Indian Heart Journal 73 (2021) 14–21

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Review Article

Endocrine causes of heart failure: A clinical primer for cardiologists

Saurav Khatiwada [a], Hiya Boro [a, *], Faraz Ahmed Farooqui [b], Sarah Alam [a]

[a] Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India
[b] Department of Cardiology, Holy Heart Advanced Cardiac Care and Research Centre, Rohtak, 124001, Haryana, India

ARTICLE INFO

Article history:
Received 2 May 2020
Accepted 3 November 2020
Available online 11 November 2020

Keywords:
Heart failure
Endocrine causes
Pheochromocytoma
Acromegaly
Hyperaldosteronism

ABSTRACT

Heart failure (HF) may be a presenting manifestation of a few endocrine disorders and should be considered in evaluation of heart failure causes. This clinically oriented review is an attempt to highlight the protean manifestations of heart failure in endocrine diseases which could present either as acute or chronic heart failure. Acute heart failure manifests as hypertensive crisis, Takotsubo syndrome, or as tachy/brady cardiomyopathies. Chronic heart failure could masquerade with features of hyperdynamic heart failure, or hypertrophic, restrictive or dilated cardiomyopathy. Rarely constrictive features or resistant heart failure could be the presenting feature. Isolated presentation as pulmonary hypertension and right heart failure are also documented. Good history-taking and physical examination with targeted investigations will help in the timely management for reversing the pathophysiology to a significant extent by appropriated management.

1. Introduction

Heart Failure (HF) is a clinical syndrome characterized by the following features: typical symptoms (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling) and signs (tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly) and objective evidence of a structural or functional abnormality of the heart at rest (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration).[1] Mechanistically, it is characterized by either impaired ventricular filling or ejection of blood as a consequence of structural or functional heart disorders. Various endocrine disorders affect the structure and/or the function of the cardiac muscles and/or electric system of the heart. They can not only worsen pre-existing HF, but can also present with HF as the initial manifestation. Awareness of these disorders is useful since treatment of the underlying endocrine disorders may lead to a significant reversal in the symptomatology and pathophysiology of HF. Identification of the specific endocrine disease in such cases helps individualize management of HF and provides an opportunity to manage the non-cardiac aspects of disease. Prior reviews have dealt with pathophysiology and cardiac manifestations of various endocrine disorders.[2,3] Here, we shall discuss endocrine disorders with potential of index presentation with HF. Except for thyroid disorders, pheochromocytoma/paraganglioma (PPGL) and primary hyperaldosteronism, other disorders dealt in this review have rare presentations. Table 1 includes a brief summary of these diseases along with common signs/symptoms, screening and confirmatory investigations. Diabetic cardiomyopathy, disorders of mineral metabolism (other than calcium metabolism), storage disorders, mitochondrial disorders, connective tissue disorders, certain syndromic causes including RASopathies leading to HF have been excluded in this review.

2. Pheochromocytoma and paraganglioma (PPGL)

Pheochromocytomas and PPGL account for 0.5% of cases with hypertension in general practice, while 10–20% of them present with HF.[4] The classic presentation of PPGL with hyper-adrenergic spells (spells of hypertension, tremors, sweating and headache) is present in only minority of the total cases.[5] Sustained systemic hypertension is the commonest presentation while HFrEF and HFpEF are not uncommon.[5,6] A review of case reports and series classifies heart failure in PPGL into these categories: dilated cardiomyopathy-38.7%, Takotsubo cardiomyopathy-23.3%, inverted Takotsubo cardiomyopathy-19.6%, Hypertrophic obstructive cardiomyopathy (HOCM)-6.1%, myocarditis-4.9%, and unspecified cardiomyopathy-8.6%.[7] PPGL has also been found in 7.5%–25% of cases with Takotsubo cardiomyopathy (TC), albeit with an earlier

* Corresponding author. Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, 110029, India.
E-mail address: hiya21288@gmail.com (H. Boro).

https://doi.org/10.1016/j.ihj.2020.11.003

Table 1
Summary of endocrine disorders leading to heart failure along with their key clinical findings and investigations.

Disease causing heart failure (Type of heart failure)	Key signs and symptoms	Investigations: screening(S) and Confirmation (C)
Pheochromocytoma/ paraganglioma (HFrEF >> HFpEF)	Episodic sweating, palpitation, headache, sustained or episodic severe hypertension	fractionated plasma metanephrines or 24-h urinary metanephrines (S); CT/MRI abdomen + pelvis (C),±MIBG scan or^{68}Ga-DOTANOC/DOTATATE PET/CT (C)
Severe primary hypothyroidism (HFpEF >> HFrEF)	Hoarse voice, slow mentation and movement, pedal edema, coarse, dry, pale skin, delayed knee jerk	Serum T4 level, Serum TSH level (S and C)
Thyrotoxicosis (HFrEF > HFpEF)	Staring look, low BMI, goitre, tachycardia, fine tremors in outstretched hands	Serum T4 level, Serum TSH level, serum total T3 levels (S and C)
Acromegaly (HFpEF >> HFrEF)	Enlarged face, hand and feet; coarse facial features with broad nose and macroglossia, low frequency voice	Serum IGF-1 level(S); Growth hormone suppression test (C biochemically); Pituitary MRI (C anatomically)
HypocalcemiaHFrEF)	Tetany, Trosseau sign and chovstek sign positive, known hypoparathyroidism, Long QTc	Serum calcium level (total or ionized)
Hypercalcemia (HFpEF)	Known Hyperparathyroidism or other hypercalcemic etiology, polyuria and dehydration, AKI, short QTc	Serum calcium level (total or ionized)
Carcinoid syndrome (HFpEF)	flushing, secretory diarrhea, bronchospasm, labile hypertension or hypotension (due to secreted vasoactive amines), significant weight loss, pellagra	24-h urinary 5-HIAA (hydroxy indole acetic acid) (S), Serum 5-HIAA (S); CT/MRI, invasive observation (-scopy) of involved organ (anatomical confirmation); somatostatin schintigraphy/ DOTANOC-PET/CT (functional scan)
Carney Complex associated cardiac myxoma	pigmented lesions of the skin and mucosa, cutaneous and cardiac myxomas, multiple endocrine and non-endocrine tumors (Cushing's syndrome, testicular, pituitary, breast, thyroid tumors)	Clinical diagnostic criteria[70] involving major and supplemental criterias.
Lipodystrophy syndromes (HFpEF (mostly) or HFrEF (esp LMNA mutation))	Regional or generalized loss of subcutaneous fats;	Clinical diagnosis; Confirmation by genetic tests for suspected genetic syndromes and autoimmune work-up, HIV serology for acquired (secondary) causes
Primary hyperaldosteronsim (HFpEF/HFrEF)	Severe sustained hypertension, hypokalemia	Aldosterone: renin ratio (S), salt loading test (C); Lateralization of adrenal lesion: adrenal venous sampling
Liddle syndrome (HFpEF/HFrEF)	Severe sustained hypertension, hypokalemia, metabolic alkalosis, low urinary chloride excretion	aldosterone and renin level: both low (S), Diagnosis mostly by therapeutic trials with triamterene, after ruling out other causes of low renin hypertension; genetic tests confirmatory
Syndrome of inappropriate mineralocorticoid excess (congential and acquired) (HFpEF/HFrEF)	Severe sustained hypertension, hypokalemia, family history positive or use of licorice	aldosterone and renin level: both low (S), Urinary cortisol to cortisone ratio >10 (S), genetic tests for congenital SAME (C), therapeutic trial of spironolactone reasonably diagnostic in low renin state after ruling out other causes
Congenital adrenal hyperplasia (11-beta hydroxylase deficiency and 17 alpha hydroxylase deficiency) (HFpEF/HFrEF)	Common: Severe sustained hypertension, hypokalemia and low renin hypertension in girls and boys Genital ambiguity, virilization in females peudoprecocity in males with 11-beta hydroxylase deficiency; primary amenorrhoea in females and primary amenorrhoea in females and undervirilization in males with 17- hydroxylase deficiency	First level screening: renin and aldosterone level (both low) Second level screening: Raised DOC, 11-deoxycortisol, androstenedione, testosterone, and dehydroepiandrostenedione-sulfate (DHEA-S) levels for 11-beta hydroxylase deficiency(S); Low/low normal androstenedione, testosterone, DHEA-S, 17-hydroxyprogesterone, aldosterone, and cortisol but raised DOC and corticosterone for 17 alpha hydroxylase deficiency (S) Genetic and other dynamic stimulation tests (hCG stimulated) for confirmation

