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PHEOCHROMOCYTOMA: AN ENDOCRINE STRESS MIMICKING DISORDER

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Abstract

Pheochromocytoma is an endocrine tumor that can uniquely mimic numerous stress-associated disorders, with variations in clinical manifestations resulting from different patterns of catecholamine secretion and actions of released catecholamines on physiological systems.

Keywords

pheochromocytoma; stress; general adaptation syndrome; adrenoceptors; catecholamines; hypothalamic pituitary adrenocortical axis; glucocorticoids

Introduction

Pheochromocytomas are rare but treacherous catecholamine-producing tumors that, if not diagnosed or appropriately treated, will almost invariably prove fatal. The tumors may display numerous clinical manifestations similar to psychological or physiological stress. These clinical manifestations result from the hemodynamic and metabolic actions of high circulating catecholamine levels and include hypertension, headache, spontaneous sweating, palpitations, anxiety or panic attacks, as well as the presence of pallor.

The catecholamines, norepinephrine and epinephrine, act on α- and β-adrenoceptors at effector sites throughout the body with different organ-specific distributions. Both catecholamines have overlapping but also distinct actions on the different groups of adrenoceptors (1). In particular, epinephrine has more potent actions on β_2-adrenoceptors than norepinephrine, while norepinephrine is a more potent β_1-adrenoceptor agonist than epinephrine. However, the proximity of sites of norepinephrine and epinephrine release to adrenoceptors and the resulting concentrations at effector sites are also important determinants of adrenoceptor-mediated responses to these two catecholamines.

Stimulation of cardiac β-adrenoceptors by catecholamines released by a pheochromocytoma can elicit severe arrhythmias, aseptic myocarditis or cardiomyopathy. Catecholamine-induced dilating cardiomyopathy is most frequently reported when catecholamine excess is very high. Norepinephrine released locally from sympathetic nerve endings within the

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vasculature causes α_1-adrenoceptor-mediated vasoconstriction resulting in hypertension. In contrast, epinephrine acts potently on β_2-adrenergic receptors of the skeletal muscle vasculature causing vasodilation which can result in hypotension. Catecholamines, particularly epinephrine, stimulate lipolysis, ketogenesis, thermogenesis and glucose production (2).

Similar to stress-related situations, pheochromocytoma-induced metabolic or hemodynamic attacks or episodes may last from a few seconds, up to one or more hours or even extend to much longer intervals in patients with chronically elevated catecholamine levels. Rarely, severe acute release of catecholamines (e.g. during severe stressful situations such as surgery, acute severe psychological stress) may result in multisystem crisis — defined as hypertension and/or hypotension, high fever, encephalopathy and signs of multiple organ failure.

Background

a.Stress

Walter B. Cannon introduced concepts of “homeostasis” and “fight or flight” responses in early 1900’s, initiating development of our understanding of relationships between individuals and their surroundings; however, it was Hans Selye, who borrowed the word “stress” from mechanics to transform the term into a definition for the nonspecific adaptation to the environment (3). Despite a still relatively vague definition with a myriad of symptoms and signs, the concept of stress has steadily evolved over the last half century and is now recognized to play a significant role in human health and disease (Table 1 and Table 2). Responses to stress are mediated through 3 main effector systems: the hypothalamic-pituitary adrenocortical (HPA) axis and adrenomedullary and sympathoneuronal systems. While cortisol is the mediating hormone for the first system, the catecholamines are responsible for actions of two last systems. Although initially seen as a non-specific response, stress is now established to elicit highly specific effector system responses depending on the nature of stressor (4–5).

b. Pheochromocytoma

Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising mainly from the adrenal gland. These chromaffin cell-derived tumors can result in significant morbidity and mortality related to catecholamine oversecretion as described above (Table 3) (6–7). The tumors can manifest with highly variable presentations, from rare and progressive hypercatecholaminergic episodes, through relatively sustained hypertension, to severe and clinically malignant disease, complicated by hypertensive crises, stroke, acute myocardial infarction and numerous other conditions (Figure 1). However, in contrast to stress where stressor-specific responses of the three main effector systems typically arise through CNS-mediated mechanisms, in pheochromocytoma the signs and symptoms occur secondary to release of catecholamines that is autonomous of any nervous system input

