REVIEW

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Idiopathic dilated cardiomyopathy: A common but mystifying cause of heart failure

ABSTRACT

While researchers try to elucidate the origins of idiopathic dilated cardiomyopathy, clinicians continue to face the challenges of identifying and treating the causes of this condition to improve symptoms and survival. We review classification schemes for dilated cardiomyopathy and the current range of diagnostic and therapeutic options and treatment goals.

KEY POINTS

Idiopathic dilated cardiomyopathy may result from a combination of factors, among them genetic predisposition, chronic viral myocarditis, and immune system dysfunction.

The clinical presentation of idiopathic dilated cardiomyopathy varies from patient to patient, but most patients present later, ie, at some point in the spectrum of heart failure.

Numerous studies show that angiotensin-converting enzyme inhibitors improve symptoms and decrease morbidity and mortality from heart failure, and that long-term beta-blocker treatment improves symptoms and lowers hospitalization and death rates.

TREAT THE UNDERLYING DISEASE. We hear this all the time. But many cases of heart failure are due to idiopathic dilated cardiomyopathy, which by definition has no known cause.

The challenge is to identify and treat the known and treatable causes of dilated cardiomyopathy early enough to improve symptoms and survival. In this article, we review current classification schemes, theories of pathogenesis, and the current range of diagnostic and therapeutic options.

BACKGROUND

Dilated cardiomyopathy is much more common than the other major forms of cardiomyopathy (hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathy). It is a heterogeneous disease characterized by ventricular and sometimes atrial dilatation, with normal or reduced wall thickness, eventually leading to varying degrees of impaired systolic function. The clinical picture at the time of diagnosis can vary widely from patient to patient; some have no symptoms, whereas others have progressive refractory heart failure.

Incidence and impact

Dilated cardiomyopathy has an incidence of more than 36.5 cases per 100,000 persons,[1] and it accounts for nearly 50,000 hospitalizations and 10,000 deaths each year in the United States.[2] The incidence has increased over the past 5 to 10 years, perhaps due both to the development of noninvasive diagnostic tools and to improved physician awareness.

TABLE 1

Known causes of dilated cardiomyopathy

Electrolyte abnormalities
- Hypocalcemia
- Hypophosphatemia
- Uremia

Endocrine abnormalities
- Cushing disease
- Diabetes mellitus
- Growth hormone abnormalities
- Hypothyroidism/hyperthyroidism
- Pheochromocytoma

Hypertension (long-standing)

Infectious causes
- Bacterial (brucellosis, diphtheria, psittacosis, typhoid fever)
- Fungal
- Mycobacterial
- Parasitic (Chagas disease, schistosomiasis, toxoplasmosis)
- Rickettsial
- Viral (coxsackie A and B viruses, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, varicella virus)

Infiltrative diseases
- Amyloidosis
- Hemochromatosis
- Sarcoidosis

Ischemia

Neuromuscular diseases
- Duchenne muscular dystrophy
- Friedreich ataxia
- Myotonic dystrophy

Nutritional abnormalities
- Carnitine
- Selenium
- Thiamine

Rheumatologic diseases
- Giant cell arteritis
- Scleroderma
- Systemic lupus erythematosus

Tachyarrhythmias

Toxins
- Amphetamines
- Antiretroviral agents
- Carbon monoxide
- Chemotherapeutic agents, radiation
- Chloroquine, phenothiazines
- Cobalt, lead, mercury
- Cocaine
- Ethanol

Valvular heart disease

Dilated cardiomyopathy is the main indication for heart transplantation

Dilated cardiomyopathy represents a major health burden. As a result, much research is underway to find better diagnostic techniques and treatments that can decrease morbidity and death. For now, dilated cardiomyopathy remains the primary indication for heart transplantation in the United States.