*HFrEF-Heart Failure with reduced ejection fraction, HFpEF-Heart Failure with preserved ejection fraction, T4-thyroxine, TSH-Thyroid stimulating hormone, IGF1-Insulin like growth factor 1, SAME-Syndrome of apparent mineralocorticoid excess, DOC-Deoxycorticosterone, DHEAS-Dehydroepiandrosterone sulphate, hCG-human chorionic gonadotrophin.

age at presentation than in classic TC.[8,9] A retrospective analysis of patients with PPGL presenting with acute Takotsubo cardiomyopathy or chronic catecholamine induced cardiomyopathy revealed better pre-operative medical improvement (69.4% vs 40.8% cases) and post-surgical recovery (97.7% vs 73.3% cases) in LVEF in the two groups respectively.[10]

The pathophysiology of Takotsubo cardiomyopathy in various endocrine disorders including pheochromocytoma/PPGL has been discussed in details in section 6. Overall, catecholamine overload may cause vasospasm of small arterioles and may be directly toxic to the myocardium.[11] History for hyper-adrenergic spells, family history of severe hypertension or premature cardiac death, and clinical features of associated genetic syndromes may be useful to screen for PPGL. In a few cases, adrenal incidentalomas may lead to diagnosis of pheochromocytomas in patients with heart failure. Table 2 lists some of the genetic syndromes and their associated

Table 2
Clinical features of common syndromic PPGL.

Multiple endocrine neoplasia type 2A (MEN2A)	Medullary thyroid cancer, primary hyperparathyroidism, and cutaneous lichen amyloidosis
Multiple endocrine neoplasia type 2B (MEN2B)	Medullary thyroid cancer, mucocutaneous neuromas, skeletal deformities (eg, kyphoscoliosis or lordosis), joint laxity, myelinated corneal nerves, and intestinal ganglioneuromas (Hirschsprung's disease)
von Hippel-Lindau syndrome (VHL)	Hemangioblastoma (involving the cerebellum, spinal cord, or brainstem), retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumors and serous cystadenomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament
Neurofibromatosis type 1 (NF1)	Neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, central nervous system gliomas, macrocephaly, and cognitive deficits
SDHx mutation	Paraganglioma and/or Pheochromocytoma, pituitary tumor, gastrointestinal stromal tumor, uterine tumor

*SDHx-Succinate Dehydrogenase.
(Adapted with modification from Lenders et al, Endocrinol Metab (Seoul). 2014).

conditions.[12] In case of clinical suspicion, plasma fractionated metanephrines or 24-h urinary fractionated metanephrines should be ordered. These are good rule out tests in the setting of heart failure. Mild elevation (up to two to three times the upper limit of normal) of these biochemical parameters may occur in HF due to heightened sympathetic response of the body and certain medications used for the management of HF. In doubtful cases, a computed tomography (CT) scan of pelvis and abdomen (including adrenal sections) can be useful to establish the diagnosis as these modalities are sensitive for pheochromocytomas and most secretory paragangliomas.[12] The latter may present as mediastinal, carotid, jugular or bladder tumors. Magnetic resonance imaging (MRI) of abdomen and pelvis provides similar diagnostic yield and can replace CT in cases where radiation or CT contrast are to be avoided. Occasionally, functional imaging is required to look for multiplicity of lesions in PPGL, syndromic pheochromocytomas, large or suspected malignant PPGL. Sometimes, it is also required to confirm the diagnosis of PPGL if structural imaging is equivocal in mild to moderate elevation of catecholamine/metanephrine levels. In these circumstances, newer modalities like ^{68}Ga-DOTATATE or ^{68}Ga-DOTANOC PET/CT have performed better with higher sensitivity than the traditional MIBG scan.[12] MIBG is a more specific test (100% specificity) to diagnose pheochromocytomas/PPGL.[13]

2.1. Severe hypothyroidism

Severe hypothyroidism can be diagnosed based on history of fatigue, lethargy, slowing of mentation, weight gain, menstrual irregularities, constipation, anasarca and tell-tale clinical signs of puffy and dry facies, hoarse and slow voice with pedal edema and hung up reflexes. However, such history may not be easy to elicit in sick comatose patients, especially in an emergency room setting. Bradycardia may be absent because of sepsis while anasarca is often a non-specific finding in patients presenting with HF. A high index of suspicion and a quick thyroid profile [Thyroid stimulating hormone (TSH) level and total/free Thyroxine (T4) level)] helps clinch a timely diagnosis. Very high values of TSH (>100 mIU/L) are rare due to the simultaneous presence of sick euthyroid syndrome or in central hypothyroidism but T4 levels are invariably low.[14]

In the Penn heart Failure study ($n = 1365$), with a mean age of 56.6 years, the mean ejection fraction of 34 (17)% and NYHA III/IV in 38%, baseline thyroid dysfunction noted were: subclinical hypothyroidism (serum TSH 4.51–19.99 mIU/ml with normal free T4)-5%, subclinical hyperthyroidism (serum TSH<0.45 mIU/ml with normal free T4)-5%, overt hyperthyroidism-1%, and overt hypothyroidism <1%.[15] The same study also showed significant correlation of high TSH (subclinical hypothyroidism), high free T4 and low total T3 levels with increased mortality over 4 years. Benefits of any intervention on these subtle thyroid function perturbation are still under investigation.

Pericardial effusion (PE) is often present in severe primary hypothyroidism although cardiac tamponade and shock are rare.[14,16,17] The incidence of PE varies from 3% to 37%, with most cases seen in severe primary hypothyroidism.[18,19] On the other hand, hypothyroidism as an etiology of pericardial effusion has been found in 14% of cases.[20–22] The primary pathophysiology of PE in hypothyroidism involves increased albumin permeability of the pericardial capillaries along with decreased albumin drainage to the lymphatic vessels.[23,24] This increases the colloidal oncotic pressure gradient between the pericardium and pericardial space, leading to fluid accumulation. Although mucopolysaccharide accumulation causing water retention is the hallmark of severe primary hypothyroidism, such accumulation is not seen in the heart or pericardium.[25] The role of autoimmunity in the genesis of pericardial diseases of hypothyroidism remains to be explained. Pericardial effusion is found to occur in both autoimmune and non autoimmune forms of hypothyroidism (post surgical, iodine deficiency).[26,27] Moreover, no specific antibodies have identified that mediate the pathophysiology of pericardial disease.[28] In addition, immune complexes in autoimmune hypothyroidism may not be able to bind to complement,[29] thus failing to exert a hypersensitivity reaction in the pericardium.

