Carcinoid Heart Disease – a hidden complication of neuroendocrine tumours

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Abstract

Carcinoid heart disease (CHD) develops in serotonin-producing neuroendocrine tumours (NET) due to fibrotic endocardial plaques with associated valve dysfunction leading most often to right-sided heart failure.

The classical carcinoid syndrome usually occurs when serotonin-producing NET metastasize to the liver. Up to 50% of those patients will exhibit carcinoid heart disease.

The pathophysiological process is not yet completely understood : serotonin is considered to be a major initiator of the fibrotic process, but other tumour secreted factors may contribute to the pathogenesis. Histopathology reveals intact valvular cusps with superimposed fibrotic plaques, leading to thickening and retraction of the valves, causing valvular dysfunction.

A high index of clinical suspicion to diagnose CHD is needed since symptoms can be rather non-specific. Transthoracic echocardiography is the gold standard for diagnosis and should probably be performed at the time of diagnosing serotonin-producing NET and then repeated annually. On the other hand, when diagnosing right-heart failure, the presence of CHD and underlying serotonin-producing NET should be taken into account.

Therapeutic options include pharmacotherapy for heart failure, control of the systemic carcinoid disease and in selected individuals cardiac valve replacement.

The elucidation of the pathologic process is necessary to develop targeted antifibrotic therapeutic agents since CHD seems to be irreversible and associated with poor prognosis. (Acta gastroenterol. belg., **2009**, 72, **34-38**).

Key words : carcinoid heart disease, pathophysiology, serotonin, diagnosis.

Introduction

Neurodendocrine tumors (NET) originate from neuroendocrine (enterochromaffin) cells and can be found in any tissue derived from endoderm. The gastrointestinal tract is the most common site with the appendix and terminal ileum as the more frequent locations of serotonin-producing NET. Other locations are the bronchial tree and the gonads.

NET are rare tumours with an incidence of approximately 2-4 per 100.000/year (1). Symptoms are often nonspecific and include abdominal pain, diarrhea, intermittent intestinal obstruction, and gastrointestinal bleeding. Although these tumors are in general slow growing, prognosis is dependent on the extent of the disease (2). The classical carcinoid syndrome develops when amine substances and neuropeptides are released into the systemic circulation. Different active compounds such as serotonin, histamine, bradykinin, tachykinin, motilin, kallikrein, catecholamines, substance P and prostaglandins are secreted. The syndrome occurs in about 10% of patients with advanced serotonin-producing NET (3). Its most typical clinical manifestations are episodic cutaneous flushing, gut hypermotility with secretory diarrhoea, bronchospasm and hypotension (4).

About 50% of patients with carcinoid syndrome will exhibit carcinoid heart disease (CHD). However, in 20% of patients with serotonin-producing NET, CHD may be the initial presentation in certain series (5). However, we question this incidence in daily practice. CHD is a major cause of morbidity and mortality. In studies there is a slight male predominance (60%) and the mean age at diagnosis is 56-63 years (6).

In a retrospective study of 200 patients, CHD was diagnosed approximately 1,5 years after diagnosis of the serotonin-producing NET (7). Larger intervals of up to 5 years have been reported.

Pathophysiology

The first clear description of the carcinoid heart disease was published by Biork in 1952 (8). CHD is characterized by fibrotic plaques on the endocardium of mainly right-sided valvular leaflets, as well as the right atrium and right ventricle.

In most cases, CHD is present in patients with hepatic metastases when hormonally active tumour products exceed the hepatic capacity for degradation. Exceptions are extensive retroperitoneal carcinoid lymph node metastases, drainage bypassing the liver via the thoracic

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duct and retroperitoneal venous collaterals and rarely ovarian metastases wich drain directly into the systemic circulation via the ovarian venous system (9).

Passage through the pulmonary circulation enables sufficient degradation, so that left heart disease usually reflects a persistent foramen ovale. Left-sided heart pathology occurs in about 10% of patients with carcinoid syndrome. Less common causes of left heart pathology are bronchial serotonin-producing NET or a poorly controlled, severe carcinoid syndrome that overwhelms the pulmonary degradation (10).