WHO classification nomenclature

The World Health Organization/International Society and Federation of Cardiology Task Force report[3] classifies dilated cardiomyopathy as primary (idiopathic or familial) or secondary (most commonly ischemic, hypertensive, valvular, alcohol-related, or viral or autoimmune in origin). According to this scheme, types of cardiomyopathy secondary to specific disease processes are "specific" cardiomyopathies. For example, dilated cardiomyopathy due to coronary artery disease is known as ischemic cardiomyopathy. The report also defined dilated types of cardiomyopathy as a cardiac muscle disorder with impaired ventricular function (ejection fraction < 40%) and increased end-diastolic and systolic volumes.[3] We will discuss specific diagnostic criteria later.

PATHOGENESIS: NEW HYPOTHESES

TABLE 1 outlines the known causes of dilated cardiomyopathy. However, in most cases, the cause is not known—hence the label "idiopathic."[4] Some experts have postulated that these cases are attributable to a single cause; however, idiopathic dilated cardiomyopathy is now thought to be multifactorial, with several new hypotheses.[5]

Genetic predisposition

Over the past few years, much attention has been given to finding a genetic cause for idiopathic dilated cardiomyopathy, as some 20% of cases of idiopathic dilated cardiomyopathy are found to have a familial link[6] and are termed *familial dilated cardiomyopathy*. Moreover, in practice, this percentage most likely represents an underestimation, as our diagnostic tools lack the sensitivity needed to demonstrate a genetic linkage. Given the absence of accepted diagnostic criteria, some investigators believe that a much larger percentage of cases are familial than was initially suspected.[7]

Most of these cases are now known to exhibit an autosomal-dominant pattern of transmission. While autosomal-recessive, X-linked, and mitochondrial patterns have been studied, these are quite rare. Several gene mutations have been isolated that are specific for each mode of transmission. Most of the isolated genes code for contractile or structural proteins within the myocyte, leading to compromised myocyte structural integrity or impaired inotropic activity or both.[8] Other genes have been found to interrupt cardiac energy metabolism via alteration of transcription factors, leading to obvious deleterious effects on overall myocyte function.[8]

Typically, penetrance is variable, and the clinical progression of the disease seems to be age-dependent, with a much higher incidence at older ages.[9] This indicates that early diagnosis may alter the clinical course in familial dilated cardiomyopathy.

Chronic viral myocarditis

Coxsackie A and B viruses or echoviruses can cause acute myocarditis, so experts have hypothesized that idiopathic dilated cardiomyopathy results from a chronic viral myocarditis with progressive myocyte damage and, eventually, death. Studies[10–12] have shown increased viral particles within the cardiac myocyte via endomyocardial biopsy and viral serology in the setting of idiopathic dilated cardiomyopathy. But these studies were quite small, with a wide range of viral involvement (10%–50%). Ongoing trials, which are nearing completion, may provide further data to support this hypothesis.

Immune system dysfunction

Both humoral and cell-mediated immune responses have been implicated in idiopathic dilated cardiomyopathy. Some investigators have proposed an autoimmune process, while others point out that impaired immune function may play a large role. HLA associations (HLA-B27, HLA-A2, HLA-DR4, and HLA-DQ4) have been identified,[13] but further evidence is required to show a causal relationship. Some have argued either that heightened immune responses may occur in response to a chronic infectious process such as viral myocarditis, or that impaired immune response may lead to increased susceptibility to chronic viral myocarditis. Likely, immune and infectious processes concurrently play a role in the development of idiopathic dilated cardiomyopathy.

CLINICAL FEATURES

The clinical presentation of idiopathic dilated cardiomyopathy varies from patient to patient, but most patients are in overt heart failure by the time they present. Patients often present with symptoms relating to left ventricular or biventricular failure. Initially, generalized fatigue, weight loss, loss of appetite, and other vague, nonspecific symptoms may predominate. Patients who present in the later stages of heart failure tend to have progressive shortness of breath on exertion, peripheral edema, orthopnea, and paroxysmal nocturnal dyspnea as the most common signs and symptoms. Less frequently, idiopathic dilated cardiomyopathy may present with syncope, chest pain, thromboembolism, dysrhythmias, and, rarely, sudden death. These are seen most often in patients who are diagnosed late in the disease course.