Patients with secondary hypothyroidism due to pituitary disease or Sheehan syndrome usually have a small cardiac silhouette and pericardial effusion is rare. However, there have been cases of pericardial effusion and cardiac tamponade reported in secondary hypothyroidism due to Sheehan syndrome.[30,31] This may be attributed to the fact that patients may have a delayed diagnosis as they may not seek medical attention due to relatively milder hypothyroidism in the initial stages.

Constrictive pericarditis (CP) leading to heart failure can occur in long standing hypothyroidism.[32] Echocardiography may not be always diagnostic in volume overload tests. In such circumstances, invasive hemodynamic testing may be required to establish the diagnosis of CP. Simultaneously, a quick screening test for TSH may provide an etiological clue towards hypothyroidism.[32]

An association of subclinical hypothyroidism with heart failure has been demonstrated in a few studies.[33,34] However, whether subclinical hypothyroidism causes or worsens preexisting heart failure has not been conclusively demonstrated.

2.2. Thyrotoxicosis (endogenous and amiodarone-induced)

The cardiac manifestations in thyrotoxicosis may range from sinus tachycardia to diastolic dysfunction and tachycardia induced cardiomyopathy.[35,36] Endogenous hyperthyroidism may present

with goiter (either multinodular as in toxic multinodular goiter or soft and diffuse as in Graves' disease), associated eye signs which may help one suspect the diagnosis. The reversibility of tachycardia induced cardiomyopathy associated with hyperthyroidism is well documented with around one third, each having total, partial or no recovery in dilated cardiomyopathy.[37,38] The predictors of recovery at six months were male sex, shorter duration of thyrotoxicosis (less than 10.4 months), beta-blocker use and higher T3 levels at presentation.[37] Historically, thyroid ablation has been one of the first endocrine manipulations tried successfully in cases of 'refractory angina' and heart failure in the first half of 20th century.[39]

Severe primary hyperthyroidism has also been reported to cause high output cardiac failure leading to liver congestion and cirrhotic transformation of liver.[40] Previous studies have demonstrated that approximately 6% of patients with hyperthyroidism developed heart failure, and nearly half of those with heart failure had LV systolic dysfunction.[41,42] Recent studies have shown association of Graves' disease with pulmonary artery hypertension (PAH).[43] Although the mechanistic explanation is not evident, tachycardia and high cardiac output have been hypothesized to contribute to PAH.[43] Animal studies have shown that thyroid hormones stimulate endothelial cell proliferation in the pulmonary vasculature.[43]

In apathetic thyrotoxicosis, cardiac involvement may be the sole manifestation. Atrioventricular block, including complete heart block leading to heart failure have been reported in apathetic thyrotoxicosis.[44]

Amiodarone-induced thyrotoxicosis (AIT) may present with worsening of heart failure symptoms, often acutely, in patients being treated with amiodarone for a variable period of time.[45] AIT has been dealt with elsewhere in excellent detail.[46] Though medical management with anti-thyroidal agents and steroids remains the mainstay of treatment, thyroidectomy has recently gained popularity in severe cases of AIT in presence of expert cardiac anesthesia support.[45]

3. Primary hyperaldosteronism (PH)

A four-fold increased risk and 4.1% prevalence of HF have been documented in a cross-sectional study of primary hyperaldosteronism.[47] PH accounts for more than 10% cases of hypertension.[48] Hypokalemia is present in only 9–37% of the cases.[48] The vast majority of sporadic PH cases are adult-onset due to bilateral idiopathic adrenal hyperplasia and unilateral or bilateral aldosterone producing adenomas, while rarely, they may manifest in children [Familial Hyperaldosteronism (FH) type III- KCNJ5 gene mutation] and young adults (FH types I and II) due to germline mutations.[48] Hypertension with left ventricular hypertrophy, hypertensive retinopathy and/or renal dysfunction, with/without family history of hypertension and complications can be the initial presentation in these disorders. Aldosterone excess has been found to have direct pathological effects on cardiomyocytes, myofibroblasts and the vascular smooth muscle, promoting cardiac hypertrophy and fibrosis.[49] Screening with plasma aldosterone level and aldosterone to renin ratio (ARR), followed by one of the confirmatory tests (saline/oral salt loading, captopril challenge or fludrocortisone loading tests) in 'screening positive' individuals can help diagnose PH.[48] Management consists of unilateral adrenalectomy in unilateral adrenal adenoma and medical management with mineralocorticoid antagonists (spironolactone or eplerenone) with or without ACE-i/ARBs, potassium sparing diuretics and calcium channel blockers in bilateral disease, usually after adrenal venous sampling for lateralization of the disease.[48] For FH type I, low dose dexamethasone monotherapy usually suffices. However bilateral/unilateral adrenalectomy is needed in type II (unilateral adenoma or bilateral hyperplasia) and type III (marked bilateral adrenal hyperplasia), especially for early-onset severe hyperaldosteronism unresponsive to dexamethasone or spironolactone therapy.[50]

4. Acromegaly

Cardiac manifestations of Acromegaly include hypertension, biventricular hypertrophy, diastolic followed by systolic dysfunction, atrial and ventricular arrhythmias, cardiac conduction defects, and valvular incompetence.[51] In the short term, an excess of growth hormone (GH) and insulin like growth factor 1 (IGF1) leads to favorable cardiac modeling driven by cardiomyocyte hypertrophy.[52] GH has been explored as possible therapy for the treatment of heart failure.[53] However, persistent elevation of GH and IGF1 results in a maladaptive response resulting in heart failure. Excess growth hormone (GH) and insulin like growth factor 1 (IGF1) promote increase in the size of cardiomyocytes, increased transcription of cardiac muscle specific genes, increase cardiac contractility, and collagen deposition and interstitial fibrosis leading to impaired ventricular relaxation.[51]

In the early stages of Acromegaly, only subtle acro-facial changes like tightening of rings in fingers, enlarged hands and feet, broad fleshy nose may be noticeable. Later, coarse facies, hoarse voice, macroglossia, dental malocclusion and other classical features get apparent. Often, patients or their caretakers may not be aware of the subtle changes due to indolent course of disease. On active probing, history of visual complaints and headache may be apparent. Measurement of serum IGF1 is a screening test that should be followed by confirmatory test, that is, growth hormone suppression test with 75 g glucose. In active Acromegaly, elevated IGF1 levels are accompanied by non-suppressed GH levels after glucose load. Subsequently, MRI of the sella turcica should be done to look for the pituitary tumor and its extent.

