteoarticular, pulmonary and thyroid disorders, as well as nephropathies (glomerulopathies), porphyria cutanea and even a higher incidence of diabetes mellitus.[4]

The association between heart diseases and chronic HCV infection has also been described. Since cardiac diseases, as well as HCV infection, have a considerable prevalence in the general population, the two conditions would be concomitantly expected in most of these individuals. However, HCV has been implicated as a risk factor for cardiovascular changes that will be described below, such as coronary atherosclerosis, cardiomyopathies, heart disease in advanced cirrhosis, cardiac arrhythmias and cardiotoxic effects of antiviral treatment.

This review aims to describe HCV-related cardiac disorders, discussing the possible pathophysiological mechanisms involved in these disorders.

Coronary artery disease

The association between HCV infection and increased risk of atherosclerotic disease, acute coronary syndromes (myocardial infarction and unstable angina), and fatal strokes has been reported, although the mechanisms that justify this predisposition are unclear. Ambrosino et al. published a recent meta-analysis involving 27 cohort studies and more than 200,000 HCV patients, in which they found an odds ratio of 1.38 for the development

Keywords

Hepatitis C, Chronic; Liver Cirrhosis; Cardiomiopathies; Arrhytmias, Cardiac; Drug Interactions; Drug - Related Side Effects and Adverse Reactions.

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of coronary artery disease (CAD) in these individuals. The presence of CAD, in the aforementioned systematic review, was defined as the onset of one of the following disorders: acute myocardial infarction, unstable angina, stable chronic angina, previous coronary artery bypass grafting, stenosis above 50% in one or more coronary vessels, as observed in coronary angiography, and electrocardiographic pattern compatible with myocardial ischemia. The findings also demonstrated an increased risk of cerebrovascular disease in individuals with hepatitis C.[5]

The possible mechanisms involved in an increased risk of coronary atherosclerosis would be related to the increase of oxidative stress, metabolic disorders such as the induction of diabetes mellitus due to the greater resistance to insulin in hepatitis C described by other authors,[6] inflammatory processes and local viral replication, a mechanism that is suggested by the demonstration of the presence of HCV in carotid atherosclerotic plaques.[7] Consistent data from these studies suggesting the association between CAD and HCV reinforce the need for monitoring patients with the virus regarding the risk of developing coronary events, and other cardiovascular risk factors should be closely monitored in this population.

Cardiomyopathies

Myocarditis

Myocarditis is related to several etiologies, such as the action of toxic and biological agents and autoimmune mechanisms (infections). Among the infections, viruses are most commonly involved. Classically, up to 1990, enteroviruses, including Coxsackie, have been described as the main causative agents. More recent studies with viral genome research on endomyocardial biopsy specimens have demonstrated the predominance of parvovirus B19 and Herpes virus 6 as etiological agents of myocarditis, although other viruses have been described, observing regional and temporal epidemiological characteristics.[8]

The description of HCV as a cause of myocarditis comes from reports in Asia where hepatitis C is very prevalent and the association between myocardiopathies of unknown etiology and HCV infection suggests that this virus could be implicated in the genesis of cardiac disorders.[9] The resolution of acute infection, myocardial fibrosis and subsequent cardiac remodeling could explain the onset of dilated cardiomyopathy, as described below.

Dilated cardiomyopathy

Idiopathic dilated cardiomyopathy (DCM) is a myocardial disease characterized by increased internal dimensions of the cardiac chambers and impairment of left ventricular (LV) systolic function without an identified etiology. Genetic mutations responsible for defects in the expression of cytoskeletal proteins from myocytes are often considered to cause this cardiac disorder. Despite the genetic mechanism demonstrated, previous myocarditis was observed in almost half of the cases, mainly of viral etiology, suggesting that the acquired component, influenced by other agents, does play an important role in the pathogenesis of this cardiac condition.[10] Although little reported in Brazil, DCM is responsible for about 25% of the causes of heart failure in developed countries.[10]