Overlap in clinical signs and symptoms

a. General

General signs and symptoms of both conditions are strikingly similar during acute episodes and can be difficult to differentiate based on severity. Anxiety, pallor, sweating, tremor, palpitations and fatigue can be severe in either case.

b. Pulmonary, GI, GU

Increased respiratory rate, diffuse abdominal pain and diarrhea are common in both situations, while more severe disturbances, such as acute mesenteric ischemia with bleeding and perforation, paralytic ileus, intestinal obstruction are mainly restricted to patients with highly functional pheochromocytoma and would perhaps be seen only in patients with very severe stress.

c. Cardiovascular

Hypertension, as well as hypotension can be seen in both conditions. Paroxysmal hypertension is more characteristic for both conditions, while sustained hypertension may be more typical for pheochromocytoma. Hypertensive crisis, shock, or stroke can occur in situations associated with severe stress and also in patients with a poorly controlled pheochromocytoma. Hypotension is vasovagal in stress and postural in pheochromocytoma.

Although rarely seen as a significant overall contributor to severe cardiovascular morbidity, stress is known to associate with arrhythmias, cardiomyopathy and sudden cardiac death. The existence of stress-related cardiac death was first described by Cannon in 1942 (8), who together with Richter (9) suggested its relation to acute overactivity of both sympatoadrenal and autonomic parasympathetic nervous systems. Hans Selye, on the other hand, suggested steroids to induce electrolyte-steroid-cardiomyopathy with necrosis (ESCN), a particular type on neurologically-driven cardiomyopathy (10). At least descriptively, these studies were supported by finding of focal cardiac damage in patients with acute neurologic disorders (11–12). The fact that epinephrine infusion causes cardiac hypertrophy was described in 1907 (13–14) and stress-induced myocardial damage can be prevented with adrenergic blockade (15). Finally, there is a recently described “broken heart syndrome”, which is identical to takotsubo syndrome and represents an acute LV ballooning and sudden death, associated with acute stress or grief (16–17).

Cardiovascular abnormalities can be acute and severe, and associate with structural myocardial changes that may or may not resolve after tumor resection (18–22). Cardiac manifestations of pheochromocytoma are thought to be frequent and potentially catastrophic in majority of patients. Structural cardiac manifestations are seen in up to 30% of patients with pheochromocytoma and include left ventricular hypertrophy, catecholamine myocarditis, dilated or obstructive cardiomyopathy, which can associate with myocardial necrosis and/or fibrosis and resultant heart failure (19,21,23–31).

Discussion

The present article describes some of the similarities between pheochromocytoma situations of stress. Therefore, pheochromocytoma can be considered as endocrine stress mimicking disorder. Both stress and pheochromocytoma can present with either acute or chronic symptoms and signs related to catecholamine excess and in stress additionally to elevated glucocorticoid levels. Hypertension, tachyarrhythmia, sweating, pallor and anxiety are common to both disorders, but particularly in acute emergency situations. Only careful and detailed history and physical examination will point correctly to either stress-related problems or pheochromocytoma.

As evident from numerous symptoms and signs, both disorders can present with elevated catecholamine levels. Interestingly, as stress-specific catecholamine responses exist, the same is valid for pheochromocytoma-specific catecholamine release. For example, physical and cold stress preferentially activates the sympathoneuronal system while hypoglycemia activates the adrenal medullary system. Multiple endocrine neoplasia type 2-related pheochromocytoma have an adrenergic phenotype while von Hippel-Lindau syndrome- and

succinate dehydrogenase subunit B--related pheochromocytoma have noradrenergic phenotype (Table 5). However, stress-related disorders are characterized by the activation of the hypothalamic-pituitary-adrenocortical axis, which is not the case in pheochromocytoma patients.

Some pheochromocytoma patients may experience a clinical course similar to Selye's stress-induced General Adaptation Syndrome (GAS) (Figure 2). The initial stage includes sporadic surges of catecholamines that produce in both conditions episodic clinical symptomatology. The pathology of the second – resistance – stage is unique for both conditions. While clinical symptomatology is more persistent and severe, and associates with structural organ damage, some patients may show a paradoxical lack of damage and apparent adaptation to the condition. At least in pheochromocytoma, such adaptation has been shown to be related to desensitization of adrenergic receptors (32–35). Such adapation in pheochromocytoma appears to be associated mainly with chronically elevated catecholamine levels, rather than paroxysmal secretion (36–38). Although sometimes seen as advantageous, this stage inevitably progresses to exhaustion of compensatory mechanisms and results in irreversible organ damage and failure. This analogy with GAS further support similarities of both conditions and strengthens the importance of understanding of the phenotypic and biochemical mimicry.