Reversibility of cardiomyopathy with pituitary surgery followed by octreotide therapy has been well documented.[54] T2-hyperintensity in Cardiac Magnetic Resonance (CMR) may represent edema associated with acromegaly which predicts reversibility with treatment.[55]

5. Disorders of calcium and vitamin D metabolism

5.1. Hypocalcemia

Dilated cardiomyopathy with a clinical presentation of carpopedal spasm, tetany, stridor and seizures should arouse the suspicion of hypocalcemia (hypoparathyroidism or pseudohypoparathyroidism). Dramatic improvement in symptoms and cardiomyopathy may be noted following calcium and vitamin D supplementation.[56–58] Hypocalcemia can be checked bedside by eliciting Trousseau and/or Chvostek signs and confirmed biochemically with total or ionized calcium levels. ECG features include prolonged QTc interval and non-specific T-wave abnormalities. Infants may develop dilated cardiomyopathy due to severe vitamin D deficiency induced hypocalcemia.[58] The exact mechanism of cardiomyopathy in hypocalcemia is not known, although hypocalcemia is known to reduce cardiac contractility. Vitamin D and PTH may have independent roles in the development of cardiomyopathy.[58]

5.2. Hypercalcemia

Increased parathyroid hormone (PTH) has been documented in large observational cohorts to be an independent predictor of chronic heart failure.[59] A prospective study in cases of hyperparathyroidism undergoing parathyroidectomy documented left ventricular hypertrophy in 82% of cases.[60] In addition, hypertension,

calcification of valves and myocardium, arrhythmias due to hypercalcemia, hypercalcemia-induced myocardial band-necrosis have been implicated in acute decompensation of preexisting heart failure.[61] Hypertension may not be reversible after parathyroidectomy.[60]

5.3. Vitamin D metabolism

A recent trial of vitamin D supplementation (VINDICATE trial) has highlighted the importance of managing hypovitaminosis D in heart failure to improve the functional status of patients.[62] At the other extreme, vitamin D toxicity (25-OH vitamin D level >150 ng/ml or elevated 1,25-hydroxy vitamin D levels with hypercalcemia and suppressed parathyroid hormone levels) induced hypercalcemia can lead to acute kidney injury and exacerbation of heart failure. Vitamin D toxicity has been shown to cause hypertension, ST segment abnormalities, shortened QT interval, and bradycardia with first-degree heart block on the ECG.[63]

6. Carcinoid syndrome

Typical symptoms of flushing, secretory diarrhea, bronchospasm, labile hypertension or hypotension (due to secreted vasoactive amines), significant weight loss, and pellagra (dark skin pigmentation in sun exposed areas) are present in most cases of carcinoid heart.[64] Yet, some cases may present with isolated right heart failure as initial presentation of the disease.[65] Restrictive cardiomyopathy may also be the sole manifestation of carcinoid syndrome.[66] The pathology is usually involvement of tricuspid and pulmonary valves with regurgitant lesions with/without stenotic lesions.[65] At one time, there was speculation about association of carcinoid syndrome with endomyocardial fibrosis.[66] However, over the years, such claims have been refuted with poverty and eosinophilia, rather than serotonin, emerging as risk factors for endomyocardial fibrosis.[67,68] In rare cases of carcinoid syndrome, pericardial involvement due to metastatic deposits with subsequent development of constrictive pericarditis may occur.[69]

7. Myxomas in carney complex (CNC)

Carney complex is an autosomal dominant disorder due to mutation in protein regulatory kinase subunit (PRKR 1 alpha). It may present with pigmented lesions of the skin and mucosa, cutaneous and cardiac myxomas along with multiple endocrine and non-endocrine tumors (adrenal nodular hyperplasia, testicular, pituitary, breast, thyroid tumors).[70] Cardiac myxomas may occur in atria (right/left) or ventricles in contrast to the sporadic myxomas located mostly in the left atrium.[70] Therefore, it may present with either left or right sided heart failure. The median age of presentation is 20 years but it can range from infancy to late adulthood.[71] Approximately 40% cases of Carney complex develop cardiac myxomas.[72]

8. Lipodystrophy syndromes

Lipodystrophy syndromes may be generalized or partial. Generalized lipodystrophy syndromes, especially the congenital variety (CGLD type 2 or BSCL2/Seipin gene mutation) are associated with predominantly hypertrophic, and rarely dilated cardiomyopathy.[73] Diagnosis of CGLD is suspected on the basis of clinical features like generalized loss of body fat with extreme muscularity, prominent veins, acanthosis nigricans, protuberant abdomen and lumbar lordosis. Investigations may reveal metabolic disorders like diabetes mellitus, dyslipidemia (hypertriglyceridemia) and steatohepatitis. Related progeroid syndromes like Werner syndrome (with features like hair loss, dermal fibrosis) may present along with features of CGLD when LMNA gene mutations are present.[74] Among the partial lipodystrophy syndromes, Dunnigan type lipodystrophy (FPLD 2) is also known to be associated with severe insulin resistance, hypertension and moderate LV dysfunction and cardiomyopathy.[73] FPLD 2 is clinically characterized by loss of fat in limbs (and sometimes trunk) while sparing the face and neck, giving an appearance of Cushingoid habitus.[75] It can often be confused with polycystic ovarian disease (PCOD) and metabolic syndrome, both of which are associated with the lipodystrophy syndrome.[75] Association of lipodystrophy syndromes with various metabolic, renal and auto-immune disorders and the availability of metreleptin as specific drug for the condition (approved only for generalized lipodystrophy) make the need of establishing an early diagnosis crucial. Coronary artery disease is also very common in lipodystrophy syndromes, making ischemic cardiomyopathy likely in addition to the proposed 'dyslipidemia and diabetes induced lipotoxic cardiomyopathy'.[73] Insulin resistance may also play a key role in the development of non ischaemic heart failure in these conditions.[76] Insulin resistance prevents normal myocardial adaptive response to injury and promotes further damage by upregulating lipotoxicity, sympathetic activation, inflammation, oxidative stress and fibrosis.[76]

9. Endocrinopathies associated with takotsubo cardiomyopathy

Takotsubo cardiomyopathy presents with acute onset heart failure with reversible regional wall motion abnormality and a normal angiogram. Catecholamine mediated cardiac dysfunction remains the most accepted mechanism of TC. Emotional stress results in hypothalamic-pituitary–adrenal axis mediated sudden surge in catecholamines.[77–79] The cardiac response to this excess of catecholamines results in transient stunning of the heart. An increase in afterload in response to the excessive sympathetic stimulation is also thought to contribute to myocardial stunning. In addition, an increased sensitivity to catecholamines has also been suggested as a possible mechanism of TC.[8] This is suggested by the association of TC with PPGL in 7.5–25% cases, screening for which is important for a cardiologist especially in absence of history of precipitating event and in presence of hyperadrenergic symptoms.[8,9] In addition, multiple case reports suggest association of estrogen deficiency in postmenopausal state, hypothyroidism or hyperthyroidism and primary or secondary adrenal insufficiency with TC.[80] These endocrine disorders putatively potentiate the catecholamine sensitivity of the myocardium. This has also been exemplified by the fact that management of adrenal insufficiency with replacement dose steroids can also precipitate systolic heart failure in some cases.[81] Unlike ischemia related cardiac dysfunction, TC is characterized by a neutrophilic predominant inflammation, contraction band necrosis and fibrosis on histopathologic examination.[82]

10. Prolactin hypothesis of peripartum cardiomyopathy

Prolactin degradation products have been implicated in a similar acute systolic heart failure syndrome, namely peri-partum cardiomyopathy.[83] It has been hypothesized that cathepsin D is expressed by cardiomyocytes in response to oxidative stress. Cathepsin D cleaves prolactin into a 16 kDa fragment, which in turn promoted endothelial cell apoptosis.[84,85] However, results of a preliminary intervention study still do not clearly prove the therapeutic benefits of inhibiting prolactin production to expedite the recovery.[86] Further RCTs are necessary to clarify the exact position of the hypothesis.