As previously described in this review, the occurrence of chronic myocarditis, mainly of viral etiology, has been postulated as one of the main hypotheses in the pathogenesis of DCM. Again, enteroviruses are the main agents pointed out in the different publications.[8] Matsumori et al.,[9] found 6.3% of HCV infection among 663 individuals with DCM in Japan.[9] These figures were not reproduced in a multicenter study conducted in Italy, which found the presence of HCV-positive serology in 12 of 309 (3.9%) patients with DCM.,[11] and in another study conducted in Brazil, which found only one case of HCV infection among 34 patients with DCM evaluated by a university hospital in Bahia.[12]

The pathophysiology of DCM as a consequence of myocarditis due to hepatitis C virus could be explained by three mechanisms described below. The first was by direct action of the virus, reinforced by viral replication in the myocytes and by the fact that the HCV core protein could damage the structure of these cells. The second mechanism would be the immune system through the activity of B, T cells and macrophages, where the latter are responsible for greater production of cytokines, of which the tumor necrosis factor alpha (TNF alpha) would play a predominant role, as demonstrated in previous studies that observed increased TNF alpha expression in the plasma and in the myocardial cells of individuals with myocarditis and DCM. TNF would affect ventricular systole by inhibition of calcium currents, reducing the entry of this ion in the myocyte, impairing the excitation-contraction coupling of the cardiac cell. In addition, it also contributes to increased nitric oxide production, inhibiting the beta-adrenergic effect on muscle contraction, causing a negative inotropic

effect. The third pathophysiological mechanism would be by induction of myocardial cellular apoptosis caused by mitochondrial disorders and fragmentation of the genomic DNA of the cell.[13] The emergence of hypofunctioning fibrotic areas during the myocardial healing process would lead to cardiac remodeling with progressive loss of ventricular systolic function, leading to heart failure, as well as a greater risk for severe ventricular arrhythmias and sudden death.[10]

Despite this association and the evidence of potential mechanisms that justify the occurrence of DCM induced by HCV, there are still no studies proving this fact.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an inherited disease characterized by an increased LV mass. This inappropriate myocardial hypertrophy is related to an architectural disorder of the cardiac fibers and different degrees of fibrosis, being a substrate for malignant ventricular arrhythmias, a frequent cause of sudden death in this population. Several types of mutations have been identified in genes that decode the structural proteins of myocyte, such as myosin heavy chains, tropomyosin and troponin T.[14]

In a multicenter study conducted by Matsumori in Japan in the early 1990s, serology for HCV was positive in 74 out of 697 patients diagnosed with HCM (10.6%), a result that contrasted with only 25 seropositives in 1,039 volunteering blood donors (2.5%). Another interesting fact in this survey was that the prevalence of HCV was higher in patients with HCM compared to the DCM population.[9] Among the clinical manifestations described in this study, arrhythmias and cardiac conduction disorders were present in nearly half of the patients. The factors that justify the association of HCM and HCV infection have not been reported.

Advanced liver disease

As we saw in the introduction to this article, about 20% of the individuals with chronic hepatitis C will develop cirrhosis. In cirrhotic patients, hepatic dysfunction and portal hypertension may lead to hemodynamic, neurohumoral and inflammatory disorders that affect cardiac function.[15]

Cirrhotic cardiomyopathy is characterized by increased cardiac output, autonomic disorders that influence the response to physiological or pharmacological stimuli, systolic and diastolic dysfunction and electrical abnormalities, without any other cause of heart disease being identified to justify the findings described. Myocardial hypertrophy is often observed and an association with fibrosis increases the risk of ventricular arrhythmias.[16] Paradoxically, some authors report that abnormalities related to liver cirrhosis could have a "protective" effect to the risk of coronary artery disease and acute coronary events. Such factors would be attributed to hepatic dysfunction and hemodynamic effects of portal hypertension, such as worsening of coagulation, presence of thrombocytopenia and platelet dysfunction, blood pressure decreased due to lower peripheral vascular resistance, abnormal lipid metabolism causing a decrease in cholesterol levels and increased levels of estrogen.[15] However, a lower incidence of coronary events in this population is controversial and, in the case of patients infected with HCV, the risk of atherosclerotic disease could be increased by other factors not well known, as previously reported.