The signaling pathways responsible for valvular changes in CHD are not completely understood. In clinical studies, patients with high levels of serotonin and high urinary 5-hydroxyindoleacetic acid (5-HIAA, the urinary excreted metabolite) levels are prone to develop cardiac valve changes (5-11). Serotonin is known to promote cell proliferation in valvular subendocardial cells (12). Furthermore, the observations that drugs altering serotonin release and its metabolism, such as the appetite suppressant drug fenfluramine and phentermine (13) or ergoline dopamine agonists used to treat Parkinson's disease (14) may cause valvular lesions similar to those found in CHD, support the pathophysiological role of serotonin, due to expression of mRNA for the different serotonin receptors in the heart (15). 5-HT2B receptors are G-protein coupled and through the phosphorylation of Src kinase and extracellular regulated kinases (ERK) they are known to activate mitogenic pathways. The activity of the transforming growth factor β (TGF-β) might be mediated and enhanced through Src-P, thus augmenting 5-HT2B-stimulated mitogenesis. TGF-β is expressed in CHD and is known to affect growth and to stimulate fibroblast to produce extracellular matrix proteins (10-15).

A recent animal study with Sprague-Dawley rats underlined the potential role of serotonin. These rats were injected daily with high serotonin doses and exhibited increased cardiac weight, valvulopathy and cardiac fibrosis, as well as skin fibrosis and hyperkeratosis (16). Concomitant use of 5-HT2B/2C receptor antagonists such as transdihydrolisuride inhibited these changes (17). Furthermore, the Mastomys gastric carcinoid model does not produce serotonin and does not develop cardiac fibrotic lesions (10).

However, in humans the critical role of serotonin in the genesis of the cardiac fibrotic process is based on indirect evidence only. Despite reduction of serotonin release by therapeutic intervention, cardiac involvement has been shown to develop and even to progress, suggesting that other agents may also contribute in this process. Further exploration is required.

Histopathology

Morphology of the cardiac valves in CHD reveals an intact leaflet with a superimposed fibrotic plaque, lining the endocardial surface of cardiac valves. Affected cardiac valves and tendinous cords have a pearly white appearance and are shortened. The thickening and shortening causes retraction and fixation of the valves, resulting in retrograde valvular leakage often combined with an antegrade outflow obstruction, as if the valve is fixed in a half open status.

The endocardial plaques are composed of myofibroblasts, smooth muscle cells, deposits of extracellular matrix and an endocardial cell layer. A recent series of the Mayo Clinic evaluated 139 valves derived from 75 patients. Proliferation of myofibroblasts was noted in all plaques, extracellular matrix included collagen in 99% and myxoid ground substance in 98%, neovascularization (94%), inflammation (94%) and elastosis (20%) (18). They occur on the endocardial surface of valvular leaflets and cardiac chambers, and on the intima of the great veins and arteries in areas exposed to high circulating concentrations of tumour products.

Myofibroblast proliferation and myxoid matrix were the characteristic findings in thickened pulmonary valves, whereas thickening of tricuspid valves was mainly attributed to collagen deposition (19).

Clinical presentation

Serotonin-producing NET are often slow growing and long-term survival may be observed. However, the median survival from onset of symptoms of carcinoid syndrome is 38 months in untreated patients. A further decline in outcome with a median survival of 11 months is described in untreated patients developing CHD (19).

The diagnosis may be delayed by the fact that in the early stages symptoms of CHD are often subtle and severe tricuspid and pulmonary valve disease can be well tolerated for months. The disease predominantly affects the right-sides valves. Tricuspid valve involvement results in hemodynamically relevant regurgitation and less frequently in valvular stenosis.

Occurrence of hemodynamically relevant pulmonary valve stenosis is more frequently noted because of the smaller orifice of the pulmonary valve.

Initial clinical features of right sided valvular disease are fatigue and exertional dyspnea, symptoms that can be difficult to differentiate from constitutional symptoms of a malignancy. Left-sided involvement occurs in less that 10%, resulting in regurgitation without concurrent stenosis. In case of progression of the CHD, worsening of dyspnea, peripheral oedema, hepatomegaly and ascites occur. Rarely patients present with symptoms of left-heart disease, restrictive cardiomyopathy and cyanosis as a result of a patent foramen ovale.

Clinical examination reveals a palpable right ventricular impulse and jugular vein distention due to tricuspid regurgitation. Also the liver may be pulsatile.

Cardiac murmurs are reported to be audible in about 90% of patients with CHD (6,19). A pan-systolic murmur is the result of tricuspid valve regurgitation and may be accompanied by a systolic ejection murmur of

pulmonary valve stenosis. An early diastolic murmur due to pulmonary valve regurgitation may be present.

Tricuspid valve murmurs classically increase in intensity during inspiration.

A study investigating murmurs in CHD showed 77% of patients had a murmur consistent with tricuspid regurgitation, 32% a murmur consistent with pulmonary stenosis and 31% a murmur consistent with pulmonary regurgitation, in 8% no murmurs were heard (6). Atrial fibrillation is often present.