11. Monogenic causes of hypertension (other than familial hyperaldosteronism)

Monogenic disorders of hypertension are single gene mutations that affect electrolyte and water resorption in kidneys, leading to severe hypertension and in many cases, cerebrovascular accidents, chronic kidney disease and cardiomyopathy. Unlike in essential hypertension, these diseases require specific drugs for blood pressure control. There are often no pathognomonic clinical phenotypes except in congenital adrenal hyperplasia (CAH), syndrome of apparent mineralocorticoid excess (SAME) and primary cortisol resistance. Although biochemical investigations can lead us to a probable diagnosis and its specific management, confirmation requires genetic studies.[87] Familial hyperaldosteronism has been described earlier. Some of the other monogenic causes of hypertension, with a potential for hypertensive cardiomyopathy are listed below.

11.1. Diseases already known to cause heart failure

11.1.1. Liddle syndrome (LS)

LS classically presents with clinical and biochemical features such as early onset hypertension, suppressed plasma renin activity, along with low plasma aldosterone, hypokalemia and metabolic alkalosis.[88] There is often a family history of hypertension with/without hypertensive complications, as it is an autosomal dominant disorder. It can also present with a milder clinical phenotype where only hypertension is evident. It is usually considered a diagnosis of exclusion after other causes of low renin hypertension like PH, primary cortisol resistance syndrome, SAME and CAH (11β-hydroxylase deficiency and 17-α hydroxylase deficiency) have been ruled out. Diagnosis is usually confirmed by genetic analysis. A case report of a geriatric patient with Liddle syndrome presenting with heart failure and hypokalemia, who responded to triamterene as anti-hypertensive therapy is available in literature.[89]

11.1.2. Syndrome apparent mineralocorticoid excess (SAME) syndrome

Classical congenital SAME syndrome, an autosomal recessive disorder, is characterized by low birth weight, severe hypertension at young age, polyuria and polydipsia, hypokalemia, low PRA and low aldosterone.[90] A number of cardiovascular deaths in children and young adults have been linked to cardiovascular complications of SAME (cardiomyopathy/heart failure).[91] It is caused by loss of function mutation of HSD11B2 gene. However, mutations in the HSD11B2 gene (at different alleles) can result in milder phenotypes that are difficult to distinguish from essential hypertension. Specific treatment with spironolactone blocks the mineralocorticoid receptor which is overwhelmed by cortisol in this disease. Similar phenotype can occur in older people abusing licorice (a confectionary agent) or grape juice, termed acquired SAME. Hypertension rapidly abates on discontinuing these agents.

11.1.3. Congenital adrenal hyperplasia(CAH) (11- beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency)

A vast majority of cases with CAH are due to 21-hydroxylase deficiency in the steroidogenic pathway presenting with hyperandrogenism with/without salt-wasting crisis. However, some forms of CAH are associated with hypertension, namely 11-beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency. These causes account for around 8–10% of all cases of CAH.[92] CAH is autosomal recessive in inheritance. In 11-beta-hydroxylase deficiency there is virilization of female genitalia or precocious puberty in both sexes.[92] In 17-alpha-hydroxylase deficiency, genotypic females present with lack of pubertal development while genotypic males have ambiguous genitalia or complete female external genitalia.[92] Hypertension usually develops in early to late childhood in these forms of CAH.[93] Presentation in pre-pubertal children is occasionally due to complications related to hypertensive cardiomyopathy.[94] Reversibility of hypertension, and left ventricular hypertrophy has also been reported with steroid treatment in 11 beta hydroxylase deficiency.[94]

11.2. Diseases not already known to cause heart failure

11.2.1. Primary cortisol resistance syndrome

Primary cortisol resistance syndrome presents with hirsutism, hypertension, hyperpigmentation and/or hypokalemia in young adults and children.[95] Cushingoid features are conspicuously absent in presence of biochemically raised ACTH and cortisol levels. Management is administration of long acting steroid dexamethasone with the intention of lowering ACTH levels.

11.2.2. Mineralocorticoid receptor activating mutation

This condition has been recently described as a cause of young-onset low renin hypertension with hypokalemia and low aldosterone levels. The symptoms are exacerbated during pregnancy to cause an eclampsia-like presentation. Only one family with this disease has been reported as yet.[96] The action of excess progesterone on the mutant mineralocorticoid receptor has been implicated as the cause of exacerbation of this condition during pregnancy. Interestingly, hypertension was worsened by the use of spironolactone, a mineralocorticoid receptor antagonist.

11.2.3. Gordon syndrome

Gordon syndrome or Pseudohypoaldosteronism type 2 is a disorder of renal electrolyte balance where hyperkalemia, hypertension and hyperchloremic metabolic acidosis are observed due to excessive sodium, chloride and potassium resorption from renal tubules. Unlike the causes of low renin hypertension mentioned above, Gordon syndrome presents with hyperkalemia. Hypertension may develop after the first decade of life. Hypertension is usually not severe and no case report of cardiomyopathy was found at the time of writing this review. Isolated hyperkalemia (asymptomatic) without hypertension and older age at presentation are also not infrequent.[97] Hypertension and hyperkalemia respond well to a low potassium, low salt diet with thiazide diuretics.

12. Conclusion

Many endocrine disorders cause or exacerbate heart failure as detailed above. In addition, certain endocrine manipulations like mineralocorticoid antagonist therapy have shown significant benefit in most forms of HFrEF (which have secondary hyperaldosteronism) and clearly also in heart failure due to primary mineralocorticoid excess (PH, SAME). A bidirectional relationship exists between endocrine disorders and heart failure. A careful search for these causative or consequential endocrine problems may go a long way to ensure timely and precise diagnosis followed by proper management in cases with heart failure.

Declaration of competing interest

The authors Dr. Saurav Khatiwada, Dr. Hiya Boro, Dr. Faraz Ahmed Farooqui and Dr. Sarah Alam state that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.11.003.

