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Pheochromocytoma induced reverse Takotsubo cardiomyopathy: literature review

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Abstract

Background. Pheochromocytoma is a rare endocrine tumor that principally secretes catecholamines, the amounts which can potentially cause life-threatening cardiovascular complications. A myriad of symptoms and clinical findings are associated with pheochromocytoma, including a Takotsubo cardiomyopathy.

Aim. The aim was to review the recent literature on the presentation, treatment and outcomes of Takotsubo cardiomyopathy induced by catecholamines producing adrenal tumor pheochromocytoma.

Methods. The article search was made using PubMed and Google Scholar databases for full-text original articles or reviews using the keywords: „pheochromocytoma“, „myocardial stunning“, „Takotsubo cardiomyopathy“, „Takotsubo syndrome“, „stress cardiomyopathy“ and their combinations. The results of primary literature search were filtered and duplicates were removed. In all, 41 publications were included in this article.

Results. Due to secretion of catecholamines patients typically present with classic triade – headache, palpitation and sweating. Clinical expression may involve various cardiovascular manifestations, most usually – hypertension. Echocardiography, ventriculography can confirm takotsubo cardiomyopathy diagnosis, while computed tomography and magnetic resonance imaging – endocrine origin of pathology and laboratory urinalysis for catecholamines metabolites could prove the diagnosis of pheochromocytoma.

Conclusions. Early suspicion and diagnosis of pheochromocytoma in case of cardiomyopathy or heart failure with symptoms of catecholamine excess and surgical intervention are crucial and may prevent from irreversible cardiac injury and death.

Keywords: pheochromocytoma; Pheochromocytoma induced Takotsubo cardiomyopathy; Takotsubo cardiomyopathy, Stress cardiomyopathy.

1. Introduction

Pheochromocytoma is a rare neuroendocrine tumor. The incidence rate is less than a case per 100 000 people per year (1). The tumor is made up of chromaffin cells and can be located either unilateraly or bilateraly in the adrenal medulla or along sympathetic ganglia. It secretes huge amounts of catecholamines and presents with a classic triade of headache, sweating and palpitation. Most pheochromocytomas are benign tumors, malignancy of this tumor is estimated to be at 10% (2,3). Pheochromocytoma is dangerous because it can secrete huge amounts of catecholamines, which can induce a variety of different diseases, by damaging tissues of the heart and blood vessels, leading to heart disease, stroke, kidney failure, vision loss. Takotsubo cardiomyopathy (TTC) is one of the rare but significant and transient diseases induced by pheochromocytoma. Approximately 2% of all patients presenting with symptoms of acute coronary syndrome (ACS) have a TTC (4). Takotsubo syndrome is a cardiomyopathy, also called a broken heart syndrome or stress-induced cardiomyopathy. It can be primary or secondary, but the main cause of TTC is catecholamine storm. TTC has the characteristic of a transient balloon-like modification of the left ventricular apex and transient wall motion abnormality. The typical ventricle shape of a basket (tsubo) which is used by Japanese fishermen to catch octopuses (tako) is seen with imaging techniques such as echocardiography or magnetic resonance imaging (MRI). This reversible cardiomyopathy usually occurs after intense emotional or physical stress. Typical symptoms of takotsubo cardiomyopathy are not specific. Initially for both the patients and the doctors it reminds of myocardial infarction – pain in the chest region, dyspnea, altered electrocardiogram (ECG) findings – newly emerged ST elevation or T wave inversion or moderate troponin rise (5). This review focuses on pathophysiology, diagnosis, management and prognosis of pheochromocytoma induced Takotsubo syndrome.

2. Materials and Methods

Scientific literature was reviewed using Pubmed and Google Scholar databases for full-text. The keywords used during search: „myocardial stunning“, „pheochromocytoma“, „Takotsubo syndrome“, „takotsubo cardiomyopathy“, „stress cardiomyopathy“ and their combinations. The results of primary literature search were filtered and duplicates were removed. In all, 41 publications were included in this article.

3. Results

3.1. Epidemiology

Previous studies showed an incidence of pheochromocytoma to be 0.04 to 0.95 cases per 100 000 people per year (1). The burst of catecholamines inherent in pheochromocytoma has significant effects on the mechanical and electrical activity of the myocardium. Takotsubo cardiomyopathy is now being increasingly identified and it may be responsible for up to 40% of cases of acute catecholamine cardiomyopathy. The incidence of TTC is estimated to be around 2% in all troponin-positive patients presenting with Acute coronary syndrome (4) There is a growing incidence of pheochromocytoma patients who present with cardiogenic shock from a catecholamine induced cardiomyopathy.