It is important to understand similarities and differences between both conditions, because of potential morbidity of untreated pheochromocytoma and the fact that when appropriately suspected and timely treated, this disease can be cured. Recognizing the differences between pheochromocytoma and stress-associated conditions, such as panic disorder, can be difficult. However, once a tumor is suspected diagnosis is made relatively straightforward by use of suitable biochemical tests (e.g., measurements of plasma free metanephrines). The cardinal rule is to first think of the tumor. While anxiolytics, antidepressants and beta-blockers can be effective in stress-associated conditions, these drugs can cause adverse reactions in pheochromocytoma.

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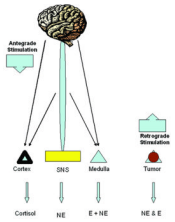

Figure 1.
Pathophysiology of stress and pheochromocytoma.

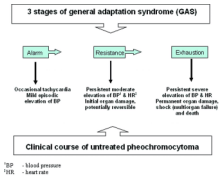

Figure 2.
Similarities between stress and pheochromocytoma disease course

Table 1

Stress Warning Signs and Symptoms*

Cognitive Symptoms	Emotional Symptoms
• Memory problems	• Moodiness
• Indecisiveness	• Anxiey/Agitation
• Inability to concentrate	• Restlessness
• Trouble thinking clearly	• Short temper
• Poor judgment	• Irritability, impatience
• Seeing only the negative	• Inability to relax
• Anxious or racing thoughts	• Feeling tense and “on edge”
• Constant worrying	• Feeling overwhelmed
• Loss of objectivity	• Sense of loneliness and isolation
• Fearful anticipation	• Depression or general unhappiness
Physical Symptoms	**Behavioral Symptoms**
• Headaches or backaches	• Eating more or less
• Muscle tension and stiffness	• Sleeping too much or too little
• Diarrhea or constipation	• Isolating yourself from others
• Nausea	• Procrastination, neglecting responsibilities
• Dizziness, lightheadedness	• Using alcohol, cigarettes, or drugs to relax
• Insomnia	• Nervous habits (e.g. nail biting, pacing)
• Chest pain, rapid heartbeat	• Teeth grinding or jaw clenching
• Weight gain or loss	• Overdoing activities (e.g. exercising, shopping)
• Skin breakouts (hives, eczema)	• Overreacting to unexpected problems
• Loss of sex drive	• Picking fights with others
• Frequent colds	
• Pallor or blushing	
• Profuse sweating	
• Tachypnea	
• Hypertension or hypotension	

Table 2

Medical conditions, caused or exacerbated by stress*

• Chronic pain	• Heart disease	• Infertility
• Migraines	• Diabetes	• Autoimmune diseases
• Ulcers	• Asthma	• Irritable bowel syndrome
• Heartburn	• PMS	• Skin problems
• High blood pressure	• Obesity/weight loss	

* Adapted with changes from www.helpguide.org and www.stress.org (The American Institute of Stress).

Table 3

Signs and symptoms of pheochromocytoma

Signs		Symptoms	
Hypertension	++++	Headaches	++++
Sustained hypertension	++	Palpitations	++++
Paroxysmal hypertension	++	Excessive sweating	++++
Postural hypotension	++	Anxiety/nervousness	+++
Tachycardia or reflex bradycardia	+++	Tremulousness	++
Pallor	++	Pain in chest/abdomen	++
Flushing (rare)	+	Weakness, fatigue	++
Weight loss	+	Nausea/vomiting	++
Fasting hyperglycaemia	++	Dizziness or faintness	+
Decreased gastrointestinal motility	+	Paresthesias	+
Increased respiratory rate	+	Constipation (rarely diarrhea)	+
Psychosis	+	Visual disturbances	+

Highest (++++) to lowest (+) frequency

Table 4

Dominant biochemical phenotype

• Sporadic pheochromocytoma – epinephrine or norepinephrine or both
• von Hippel-Lindau syndrome – norepinephrine
• Multiple endocrine neoplasia – epinephrine or epinephrine and norepinephrine
• Succinate dehydrogenase subunit B – norepinephrine