References

1. Dickstein K, Authors/Task Force Members, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008‡: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European society of cardiology. Developed in collaborati. *Eur J Heart Fail*. 2008 Oct;10(10):933–989. https://doi.org/10.1016/j.ejheart.2008.08.005.
2. Binu A, Cherian K, Kapoor N, Chacko S, George O, Paul T. The heart of the matter: cardiac manifestations of endocrine disease. *Indian J Endocrinol Metab*. 2017;21(6):919. https://doi.org/10.4103/ijem.IJEM_212_17.
3. Albakri A. Endocrine cardiomyopathy: a review and pooled analysis of pathophysiology, diagnosis and clinical management. *Res Rev Insights*. 2019;3(1). https://doi.org/10.15761/RRI.1000153.
4. Reyes HA, Paquin JJ, Harris DM. Pheochromocytoma, "the great masquerader," presenting as severe acute decompensated heart failure in a young patient. *Case Rep Cardiol*. 2018;2018:1–5. https://doi.org/10.1155/2018/8767801.
5. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. *Endocrinol Metab Clin N Am*. 2011 Jun;40(2):295–311. https://doi.org/10.1016/j.ecl.2011.02.002.
6. Zhang R, Gupta D, Albert SG. Pheochromocytoma as a reversible cause of cardiomyopathy: analysis and review of the literature. *Int J Cardiol*. 2017 Dec;249:319–323. https://doi.org/10.1016/j.ijcard.2017.07.014.
7. Agrawal S, Shirani J, Garg L, et al. Pheochromocytoma and stress cardiomyopathy: insight into pathogenesis. *World J Cardiol*. 2017;9(3):255–260. https://doi.org/10.4330/wjc.v9.i3.255.
8. Coupez E, Eschalier R, Pereira B, et al. A single pathophysiological pathway in Takotsubo cardiomyopathy: catecholaminergic stress. *Arch Cardiovasc Dis*. 2014 Apr;107(4):245–252. https://doi.org/10.1016/j.acvd.2014.04.001.
9. Batisse-Lignier M, Pereira B, Motreff P, et al. Acute and chronic pheochromocytoma-induced cardiomyopathies: different prognoses? *Medicine (Baltim)*. 2015 Dec;94(50), e2198. https://doi.org/10.1097/MD.0000000000002198.
10. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014 Jun 1;99(6):1915–1942. https://doi.org/10.1210/jc.2014-1498.
11. Paul T, Varghese R, John A. Catecholamine induced cardiomyopathy in pheochromocytoma. *Indian J Endocrinol Metab*. 2013;17(4):733. https://doi.org/10.4103/2230-8210.113771.
12. Lenders JWM, Eisenhofer G. Update on modern management of pheochromocytoma and paraganglioma. *Endocrinol Metab*. 2017;32(2):152. https://doi.org/10.3803/EnM.2017.32.2.152.
13. Ilias I, Divgi C, Pacak K. Current role of metaiodobenzylguanidine in the diagnosis of pheochromocytoma and medullary thyroid cancer. *Semin Nucl Med*. 2011 Sep;41(5):364–368. https://doi.org/10.1053/j.semnuclmed.2011.03.003.
14. Majid-Moosa A, Schussler JM, Mora A. Myxedema coma with cardiac tamponade and severe cardiomyopathy. *Bayl Univ Med Cent Proc*. 2015 Oct;28(4):509–511. https://doi.org/10.1080/08998280.2015.11929326.
15. Kannan L, Shaw PA, Morley MP, et al. Thyroid dysfunction in heart failure and cardiovascular outcomes. *Circ Heart Fail*. 2018 Dec;11(12). https://doi.org/10.1161/CIRCHEARTFAILURE.118.005266.
16. Werlang ME, Pimentel MR, Diaz-Gomez JL. Thoracentesis-reverting cardiac tamponade physiology in a patient with myxedema coma and large pleural effusion. *Bayl Univ Med Cent Proc*. 2017 Jul 1;30(3):295–297. https://doi.org/10.1080/08998280.2017.11929620.
17. Wiersinga WM. Myxedema and coma (severe hypothyroidism). Endotext [Internet]. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *South Dartmouth (MA)*. MDText.com, Inc.; 2000 [cited 2020 Jul 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279007/.
18. Kerber RE, Sherman B. Echocardiographic evaluation of pericardial effusion in myxedema. Incidence and biochemical and clinical correlations. *Circulation*. 1975 Nov;52(5):823–827. https://doi.org/10.1161/01.CIR.52.5.823.
19. Hardisty CA, Naik DR, Munro DS. Pericardial effusion IN hypothyroidism. *Clin Endocrinol*. 1980 Oct;13(4):349–354. https://doi.org/10.1111/j.1365-2265.1980.tb03395.x.
20. Nouh MS, Famuyiwa OO, Sulimani RA, Al-Nuaim A. The spectrum of echocardiographic abnormalities in hypothyroidism and the effect of hormonal treatment. *Ann Saudi Med*. 1991 Nov;11(6):611–615. https://doi.org/10.5144/0256-4947.1991.611.
21. Kudo Y, Yamasaki F, Doi T, Doi Y, Sugiura T. Clinical significance of low voltage in asymptomatic patients with pericardial effusion free of heart disease. *Chest*. 2003 Dec;124(6):2064–2067. https://doi.org/10.1378/chest.124.6.2064.
22. Levy P-Y, Corey R, Berger P, et al. Etiologic diagnosis of 204 pericardial effusions. *Medicine*. 2003 Nov;82(6):385–391. https://doi.org/10.1097/01.md.0000101574.54295.73.
23. Parving H-H, Hansen JM, Nielsen SL, Rossing N, Munck O, Lassen NA. Mechanisms of edema formation in myxedema — increased protein extravasation and relatively slow lymphatic drainage. *N Engl J Med*. 1979 Aug 30;301(9):460–465. https://doi.org/10.1056/NEJM197908303010902.
24. Stewart RH, Rohn DA, Allen SJ, Laine GA. Basic determinants of epicardial transudation. *Am J Physiol Heart Circ Physiol*. 1997 Sep 1;273(3):H1408–H1414. https://doi.org/10.1152/ajpheart.1997.273.3.H1408.