Most patients are already in heart failure when they present

Potential sequelae

A small percentage of patients develop pulmonary or systemic emboli, usually in the later stages of disease, but earlier if the treatment regimen is not optimal. Cardiac dysrhythmias such as ventricular tachycardia and supraventricular tachycardia are not uncommon. Approximately 25% to 35% of patients have intermittent nonsustained ventricular tachycardia, while fewer have supraventricular tachycardia (usually atrial fibrillation). Thus, syncope and sudden death are usually a function of the severity of dysrhythmia.

DIAGNOSIS

The diagnosis of idiopathic dilated cardiomyopathy involves first excluding known causes of dilated cardiomyopathy, which may or may not be reversible. Although most cases of dilated cardiomyopathy are irreversible, ruling out reversible causes is essential, as this will affect the diagnostic approach and treatment scheme. **TABLE 2** outlines specific inclusion and exclusion

TABLE 2

Diagnostic criteria for idiopathic dilated cardiomyopathy

Inclusion criteria

Ejection fraction of the left ventricle < 45% and/or fractional shortening < 25% (> 2 SD below the mean), as ascertained by echocardiography, radionuclide scanning, or angiography

Left-ventricular end-diastolic diameter > 117% of the predicted value corrected for age and body surface area, which corresponds to 2 SD above the predicted normal limit +5%

Exclusion criteria

Systemic hypertension (> 160/100 mm Hg)

Coronary artery disease (> 50% in one or more major branches)

Chronic excess alcohol (> 40 g/day in women, > 80 g/day in men for more than 5 years after 6-month abstinence

Systemic disease known to cause dilated cardiomyopathy

Pericardial diseases

Congenital heart disease

Cor pulmonale

Rapid, sustained supraventricular tachycardia

criteria for idiopathic dilated cardiomyopathy based on a report by Mestroni et al.[14]

Always ask about alcohol and cocaine use

Detailed history and physical examination

As with any disease, a detailed and directed history and physical examination are critical. The clinician should conduct the history so as to identify clues of known causes of dilated cardiomyopathy. For example, always ask the patient about alcohol use, cocaine use, past illnesses (including infections involving the heart, history of arrhythmias), past medications taken, travel (for possible infectious exposure), pregnancies, and occupations (to rule out exposure to specific toxins). A thorough family history is also paramount because of the reasonably high incidence of familial dilated cardiomyopathy, as discussed above.

Laboratory testing

Routine laboratory testing should include tests for known causes of dilated cardiomyopathy, such as fasting blood sugar (diabetes mellitus), thyroid studies (hypothyroidism or hyperthyroidism), iron studies (hemochromatosis and iron overload), a comprehensive metabolic panel, liver function tests, creatine kinase, and erythrocyte sedimentation rate (TABLE 1).

In patients strongly suspected of having familial dilated cardiomyopathy, genetic testing may be prudent. The diagnosis of familial dilated cardiomyopathy is usually made if idiopathic dilated cardiomyopathy is found in two or more members of the same family, or if there is a history of a first-degree relative with sudden death of unknown cause before age 35.[14]

Chest radiography

Radiographs usually show cardiomegaly with or without pulmonary vascular congestion, depending on the degree of heart failure.

Electrocardiography

Electrocardiograms are usually normal in patients who have dilated cardiomyopathy but are asymptomatic. However, electrocardiograms in symptomatic patients often show conduction defects, atrial dysrhythmias, and ventricular hypertrophy. The test is worth performing in any patient suspected of having dilated cardiomyopathy, because evidence of ischemia, hypertrophy, or conduction system disease helps direct further testing to rule out known causes of these changes.

Echocardiography

Echocardiography is useful in any patient suspected of having any form of dilated cardiomyopathy: it is quick, noninvasive, and relatively inexpensive and aptly visualizes most of the anatomy of the heart. It helps rule out known causes of dilated cardiomyopathy, such as valvular heart disease, in which four-chamber dilatation is seen with an impaired left ventricular ejection fraction (< 40%).

Exercise testing, coronary angiography

Exercise testing should be included as part of the workup to assess for coronary artery disease. It may also help in evaluating functional capabilities in patients with previously diagnosed idiopathic dilated cardiomyopathy.