Autonomic dysfunction is also an important marker of cirrhotic cardiomyopathy. Increased sympathetic activity and the renin-angiotensin-aldosterone system contribute to increased cardiac output, sodium and water retention and consequent increase in blood volume, associated with a reduction in peripheral vascular resistance due to the greater release of nitric oxide in the peripheral circulation, besides influencing ventricular remodeling with greater hypertrophy and worsening of the systolic and diastolic functions. The hyperadrenergic state facilitates the release of cytokines and the stimulation of cellular apoptosis, increasing myocardial impairment.[15]

One of the main disorders caused by cirrhotic cardiomyopathy is the relative hypoxemia caused by vasodilation of the pulmonary arterial bed (Hepatopulmonary Syndrome). A significant increase in the diameter of the pulmonary capillaries produced by a higher concentration of nitric oxide in the arteriolar and pulmonary capillary beds would allow the passage of several erythrocytes simultaneously in the alveolar exchange area, leading to a lower oxygenation of these, resembling the right-left shunt effect. On the other hand, increased production of vasoconstricting agents in the splanchnic circulation could cause the so-called portopulmonary hypertension — initially reversible — but with the development of endothelial hyperplasia, local thrombosis and vessel obstruction, this pulmonary arterial hypertension becomes irreversible.[17]

Special attention should be given to the electrophysiological disorders in cirrhotic cardiomyopathy. Previous studies have reported cardiac arrhythmias as the main clinical manifestation in patients with cardiac abnormalities related to HCV infection and in patients with liver cirrhosis due to any etiology. The increase in the QT interval is the most frequently observed abnormality, with an incidence of up to 50% in this population, apparently more pronounced the greater the activity of the disease and the worse the liver function.[18] Specifically in the case of hepatitis C, QT increase may be higher in patients coinfected with HIV.[19] Long QT has been described as a predictor of mortality in liver cirrhosis.[16]

The use of some common drugs in cirrhotic patients is also related to increased QT interval. An example are the fluoroquinolones used in the treatment of spontaneous bacterial peritonitis. Similarly, in HIV coinfected patients, the associated antiretroviral therapy has also been described as a cause of significant QT interval increase.[20] The onset of severe ventricular arrhythmias, such as polymorphic ventricular tachycardia (Torsade de pointes) associated with long QT, may be a rare cause of sudden death in this population.

In addition to ventricular arrhythmias, supraventricular tachyarrhythmias such as atrial fibrillation and flutter are more often diagnosed in cirrhotic patients. Lee et al.,[21] found that the presence of hepatic cirrhosis is an independent predictor for the occurrence of atrial fibrillation (AF), especially in the population younger than 65. However, although the presence of AF is related to higher mortality in the general population, this arrhythmia had no correlation with higher mortality in the cirrhotic group, which could be explained by the high proportion of deaths in this group, about five times higher compared to the control group.[21]

Atrioventricular and intraventricular conduction disorders are also described in these patients with a higher prevalence in the general population.[16] However, the findings related to autonomic dysfunction with chronotropic deficit are the main abnormalities related to heart rhythm. The explanation for this fact is mainly the progressive loss of sensitivity of cardiac beta-adrenergic receptors, despite the high sympathetic tone in cirrhosis. In addition, decreased response to beta-adrenergic stimulus would also be related to the involvement of other elements of sympathetic signal transduction, including the receptor itself, G protein and adenylyclase activity, decreasing AMPc levels.[22] Other studies reported that the chronotropic incompetence observed in physical or pharmacological stress response tests could be a predictor of cardiovascular events (myocardial infarction and heart failure) in cirrhotic patients that had a liver transplant.[23,24]

The treatment of cardiac disorders in cirrhotic patients presents some peculiarities in comparison to other forms of myocardiopathies. The use of non-cardioselective beta-blockers (e.g. propranolol) can prevent the bleeding of esophageal varices, decrease the risk of severe arrhythmias associated with increased QT interval and improve diastolic dysfunction, playing an important role in decreasing the deleterious effects of hyperadrenergic state. The use of angiotensin-converting enzyme inhibitors may prevent cardiac remodeling and arrhythmias such as atrial fibrillation and should be used with caution because of the risk of hypotension, since these patients already have a lower peripheral vascular resistance. Aldosterone inhibitors, such as spironolactone, have a better effect on blood volume reduction than loop diuretics in this population, and also contribute to the reduction of myocardial fibrosis. Liver transplant may reverse most of the cardiac abnormalities mentioned.[15]