25. Brewer DB. Myxoedema: an autopsy report with histochemical observations on the nature of the mucoid infiltrations. *J Pathol Bacteriol*. 1951;63:503–512. https://doi.org/10.1002/path.1700630318.
26. Lim ASAL, Paz-Pacheco E, Reyes M, Punzalan F. Pericardial decompression syndrome in a patient with hypothyroidism presenting as massive pericardial effusion: a case report and review of related literature. *BMJ Case Rep*. 2011 Oct 4;(oct03 1):2011. bcr0420114117–bcr0420114117.
27. Thomas JE, Bwakura TR, Dzichauya TJ, Griffiths S. Iodine deficiency disorder (IDD) presenting as hypothyroidism with a large pericardial effusion. *Cent Afr J Med*. 1990 Aug;36(8):205–206.
28. Tucker WS, Niblack GD, Mclean RH, et al. Serositis with autoimmune endocrinopathy: clinical and immunogenetic features. *Medicine (Baltim)*. 1987 Mar;66(2):138–147. https://doi.org/10.1097/00005792-198703000-00005.
29. Mariotti S, Degroot LJ, Scarborough D, Medof ME. Study of circulating immune complexes in thyroid diseases: comparison of raji cell radioimmunoassay and specific thyroglobulin-antithyroglobulin radioassay*. *J Clin Endocrinol Metab*. 1979 Nov;49(5):679–686. https://doi.org/10.1210/jcem-49-5-679.
30. Boro H, Goyal A, Tandon N. Spontaneous conception, pericardial effusion, and pseudohypertrophic myopathy mimicking muscular dystrophy in delayed presentation of sheehan syndrome. *Neurol India*. 2020;68(1):179. https://doi.org/10.4103/0028-3886.279696.
31. Goswami R, Tandon N, Singh B, Shah P, Ammini AC. Circulatory collapse in a 30-year-old amenorrheic woman. *Postgrad Med*. 1996 Aug 1;72(850):501–504. https://doi.org/10.1136/pgmj.72.850.501.
32. Tyagi G, Doctorian T, Rabkin D, Hilliard A. Constrictive pericarditis IN a patient with long standing hypothyroidism. *J Am Coll Cardiol*. 2015 Mar;65(10):A758. https://doi.org/10.1016/S0735-1097(15)60758-6.
33. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med*. 2005 Nov 28;165(21):2460–2466. https://doi.org/10.1001/archinte.165.21.2460.
34. Grais IM, Sowers JR. Thyroid and the heart. *Am J Med*. 2014 Aug;127(8):691–698. https://doi.org/10.1016/j.amjmed.2014.03.009.
35. Yue W-S, Chong B-H, Zhang X-H, et al. Hyperthyroidism-induced left ventricular diastolic dysfunction: implication in hyperthyroidism-related heart failure: hyperthyroidism and diastolic dysfunction. *Clin Endocrinol*. 2011 May;74(5):636–643. https://doi.org/10.1111/j.1365-2265.2011.03981.x.
36. Dahl P, Danzi S, Klein I. Thyrotoxic cardiac disease. *Curr Heart Fail Rep*. 2008 Sep;5(3):170–176. https://doi.org/10.1007/s11897-008-0026-9.
37. Oliveros-Ruiz L, Vallejo M, Diez Canseco LF, Cárdenas M, Hermosillo JAG. Determinants of thyrotoxic cardiomyopathy recovery. *BioMed Res Int*. 2013;2013:1–7. https://doi.org/10.1155/2013/452709.
38. Al-Ghamdi AS, Aljohani N. Graves' thyrotoxicosis-induced reversible cardiomyopathy: a case report. *Clin Med Insights Case Rep*. 2013 Jan;6, CCRep.S10534. https://doi.org/10.4137/CCRep.S10534.
39. Blumgart HL, Freedberg AS, Kurland GS. Radioactive iodine treatment of angina pectoris and congestive heart failure. *Circulation*. 1957 Jul;16(1):110–119. https://doi.org/10.1161/01.CIR.16.1.110.
40. Fischer MR, Spes CH, Huss R, Gärtner R. Immunogene Hyperthyreose mit hyperdynamischem Herzversagen und beginnendem zirrhotischem Umbau der Leber. *Dtsch med Wochenschr*. 2008 Mar 25;122(11):323–327. https://doi.org/10.1055/s-2008-1047616.
41. Siu C-W, Yeung C-Y, Lau C-P, Kung AWC, Tse H-F. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. *Heart*. 2007 Apr;93(4):483–487. https://doi.org/10.1136/hrt.2006.100628.
42. Khan R, Sikanderkhel S, Gui J, et al. Thyroid and cardiovascular disease: a focused review on the impact of hyperthyroidism in heart failure. *Cardiol Res*. 2020 Apr;11(2):68–75. https://doi.org/10.14740/cr1034.
43. Bogaard HJ, Husseini AA, Farkas L, et al. Severe pulmonary hypertension: the role of metabolic and endocrine disorders. *Pulm Circ*. 2012 Apr;2(2):148–154. https://doi.org/10.4103/2045-8932.97592.
44. Al Bannay R, Husain A, Khalaf S. Complete heart block in thyrotoxicosis, is it a manifestation of thyroid storm? A case report and review of the literature. *Case Rep Endocrinol*. 2012;2012:1–3. https://doi.org/10.1155/2012/318398.
45. Isaacs M, Costin M, Bova R, et al. Management of amiodarone-induced thyrotoxicosis at a cardiac transplantation centre. *Front Endocrinol*. 2018 Aug 22;9:482. https://doi.org/10.3389/fendo.2018.00482.
46. Tsang W, Houlden RL. Amiodarone-induced thyrotoxicosis: a review. *Can J Cardiol*. 2009 Jul;25(7):421–424. https://doi.org/10.1016/S0828-282X(09)70512-4.
47. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016 May 1;101(5):1889–1916. https://doi.org/10.1210/jc.2015-4061.
48. Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006 Dec;48(11):2293–2300. https://doi.org/10.1016/j.jacc.2006.07.059.
49. White PC. Aldosterone: direct effects on and production by the heart. *J Clin Endocrinol Metab*. 2003 Jun 1;88(6):2376–2383. https://doi.org/10.1210/jc.2003-030373.