Coronary angiography may also be required to definitively exclude ischemic heart disease as a cause of dilated cardiomyopathy. Idiopathic dilated cardiomyopathy remains a possible diagnosis even if none of the major

vessels is occluded by more than 50%, as the degree of dilatation may be out of proportion to the extent of ischemia. Newer tests such as dobutamine echocardiography and radionuclide imaging may help distinguish ischemic cardiomyopathy from idiopathic dilated cardiomyopathy.

Viral serologic testing

The role of viral serologic testing in idiopathic dilated cardiomyopathy remains controversial. It may be helpful in patients with chronic immunosuppression (ie, human immunodeficiency virus, cancer). While it is useful in patients with suspected acute viral myocarditis, at this time viral serologic testing is not routinely recommended in patients with suspected dilated cardiomyopathy, because the results of serologic testing do not influence the treatment.

Endomyocardial biopsy

Endomyocardial biopsy should not be performed on all patients with suspected idiopathic dilated cardiomyopathy.[15] Instead, it should be reserved for patients with suspected infiltrative disease of the myocardium, such as hemochromatosis or amyloidosis. It may also be considered in patients with fulminant heart failure to exclude giant cell myocarditis, which requires early and aggressive treatment. As our understanding of the pathogenesis of dilated cardiomyopathy improves and our treatment options expand, endomyocardial biopsy will undoubtedly be used more.

Skeletal muscle biopsy

Skeletal muscle biopsy may be performed in rare cases in which a primary muscle disorder (ie, Duchenne muscular dystrophy) is suspected.

TREATMENT

The treatment of idiopathic dilated cardiomyopathy is similar to that of other types of low-output heart failure with systolic impairment. Lifestyle modification is important, with thorough patient education about proper diet and exercise and the need to avoid all cardiotoxins (eg, alcohol). ACE inhibitors, beta-blockers, diuretics, digoxin, anti-arrhythmics, and anticoagulation are all used to some extent in the medical management of all types of heart failure, including idiopathic dilated cardiomyopathy. We discuss below the significance of several of these medications in the treatment of low-output heart failure secondary to idiopathic dilated cardiomyopathy.

Angiotensin-converting enzyme inhibitors

By suppressing the activation of the renin-aldosterone-angiotensin system, thereby decreasing both preload and afterload, and by preventing, slowing, or perhaps even reversing remodeling, angiotensin-converting enzyme (ACE) inhibitors are paramount in the treatment of idiopathic dilated cardiomyopathy. More than 30 large placebo-controlled clinical trials have shown that ACE inhibitors improve symptoms and significantly decrease morbidity and mortality in heart failure, including heart failure due to idiopathic dilated cardiomyopathy. At present, enalapril, captopril, lisinopril, quinapril, ramipril, and fosinopril are all approved for the treatment of low-output heart failure due to any cause.

Beta-blockers

Beta-blockers have recently become standard treatment for chronic compensated heart failure, complementing the use of ACE inhibitors. By dampening the adrenergic neurohormonal release, beta-blockers have also been shown in numerous studies to decrease cardiovascular morbidity and mortality in heart failure. The caveat is that is that beta-blockers may in fact be of more benefit to those with cardiomyopathy due to ischemia.[16,17]

More than 30 large studies show that ACE inhibitors reduce morbidity and mortality in heart failure

Some investigators have observed that most patients with idiopathic dilated cardiomyopathy derive some benefit from beta-blocker treatment, while a small percentage may demonstrate disease regression or even normalization of the myocardium. As evidenced by some 20 large, placebo-controlled, randomized trials including the US carvedilol trials, the Cardiac Insufficiency Bisoprolol Study (CIBIS I and II), and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), long-term treatment with beta-blockers improves symptoms and lowers hospitalization and death rates. At present, carvedilol and meto-

TABLE 3

Predictors of poor prognosis in idiopathic dilated cardiomyopathy

Biochemical features
- Elevated levels of angiotensin II
- Elevated levels of atrial natriuretic factor
- Elevated levels of epinephrine (adrenaline)
- Elevated levels of norepinephrine (noradrenaline)