Treatment of hepatitis C

Interferon and Ribavirin

Interferon (IFN) has several biological properties which mainly include antiviral, immunomodulatory and antiproliferative actions. Alpha-IFN (produced by leukocytes), widely used in the treatment of patients with hepatitis C, has several side effects, including cardiac abnormalities that are rare but may represent a greater risk of serious complications.[25]

In the early 1990s, Sonnenblik et al. published a record of 44 patients with cardiac complications related to IFN therapy, including 58% incidence of arrhythmias, 21% of acute coronary syndromes, 12% of cardiomyopathies and 9% of other manifestations, including pericarditis. Of the 25 patients that presented arrhythmias, two had severe ventricular tachyarrhythmias and one had sudden death. Of the eight patients with acute myocardial infarction, six died.[26]

The introduction of alpha interferon pegylate (peginterferon) allowed to increase the interval of subcutaneous administration of IFN to once a week, instead of three times a week in the previous treatment. The association of peginterferon with ribavirin added

greater efficacy to the treatment of hepatitis C compared to conventional IFN, with sustained virologic response rates (absence of viral RNA detection after treatment) in about 50% of the cases. However, many patients discontinued treatment because of adverse drug-related effects. The cardiovascular effects of this treatment are rare and arise as reports of cases in the literature involving supraventricular and ventricular arrhythmias, atrioventricular and intraventricular conduction disorders, cardiomyopathies and pericarditis.[27] On the other hand, Almawardy et al.,[28] studied 120 patients with heart disease that underwent antiviral therapy of hepatitis C with peginterferon and ribavirin and did not find any significant disorders in the incidence of complications or worsening of heart disease in this group of patients.[28]

Direct action antivirals

At the beginning of the current decade, direct-acting antivirals (DAAs) were incorporated into the treatment of hepatitis C in combination with peginterferon for patients with HCV genotype 1.[29] More recently, the introduction of new agents, including sofosbuvir, has led to sustained virologic response rates in more than 90% of the cases. Sofosbuvir is a nucleotide analogue (SN5b) that inhibits HCV polymerase and prevents viral replication. It presents a high genetic barrier to the development of resistance, but should be always associated with another second-generation antiviral such as daclatasvir, simeprevir or ledispavir and possibly ribavirin. The treatment of hepatitis C could be then done with drugs of oral administration only.[30]

In March 2015, an alert was issued by the FDA (Food and Drug Administration), reporting nine cases of bradycardia with severe clinical repercussion in patients using sofosbuvir associated with the concomitant use of amiodarone in the United States. Six of these cases were observed in the first 24 hours of treatment and the others before the end of the second week. Three patients required pacemaker implantation and another case resulted in death.[31] The mechanism by which this association would provoke such disorder has not been elucidated. Such information generated a warning that the use of sofosbuvir in patients using amiodarone should not be recommended or, if the latter were essential for the treatment of potentially serious arrhythmias, the patient should be monitored within the first 48 hours of treatment with sofosbuvir in a hospital environment.

Subsequently, in November 2015, a communication published in the New England Journal of Medicine reported three cases of severe bradyarrhythmia among more than 400 patients treated with AADs, including sofosbuvir, in a French reference center. Of these, two presented severe bradycardia due to sinus dysfunction and there was one case of atrioventricular block with syncope, requiring definitive pacemaker implantation in the three patients. Only one patient was on amiodarone, one was on low-dose propranolol, and the third one did not use drugs known to be heart rate depressants.[32]

Although the safety and efficacy profile of these regimens has been tested in controlled studies, the actual influence of the new antiviral agents on heart rhythm still remains unanswered. The occurrence of drug interactions between AADs and antiarrhythmic drugs or other hepatic metabolizing drugs and bradyarrhythmia prior to treatment are possible mechanisms that justify the complications described.