50. Mulatero P, Williams TA, Monticone S, Veglio F. Is familial hyperaldosteronism underdiagnosed in hypertensive children? *Hypertension*. 2011 Jun;57(6): 1053–1055. https://doi.org/10.1161/HYPERTENSIONAHA.111.172916.
51. Sharma AN, Tan M, Amsterdam EA, Singh GD. Acromegalic cardiomyopathy: epidemiology, diagnosis, and management. *Clin Cardiol*. 2018 Mar;41(3): 419–425. https://doi.org/10.1002/clc.22867.
52. Saccà L, Napoli R, Cittadini A. Growth hormone, acromegaly, and heart failure: an intricate triangulation. *Clin Endocrinol*. 2003 Dec;59(6):660–671. https://doi.org/10.1046/j.1365-2265.2003.01780.x.
53. Volterrani M, Giustina A, Manelli F, Cicoira MA, Lorusso R, Giordano A. Role of growth hormone in chronic heart failure: therapeutic implications. *Ital Heart J*. 2000 Nov;1(11):732–738. PMID: 11110515.
54. Legrand V, Becker A, Pham VT, Demouun JC, Stevenaert A. Dramatic improvement of severe dilated cardiomyopathy in an acromegalic patient after treatment with octreotide and trans-sphenoidal surgery. *Eur Heart J*. 1994 Sep;15(9): 1286–1289. https://doi.org/10.1093/oxfordjournals.eurheartj.a060668.
55. Gouya H, Vignaux O, Le Roux P, et al. Rapidly reversible myocardial edema in patients with acromegaly: assessment with ultrafast T2 mapping in a single-breath-hold MRI sequence. *Am J Roentgenol*. 2008 Jun;190(6):1576–1582. https://doi.org/10.2214/AJR.07.2031.
56. Oliveira Martins Duarte J, Pestana Pereira PML, Sobral ASG, et al. A rare and reversible case of heart failure—hypocalcemia due to hypoparathyroidism. *Clin Case Rep*. 2019 Oct;7(10):1932–1934. https://doi.org/10.1002/ccr3.2397.
57. Parepa I. Hypocalcemic cardiomyopathy - a rare heart failure etiology in adult. *Acta Endocrinol*. 2019;15(1):107–112. https://doi.org/10.4183/aeb.2019.107.
58. Bansal B, Bansal M, Bajpai P, Garewal HK. Hypocalcemic cardiomyopathy—different mechanisms in adult and pediatric cases. *J Clin Endocrinol Metab*. 2014 Aug 1;99(8):2627–2632. https://doi.org/10.1210/jc.2013-3352.
59. Bansal N, Zelnick L, Robinson-Cohen C, et al. Serum parathyroid hormone and 25-hydroxyvitamin D concentrations and risk of incident heart failure: the multi-ethnic study of atherosclerosis. *J Am Heart Assoc*. 2014 Dec 17;3(6). https://doi.org/10.1161/JAHA.114.001278.
60. Stefenelli T, Abela C, Frank H, et al. Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. *J Clin Endocrinol Metab*. 1997 Jan;82(1):106–112. https://doi.org/10.1210/jcem.82.1.3666.
61. Knoll K, Kurowski V, Schunkert H, Sager HB. Management of hypercalcaemia-induced heart failure using mechanical circulatory support. *Eur J Cardio Thorac Surg*. 2018 Oct 1;54(4):784–785. https://doi.org/10.1093/ejcts/ezy139.
62. Witte KK, Byrom R, Gierula J, et al. Effects of vitamin D on cardiac function in patients with chronic HF. *J Am Coll Cardiol*. 2016 Jun;67(22):2593–2603. https://doi.org/10.1016/j.jacc.2016.03.508.
63. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Płudowski P, Jones G. Vitamin D toxicity–A clinical perspective. *Front Endocrinol*. 2018 Sep 20;9:550. https://doi.org/10.3389/fendo.2018.00550.
64. Fox DJ. Carcinoid heart disease: presentation, diagnosis, and management. *Heart*. 2004 Oct 1;90(10):1224–1228. https://doi.org/10.1136/hrt.2004.040329.
65. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation*. 1993 Apr;87(4): 1188–1196. https://doi.org/10.1161/01.CIR.87.4.1188.
66. Vijayaraghavan G, Sivasankaran S. Tropical endomyocardial fibrosis in India: a vanishing disease!. *Indian J Med Res*. 2012 Nov;136(5):729–738.
67. Crawford MA. Endomyocardial fibrosis and carcinoidosis. A common denominator? *Am Heart J*. 1963 Aug;66(2):273–276. https://doi.org/10.1016/0002-8703(63)90046-2.
68. Rutakingirwa M, Ziegler JL, Newton R, Freers J. Poverty and eosinophilia are risk factors for endomyocardial fibrosis (EMF) in Uganda. *Trop Med Int Health*. 1999 Mar;4(3):229–235. https://doi.org/10.1046/j.1365-3156.1999.43376.x.
69. Johnston SD, Johnston PW, O'Rourke D. Carcinoid constrictive pericarditis. *Heart*. 1999 Nov 1;82(5):641–643. https://doi.org/10.1136/hrt.82.5.641.
70. Correa R, Salpea P, Stratakis CA. Carney complex: an update. *Eur J Endocrinol*. 2015 Oct;173(4):M85–M97. https://doi.org/10.1530/EJE-15-0209.
71. Courcoutsakis NA, Tatsi C, Patronas NJ, Lee C-CR, Prassopoulos PK, Stratakis CA. The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney complex): imaging findings with clinical and pathological correlation. *Insights Imaging*. 2013 Feb;4(1):119–133. https://doi.org/10.1007/s13244-012-0208-6.
72. [Internet] Espiard S, Bertherat J. Carney complex [cited 2020 Jul 21]. In: Stratakis CA, ed. *Front Horm Res*. Basel: S. KARGER AG; 2013:50–62. Available from: https://www.karger.com/Article/FullText/345669.
73. Lupsa BC, Sachdev V, Lungu AO, Rosing DR, Gorden P. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. *Medicine (Baltim)*. 2010 Jul;89(4):245–250. https://doi.org/10.1097/MD.0b013e3181e9442f.
74. Vigouroux C, Caux F, Capeau J, Christin-Maitre S, Cohen A. LMNA mutations in atypical Werner's syndrome. *Lancet*. 2003 Nov;362(9395):1585. https://doi.org/10.1016/S0140-6736(03)14760-5.
75. Garg A, Peshock RM, Fleckenstein JL. Adipose tissue distribution pattern in patients with familial partial lipodystrophy (dunnigan variety). *J Clin Endocrinol Metab*. 1999 Jan;84(1):170–174. https://doi.org/10.1210/jcem.84.1.5383.
76. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy. *J Am Coll Cardiol*. 2008 Jan;51(2):93–102. https://doi.org/10.1016/j.jacc.2007.10.021.
77. Biondi B. Mechanisms in endocrinology: heart failure and thyroid dysfunction. *Eur J Endocrinol*. 2012 Nov;167(5):609–618. https://doi.org/10.1530/EJE-12-0627. Epub 2012 Sep 6.
78. Vydt T, Verhelst J, De Keulenaer G. Cardiomyopathy and thyrotoxicosis: tachycardiomyopathy or thyrotoxic cardiomyopathy? *Acta Cardiol*. 2006 Feb;61(1):115–117. https://doi.org/10.2143/AC.61.1.2005149.
79. Gupta S, Goyal P, Idrees S, Aggarwal S, Bajaj D, Mattana J. Association of endocrine conditions with Takotsubo cardiomyopathy: a comprehensive review. *J Am Heart Assoc*. 2018 Sep 26;(19):7. https://doi.org/10.1161/JAHA.118.009003 [cited 2020 Jul 27].
80. De Giorgi A, Fabbian F, Tiseo R, et al. Takotsubo cardiomyopathy and endocrine disorders: a mini-review of case reports. *Am J Emerg Med*. 2014 Nov;32(11): 1413–1417. https://doi.org/10.1016/j.ajem.2014.07.030.
81. Ozcan F, Ustun I, Berker D, Aydin Y, Delibasi T, Guler S. Inverted T waves in patient with Addisonian crisis. *J Natl Med Assoc*. 2005 Nov;97(11):1539–1540. PMID: 16334501.
82. Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Morgante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia. A histologic, ultrastructural, and biochemical study. *Chest*. 1991 Feb;99(2): 382–385. https://doi.org/10.1378/chest.99.2.382.
83. Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell*. 2007 Feb;128(3): 589–600. https://doi.org/10.1016/j.cell.2006.12.036.
84. Triebel J, Clapp C, Martínez de la Escalera G, Bertsch T. Remarks on the prolactin hypothesis of peripartum cardiomyopathy. *Front Endocrinol*. 2017 Apr 11. https://doi.org/10.3389/fendo.2017.00077 [Internet].
85. Honigberg MC, Givertz MM. Peripartum cardiomyopathy. *BMJ*. 2019 Jan 30;364:k5287. https://doi.org/10.1136/bmj.k5287.
86. Hilfiker-Kleiner D, Haghikia A, Berliner D, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. *Eur Heart J*. 2017 Sep 14;38(35):2671–2679. https://doi.org/10.1093/eurheartj/ehx355.
87. Monticone S, Losano I, Tetti M, Buffolo F, Veglio F, Mulatero P. Diagnostic approach to low-renin hypertension. *Clin Endocrinol*. 2018 Oct;89(4):385–396. https://doi.org/10.1111/cen.13741.
88. Cui Y, Tong A, Jiang J, Wang F, Li C. Liddle syndrome: clinical and genetic profiles. *J Clin Hypertens*. 2017 May;19(5):524–529. https://doi.org/10.1111/jch.12949.
89. Pepersack T, Allegre S, Jeunemaître X, Leeman M, Praet J-P. Liddle syndrome phenotype in an octogenarian. *J Clin Hypertens*. 2015 Jan;17(1):59–60. https://doi.org/10.1111/jch.12450.
90. New MI, Geller DS, Fallo F, Wilson RC. Monogenic low renin hypertension. *Trends Endocrinol Metab*. 2005 Apr;16(3):92–97. https://doi.org/10.1016/j.tem.2005.02.011.
91. Dave-Sharma S, Wilson RC, Harbison MD, et al. Examination of genotype and phenotype relationships in 14 patients with apparent mineralocorticoid excess. *J Clin Endocrinol Metab*. 1998 Jul;83(7):2244–2254. https://doi.org/10.1210/jcem.83.7.4986.
92. Zachmann M, Tassinari D, Prader A. Clinical and biochemical variability of congenital adrenal hyperplasia due to llβ-hydroxylase deficiency, A study of 25 patients. *J Clin Endocrinol Metab*. 1983 Feb;56(2):222–229. https://doi.org/10.1210/jcem-56-2-222.
93. Jarallah ASA. Reversible cardiomyopathy caused by an uncommon form of congenital adrenal hyperplasia. *Pediatr Cardiol*. 2004 Dec;25(6):675–676. https://doi.org/10.1007/s00246-003-0612-2.
94. Goyal A, Boro H, Khadgawat R. Male gender identity and reversible hypokalemic hypertension in a 46,XX child with 11-beta-hydroxylase deficiency congenital adrenal hyperplasia. *Cureus*. 2019 Jul 26. https://doi.org/10.7759/cureus.5248.
95. Charmandari E, Kino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (chrousos syndrome) and hypersensitivity. In: Maghnie M, Loche S, Cappa M, Ghizzoni L, Lorini R, eds. *Endocr Dev. Basel*. S. KARGER AG; 2013:67–85. Available from: https://www.karger.com/Article/FullText/342505.
96. Geller DS. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science*. 2000 Jul 7;289(5476):119–123. https://doi.org/10.1126/science.289.5476.119.
97. Mehandru S, Haroon A, Singh V, et al. Atypical presentation of Gordon syndrome and its management: a report of three patients. *J Med Cases*. 2017;8(8): 252–255. https://doi.org/10.14740/jmc2874w.