Diagnosis

It is important to maintain a high index of clinical suspicion to diagnose CHD since more than 50% of patients with the carcinoid syndrome will develop CHD. It may be preferable to perform an echocardiography at the time of diagnosis of a serotonin-producing NET.

Biochemical markers

The end product of the serotonin metabolism, 5-HIAA (5-hydroxyindole-acetic acid), is secreted in urine. It is also a reliable marker of the presence and the activity of serotonin-producing NET. Intake of tryptophan-rich foods such as tomatoes, bananas, eggplant, avocados, plums, plantain, pineapples, walnuts an kiwis, can result in false elevations. Conversely, levodopa can falsly lower the urinary 5-HIAA concentration. Some studies suggest that higher concentrations of urinary 5-HIAA are related to the occurrence of CHD, disease progression and a worse prognosis (20).

Chromogranin A (CgA), an acidic glycoprotein stored in secretory granules of neuroendocrine cells, has a diagnostic value in addition to reflecting hormonal control. We would like to refer to the related article in this joint publication by Borbath *et al*.

In response to increased wall tension, natriuretic peptides are produced within the atria and ventricles of the heart in the setting of heart failure and then released in the circulation. High serum concentrations of atrial natriuretic peptide (ANP) are likely to be associated with CHD and worse prognosis. However, some data show a greater diagnostic accuracy for CHD when the N-terminal fragment of the brain natriuretic peptide prohormone (NT-proBNP) is measured instead of ANP (21).

Radiology

The chest X-ray may display an increased cardiothoracal index and rather non-specific findings such as pleural effusions and pulmonary nodules. It is normal in up to 50% of all patients. MRI and 64-slice CT-scans can be useful in evaluating the pulmonary valve when visualisation by echocardiography is difficult (10,19-20).

Electrocardiogram

An electrocardiogram is of limited value. In half of the patients it is normal. Otherwise non-specific ST-segment changes, p-pulmonale, sinus tachycardia, atrial fibrillation and low voltage QRS complexes are detected (10,17-18).

Echocardiography

The key element in establishing the diagnosis of CHD is the transthoracic echocardiography. On 2-dimensional echography the typical findings of thickened and retracted tricuspid valve leaflets can be shown. Tricuspid regurgitation is present in almost all patients, tricuspid stenosis in 59%, pulmonary valve regurgitation in about 50% and pulmonary stenosis in about 25%.

Chronic tricuspid and pulmonary valve regurgitation leads to a chronic volume overload of the right-sided heart, resulting in enlarged right ventricle and atrium. Ventricular septal wall motion abnormalities are seen in almost 50%.

The presence of pulmonary stenosis in combination with tricuspid regurgitation is hemodynamically disadvantageous, as indeed pulmonary stenosis is thought to worsen the severity of tricuspid regurgitation. Visualisation of the pulmonary valve leaflets may be challenging as they can be severely retracted. The degree of stenosis is often underestimated due to low cardiac output and severe tricuspid regurgitation.

Left-sided valvular involvement is infrequent (< 10%) and characterized by valve thickening and retraction. It results in reduced mobility, regurgitation and seldom in stenosis (10,19-20). Myocardial metastases are rare. When thransthoracic visualization is inadequate, transesophagal echocardiography can be undertaken.

Treatment

Management is aimed at relief of symptoms. Patients with CHD require a multidisciplinary approach of an experienced team focused on symptom and disease control as treatment is complex.

Management of the cardiac disease can be divided into treatment of the right heart failure and surgical interventional treatment of valvular pathology.

Management of the systemic disease requires pharmacotherapy to reduce the secretion of tumour products. Relief of symptoms can also be achieved surgically by debulking the tumour and in case of hepatic metastates, by embolisation of the hepatic artery.

Pharmacotherapy and tumor debulking

The use of somatostatin analogs, binding to somatostatin receptors on the surface of serotonin-producing tumour cells, decrease the secretion of bioactive substances and in addition may reduce the negative hemodynamic effects that vasoactive agents may have on CHD and secondary heart failure (10).

Octreotide is an eight aminoacid peptide binding to somatostatin receptors. It is currently used as a short-

acting formulation, administered 3 times daily subcutaneously, and as a long-acting release formulation (LAR), injected as a once-a-month intramuscular depot. A newer somatostatin analogue, lanreotide, may be used as an alternative to octreotide LAR. Some studies demonstrated evidence that the use of interferon-α create hormonal control in the carcinoid syndrome and reduce tumour size. However, there are no data available demonstrating a regression of established carcinoid heart disease by using somatostatin analogues or interferon-α (6-10).