Although, not every patient with this tumor presents symptoms. According to Sutton et al, pheochromocytoma was only diagnosed after the autopsy in 76% of patients without any prior clinical suspicion. Although 50% of all the patients had hypertension, the pheochromocytoma was only clinically diagnosed post mortem (6).

3.2. Pathophysiology

Over the last few decades there is an ongoing discussion over TTC pathophysiology. Until this day the precise pathophysiology of Takotsubo syndrome is obscure, however there are a few hypotheses. TTC can be primary or secondary. In primary TTC, the patient seeks medical care as a result of acute cardiac symptoms, usually induced by stressful triggers, often emotional. In secondary TTC, there is an already underlying disease which causes an activation of sympathetic nervous system or a storm of catecholamines and provokes an acute TTC as a complication of a primary disease. The activation of sympathetic nervous system induces the release of adrenaline leading to coronary artery spasm, microvascular dysfunction, acute myocardial dysfunction and inflammation.

Takotsubo cardiomyopathy (TTC) was first described in Japan in 1980s. It is described as an acute but often reversible left ventricular dysfunction mainly triggered by emotional and physical stress. Multiple variants of TTC have been reported including reverse Takotsubo cardiomyopathy (rTTC) which is a variant characterized by the basal akinesis/hypokinesis associated with apical kinesis that resolves spontaneously within a few days or weeks. The hallmark of rTTC is a clinical presentation similar to an acute coronary syndrome (ACS) with no evident obstructive coronary artery disease. The proportion of patients presenting with the rTTC ranges from 1-23%. Reverse Takotsubo syndrome has been associated with younger age, less decrease in left-ventricular ejection fraction. The exact mechanisms of TTC are unknown, catecholamine cardiotoxicity, coronary artery spasm, coronary microvasculature impairment and estrogen deficiency are the most possible causes.

Pheochromocytoma is a neuroendocrine tumor secreting norepinephrine, epinephrine, and rarely dopamine. Because of the catecholamines secreted into the bloodstream, pheochromocytoma can be a very harmful tumor. It can lead to serious cerebrovascular and/or cardiovascular complications. The exact mechanism of damage to the myocardium caused by sympathetic stimulation is unknown. One possibility is that personally relevant psychological stress and increased sympathetic tone may promote transient myocardial ischemia in patients with or without coronary artery disease (7,8). Another possibility is direct toxic influence of excess catecholamines in bloodstream to myocytes. Activation of sympathetic adrenergic system leads to cyclic AMP-mediated calcium overload, which leads to proteolytic myofilament injury and decreased myocyte viability (9,10). Catecholamines are known to be a potential source of free radicals that promote lipid peroxidation and thus impairing selective membrane permeability, leading to the development of cardiomyopathy (10,11). It is recognized that excess of catecholamines cause TTC. There is evidence that patients with TTC have elevated levels of plasma catecholamines, up to 3 times higher than the patients hospitalized with acute coronary syndrome (12). It has also been documented that administered catecholamines and β-adrenoreceptor agonists trigger TTC (5,13). The reason why the apex of the heart is more susceptible to impairment, is thought to be due to different allocation of the sympathetic nerves (14,15) and different density of those nerves in the cardiac muscle (16).

3.3. Diagnosis

The recognition of TTC has increased in recent decades. Nevertheless, the diagnosis of Takotsubo cardiomyopathy remains complicated. Widely

recognized diagnostic criteria were published by the Mayo Clinic in 2004 and were updated in 2008 (5,17). There are other known slightly different diagnostic criteria for TTC published by the Japanese Takotsubo Cardiomyopathy Group (18), the Gothenburg Group (19), the Takotsubo Italian Network (20), the Johns Hopkins criteria (13), the Taskforce on TTC of the Heart Failure Association of the European Society of Cardiology (21), recommendations by Madias (22) and InterTAK diagnostic criteria (23). The variety of guidelines demonstrate the lack of worldwide consensus on diagnosing TTC. The stress cardiomyopathy tends to target postmenopausal women especially after recent physical or emotional stress or women with psychiatric or neurologic disorders (21,24,25). Typical TTC mimics acute coronary syndrome and patients complain of chest pain, dyspnea, examination shows ST-segment elevation or depression, T-wave inversion on ECG and elevation of serum cardiac troponin and B-type natriuretic peptide (BNP). The only way to exclude coronary disease and a gold standard in diagnosing the syndrome is coronary angiography with left ventriculography (23). Because of the similarity to acute coronary syndrome the disease is difficult to diagnose. It is also worth mentioning that TTC can occur for patients with coronary artery disease (CAD) and the presence of CAD does not contradict TTC diagnosis (17). Another important test is echocardiography. The typical signs include apical ballooning, left ventricle wall motion abnormality or a global left ventricle akinesia involving the entire apex, midventricular or basal segments (26).