Most reported cases of severe bradyarrhythmia associated with the new antivirals were associated with previous use of the antiarrhythmic drug amiodarone. Amiodarone has extensive hepatic metabolism inhibiting CYP3A4, CYP2D6 and CYP2C9, CYP450 isoenzymes (Cytochrome P 450). In addition, it has a P-glycoprotein inhibitory effect (Gp-P), which is also present in cardiomyocytes. As sofosbuvir is a substrate of Gp-P, lower transport of this substance would lead to its increased intracellular concentration and consequent cardiotoxicity, leading to bradyarrhythmia. One criticism to this model is the fact that bradycardia has not been described as an adverse reaction in previous studies using high doses of sofosbuvir. On the other hand, other substrates of Gp-P, such as ritonavir (antiretroviral drug), have been related to bradyarrhythmia, raising the hypothesis that drugs with this potential could interact with sofosbuvir.[33] Simeprevir, one of the antivirals that may be associated with sofosbuvir in the treatment of hepatitis C, is a moderate inhibitor of CYP3A4, which has the potential to increase the effect of amiodarone. Another mechanism that could explain the events of bradycardia with the association between the antivirals and amiodarone would be the high plasma binding of this antiarrhythmic drug and the antivirals simeprevir and daclatasvir, promoting a higher plasma concentration of free amiodarone, increasing its effects on the cardiac tissue.[34]

Recently, Millard et al. published an experimental study demonstrating in vitro that the electrophysiological

disorders caused by the association between sofosbuvir and amiodarone are related to the intracellular calcium management in the myocytes, influencing the mechanism of excitation-contraction coupling. This disorder, whose molecular mechanisms involved were not elucidated, would affect the duration of the potential of action and the automatism of the cardiac cells.[35]

One of the cases of bradycardia reported in the treatment of hepatitis C with new antiviral agents was associated with the use of the beta-blocker propranolol, a drug widely used in patients with chronic liver disease, especially with cases of portal hypertension. The drug interaction of this agent with the direct-acting antivirals would not be expected according to the pharmacokinetic properties of these substances.[34]

In fact, the rare occurrence of severe bradyarrhythmia during the treatment of hepatitis C using the new direct-acting antivirals is not well understood. Caldeira et al., in a meta-analysis involving six large studies, did not find cardiovascular events in 1,625 patients using antiviral regimens, including sofosbuvir.[36] Durante-Mangoni et al.,[37] studied 26 patients with HCV using sofosbuvir treatment regimens by performing serial ECGs during treatment, not observing changes in HR behavior, including in patients using beta-blocker, suggesting that this medication does not present an additional risk to the development of bradyarrhythmia in association with new antiviral agents.[37] Hagiwara et al.,[38] described the cardiovascular disorders related to antiviral treatment in 3 cases (3.3%), among 91 patients using sofosbuvir and ledispavir. According to the authors, one of the patients presented bradycardia and increased QT interval, another patient developed atrial fibrillation and a third patient had increased QT interval associated with previous heart failure. The three patients presented clinical improvement with discontinuation of treatment.[38]

Conclusion

The questioning of the association between hepatitis C and the onset of heart diseases has been a target of study and controversy in recent years. A body of evidence suggests that HCV can directly or indirectly cause structural and electrical heart disorders, especially in cases of advanced liver disease. However, there is no consensus among the authors that HCV infection would be a risk factor for coronary artery disease and the onset of primary cardiomyopathies.

Similarly, it is still unclear whether treatment of hepatitis C with direct-acting antivirals could cause severe bradyarrhythmia or whether this risk is particularly observed with the combination of amiodarone or other drug interactions. While new studies do not clarify these issues, these hypotheses should not be overlooked in the clinical approach of this infection.

Author contributions

Conception and design of the research: Rezende AGS. Acquisition of data: Rezende AGS. Analysis and interpretation of the data: Rezende AGS. Writing of the manuscript: Rezende AGS. Critical revision of the manuscript for intellectual content: Rezende AGS, Lopes EP, Markman-Filho B.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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