Clinical features
- History of syncope
- Male sex
- New York Heart Association class IV
- Older age
- Persistent third heart sound, gallop rhythm
- Signs of right heart failure

Electrocardiographic features
- Atrial fibrillation
- First-degree or second-degree atrioventricular block
- Left bundle branch block
- Ventricular tachycardia

Exercise test features
- Peak oxygen consumption < 12 mL/kg/minute

Hemodynamic features
- Cardiac index
- High right atrial pressure
- Low mean arterial pressure
- Pulmonary capillary wedge pressure >20 mm Hg

Ventriculographic features
- Decreased ventricular mass-volume ratio
- Global diffuse wall motion abnormality
- Low left ventricular ejection fraction
- Large left ventricular end-diastolic dimension
- Right ventricular dilatation
- Spherical left ventricular geometry

prolol are the only two beta-blockers approved for the treatment of chronic compensated heart failure.

Antiarrhythmics, implantable cardiac defibrillator

As discussed earlier, many patients with idiopathic dilated cardiomyopathy experience some type of dysrhythmia, such as supraventricular tachycardia or nonsustained ventricular tachycardia. As maintaining sinus rhythm is essential to maximize cardiac output and reduce the occurrence of emboli, treatment of supraventricular tachycardia in these patients does not differ from that in any other clinical setting. Nonsustained ventricular tachycardia, a very common entity in these patients, usually requires no treatment, whereas symptomatic sustained ventricular tachycardia may require placement of an implantable cardiac defibrillator. Several trials are underway to determine if implantable defibrillators are useful in idiopathic dilated cardiomyopathy.

Anticoagulants

Currently, the role of anticoagulants in idiopathic dilated cardiomyopathy is not well defined. However, if the patient has a history of thromboembolism or persistent or paroxysmal atrial fibrillation, or has severe chamber dilatation, the clinician may consider initiating anticoagulant therapy, typically warfarin.

If all else fails, cardiac transplantation

When all other treatment options prove unsuccessful and the patient is deemed to have terminal-stage heart failure, heart transplantation may be considered. Idiopathic dilated cardiomyopathy remains the primary indication for heart transplantation in the United States. Success rates are high and continue to improve. Prognosis after transplantation has also improved dramatically, as survival rates at 5 years and 10 years are now 74% and 55%, respectively.[18] Cardiac transplantation seems to be of more benefit in patients with idiopathic dilated cardiomyopathy than in patients with dilated cardiomyopathy due to a known cause. Unfortunately, the scarcity of donor hearts currently limits the use of this treatment option.

PROGNOSIS

Clinical survival studies show varying results, some of which may not be applicable at this time with the advent of newer treatments. Before ACE inhibition was commonplace, the mean survival rate at 5 years was approximately 50%.[19] At this time, some investigators suggest that the mean survival rate at 5 years is closer to 80%.[20] Such improved survival is thought to be due to improved physician awareness of the condition, more advanced diagnostic and monitoring techniques, and improved medical and surgical

treatments.

During the clinical course of idiopathic dilated cardiomyopathy, a number of clinical and diagnostic measures may be monitored to predict prognosis (TABLE 3). The most important and best predictors are the New York Heart Association heart failure functional class, the left ventricular ejection fraction, and the peak oxygen consumption.

FUTURE CONSIDERATIONS

As our understanding of the pathogenesis of idiopathic dilated cardiomyopathy evolves, many of the currently proposed etiologic pathways may be elucidated and new ones discovered, and future treatments may be tailored to particular pathways. For example, several studies are currently examining the potential role of immunosuppressive drugs in the treatment of idiopathic dilated cardiomyopathy, with some encouraging preliminary results.[21]

As the prevalence of heart failure steadily rises, the fact that more than half of all dilated cardiomyopathy cases are still labeled idiopathic is disturbing and frustrating to many clinicians. We hope that the intensive research efforts now underway provide a better understanding of and better treatment options for idiopathic dilated cardiomyopathy in the future.

Too many cases of dilated cardiomyopathy are still labeled 'idiopathic'

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