With catecholamines secreting tumor it is more complicated. First step is to suspect pheochromocytoma. The tumor tends to mimic various other diseases, therefore it is difficult to make the diagnosis. The first signs include a classic triade: episodic headache (90%), diaphoresis (60-70%), palpitations (70%). Sustained or paroxysmal hypertension is another diagnostic sign, unfortunately very unspecific. The main biochemical tests for pheochromocytoma are measurements for free metanephrine and catecholamine concentrations and 24-hour urine fractionated metanephrines. The tests are not applicable when tumor is smaller than 1cm in size therefore does not release catecholamines or tumors that only secrete dopamine (27). Testing of catecholamines for pheochromocytoma diagnosis is accurate. Characteristic analysis revealed 94% sensitivity and 93% specificity for measurement of plasma free metanephrines and 91% sensitivity and 93% specificity for urinary fractionated metanephrines testing (28). One more important test for diagnosing pheochromocytoma is chromogranin A, whose sensitivity reaches 93% and specificity 96%. Changes in the concentration of chromogranin A have correlation with malignancy and the size of the tumor (29). Striking similiarities between TTC syndrome and those secondary to pheochromocytoma are difficult to rule out the source. Computed tomography (CT) or MRI are the radiological technique of choice for evaluating an adrenal origin. Though CT and MRI provide an excellent information of pathological masses, laboratory data for sensitive urinary catecholamine metabolites and normetanephrine are necessary for further support of the diagnosis of pheochromocytoma.

3.4. Management

The only solution is management of primary disease (i.e. adrenalectomy). However, the preoperative, operative and postoperative management is tough. Although there is not a standardized protocol for medical management of pheochromocytoma induced cardiomyopathy with

pheochromocytoma, α-adrenergic blockade (e.g. phenoxybenzamine, doxazocin) for 10-14 days before the surgery tend to prevent acute adrenal and hypertensive crisis, β-adrenergic antagonist placement contribute to a smooth induction of anesthesia; moreover, they help to maintain steady blood pressure during the surgery (30,31). To decrease the risk of pulmonary edema, after stabilization of cardiac insufficiency, if present, cardioselective β–1 antagonists (atenolol, metoprolol) are recommended. β-adrenergic antagonists are contraindicated when stress cardiomyopathy is diagnosed, as they can lead to the development of pulmonary edema. Calcium channel blockers reduce catecholamine induced coronary artery spasm (32). Prescribing diazepam, secobarbital or meperidine preoperatively prevents a release of tumor catecholamines (33). Postoperatively it is important to monitor the patient, as hypertensive, hypotensive or hypoglycemic crisis is still a possibility, most probably vasopressor support is often necessary to maintain blood pressure support in the sudden absence of excess catecholamines following adrenalectomy (34).

To this day, there are no recognized guidelines for TTC management. Because of the same onset of symptoms, treatment starts the same way as for acute coronary syndrome – with morphine, supplemental oxygen, nitroglycerin, aspirin and heparin. The treatment is symptomatic (21,35). For patients with severe decrease in left ventricular ejection fraction (LVEF), treatment with β-adrenergic antagonists or α-adrenergic agonists should be considered. Calcium channel blockers can also be used for decreasing left ventricle (LV) outflow pressure gradient. For patients with apex akinesia an anticoagulant therapy is recommended until the contractility improves (36).

3.5. Prognosis

TTC is a reversible disease. The recovery time varies depending on the severity of the acute episode. Left ventricular systolic dysfunction usually subsides in a few weeks, ECG changes and BNP levels may take longer to recover, up to 12 months, in some cases the changes may be permanent if scarring of the cardiac muscle occurs (21,37). Pheochromocytoma is fully treatable in a surgical way only if there are no contraindications for an adrenalectomy.

4. Conclusions

Pheochromocytoma is a tumor in disguise also called “multiple faces” disease or the “great mimic”. A physician should always suspect the possibility, especially when clinical manifestation is otherwise non-explainable or symptoms are not easily controlled. The occurrence of paroxysmal hypertension refractory to usual antihypertensive therapy, headaches, sweating, palpitations should raise concern and suspicion. The most important thing to be aware of with pheochromocytoma and catecholamine induced cardiomyopathy is the liability of blood pressure during surgery. Only early diagnosis and complete surgical resection can help achieving cure and possible reversibility of cardiac dysfunction. The possibility of renewal for both pathologies when handled precisely is slim.

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