In addition to hormonal therapy, transarterial (chemo)embolisation or debulking surgery may be an option to achieve hormonal control, which is discussed by Hendlisz *et al.* in this joint publication. There is limited efficacy for cytotoxic chemotherapy in patients with serotonin producing NETs with response rates around 20% (19). Chemotherapy should be reserved for patients with refractory symptoms or for patients with poor prognostic factors.

Treatment of right-heart failure

Therapeutic options in patients with symptoms of right-heart failure related to CHD are limited. Water and salt restriction, compression stockings and the use of diuretics may relieve symptoms. As the right-heart failure advances, medical treatment is usually ineffective. Digoxin, vasodilators and angiotensine-converting enzyme inhibitors can be considered, but have no proven efficacy in these patients.

Arterial hypertension needs to be controlled if present and bacterial endocarditis prophylaxis is indicated.

Cardiac Surgery

Patients with CHD should have cardiologic visits on annual or biannual basis. The timing of cardiac surgery is individualized and should be considered when symptoms of right heart failure appear such as fatigue, impaired exercise captivity, progressive right ventricular enlargement or decline in right ventricular systolic function.

In selected cases, balloon valvuloplasty has been used to treat stenotic right heart valvulopathy with mixed results. However, rapid recurrence of symptoms has been described as well as short-lasting symptomatic benefit (10).

Replacement of damaged tricuspid valves and pulmonary valves is the operation of choice. It should preferably be undertaken in mildly symptomatic patients as progression of heart failure will increase the perioperative mortality. The main perioperative complications are bleeding and right ventricular failure (7).

It is also advisable to control circulating tumour products in order to reduce perioperative complications, provoked by carcinoid crises. This involves the use of an intravenous bolus or infusion of octreotide (50-100 μg/h). The treatment should be started at least 2 hours before surgery and continued for at least 48 hours after surgery.

Regarding the choice of prosthesis there is no real consensus and every decision should be individualized (10,19). Recommendations in the past favoring the use of mechanical prosthesis were based on early degeneration of bioprosthesis (related to the presence of vasoactive substances in the circulation) and a less favorable hemodynamic profile. However, the anticoagulation required for mechanic valves may represent a considerable risk for bleeding in patients with advanced liver metastases and in patients undergoing subsequent surgical procedures to achieve hormonal control. Furthermore, mechanic valve prosthesis in the tricuspid position are at greater risk of thrombosis.

Data for surgical management of left heart carcinoid disease are limited.

Prognosis

The use of pharmacotherapy has resulted in improvement of symptom control and survival in patients with advanced serotonin-producing NET. However, the presence of CHD results in an increased risk of morbidity and mortality, with median survival rates of 11 months only in untreated patients. The severity of structural and functional tricuspid valve abnormalities and the increased size of the right ventricle have been shown to be predictors of poor outcome (19). Treatment of the advanced NET and/or its metastases does not result in regression of established CHD.

These data suggest that early detection appears to have important prognostic implications.

In a recent retrospective analysis of 200 patients with CHD from the Mayo Clinic, an increase in median survival from 1,5 years to 4,4 years over the past two decades was demonstrated. In a multivariate analysis, cardiac surgery was associated with a risk reduction of 0,48 (98% confidence interval, 0,31-0,73 ; $P < 0,001$) whereas other treatment modalities were not independently associated with a decreased mortality risk (7-19).

The improvement in survival in this analysis from the Mayo Clinic might reflect the use of somatostatin analogues, the use of surgical cytoreduction and hepatic arterial embolization, the early detection of CHD and more frequently used cardiac surgery with recently a better outcome. However, evidence for these correlations is still lacking.

Conclusions and research agenda

CHD represents a serious complication in patients with secreting neuroendocrine tumours. Over 50% of patients with carcinoid syndrome will develop CHD, associated with increased morbidity and mortality.

We have evidence that high serum concentration of serotonin may initiate the pathologic process that will evolve in mainly right heart disease.

There is no evidence that pharmacotherapy or other treatment modalities have been able to regress established CHD. Moreover, CHD may develop or progress even if secretion of tumour products is well controlled. Further clarification of the pathogenesis of CHD represents an unmet need.

High level of clinical suspicion with early detection of CHD and early cardiac surgical interventions may result in an improved survival of patients with CHD. Some questions remain unanswered, such as the reversibility of CHD, the exact incidence, issues concerning early diagnostic markers and follow-up of patients diagnosed with CHD. Management of patients with CHD is complex and a multidisciplinary approach is therefore needed with inviting a cardiologist to the conference.

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