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FAMILIAL HYPOCALCIURIC HYPERCALCEMIA AND EARLY SEVERE AORTIC STENOSIS IN A PATIENT WITH TWO DIFFERENT HEART FAILURE EPISODES

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ABSTRACT

Introduction: Familial hypocalciuric hypercalcemia (FHH) is a rare hereditary cause of mild hypercalcemia that usually follows a benign clinical course. Calcific aortic stenosis (AS) in a trileaflet aortic valve is uncommon before 65 years of age. Emerging evidence suggests that disturbances in calcium metabolism may contribute to aortic valve calcification.

Case description: A 58-year-old woman presented in 2012 with acute heart failure (HF) and left ventricular ejection fraction (LVEF) of 32%. Coronary angiography was normal, and endomyocardial biopsy was not suggestive of myocarditis. She achieved complete recovery with guideline-directed medical therapy, consistent with resolved idiopathic cardiomyopathy. Echocardiography at that time showed only mild aortic valve thickening. She had chronic mild hypercalcemia consistent with FHH, supported by family history, normal parathyroid hormone levels, and fractional excretion of calcium <1%. Genetic testing was negative. During the following decade, progressive aortic valve calcification was documented. In 2023, echocardiography revealed severe AS with a functionally bicuspid valve (peak/mean gradients 105/69 mmHg; valve area 0.5 cm^2) and LVEF of 41%, presenting with a second episode of acute HF. She underwent surgical aortic valve replacement with full symptomatic recovery.

Conclusion: This case suggests a possible association between FHH and accelerated valvular calcification leading to premature severe AS. It is also notable for two separate HF episodes caused by different aetiologies: reversible cardiomyopathy initially, followed a decade later by severe AS. Although FHH is generally considered benign, chronic hypercalcemia may justify closer long-term cardiovascular surveillance.

KEYWORDS

Hypercalcemia, familial hypocalciuric hypercalcemia, aortic valve stenosis, aortic valve calcification, heart failure

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LEARNING POINTS

- Familial hypocalciuric hypercalcemia may be associated with accelerated valvular calcification and premature severe aortic stenosis.
- Serial imaging over 10 years documented progression from mild valve thickening to severe calcific aortic stenosis.
- The case describes two distinct episodes of heart failure caused by different underlying mechanisms.

INTRODUCTION

Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant hereditary cause of mild hypercalcaemia. Most patients remain asymptomatic and usually the disease has a benign course[1]. This disorder results from inactivating mutations affecting the calcium-sensing receptor signalling pathway, with three genetic subtypes identified: FHH type 1 (*CASR* mutations), accounting for most cases; FHH type 2 (*GNA11* mutations); and FHH type 3 (*AP2S1* mutations)[2].

Calcific aortic stenosis (AS) is the most common valvular heart disease, with prevalence increasing exponentially with age[3]. Severe AS in patients younger than 60 years remains uncommon. The pathophysiology involves an initiation phase of endothelial injury and inflammation, followed by a propagation phase dominated by transformation of valve interstitial cells and progressive calcification[4].

Evidence suggests that disturbances in calcium metabolism may be associated with aortic valve calcification[5]. Hypercalcemia has been shown to promote valve interstitial cells calcification[6].

Studies have demonstrated significantly increased aortic valve calcification area in patients with primary hyperparathyroidism (PHPT) compared to controls[7]. Similarly, chronic kidney disease (CKD) is associated with accelerated calcific AS occurring at an earlier age, with CKD-metabolic bone disease representing one of the strongest components of this process[8]. Despite the recognized association between hypercalcemia and valvular calcification in PHPT and CKD, the relationship between chronic hypercalcemia from FHH and severe AS remains poorly documented. We present a case of severe calcific AS in a patient with FHH, highlighting a potential association between these two entities.

CASE DESCRIPTION

We report the case of a 58-year-old woman with a known history of non-ischemic acute heart failure (HF) with reduced left ventricular ejection fraction (LVEF) since 2012. At that time, investigation of HF aetiology included a transthoracic echocardiogram which revealed a moderately impaired left ventricular systolic function with an ejection fraction of 32%, without regional wall motion abnormalities. The left ventricle was severely dilated with mildly hypertrophic walls. Left atrial mild dilatation was noted. The aortic valve leaflets were thickened, with moderate aortic regurgitation due to two confluent central jets. Mild mitral and tricuspid regurgitation were present. Right ventricular function was preserved. A minimal pericardial effusion was observed. No intracavitary masses were identified. Secondary causes of cardiomyopathy were excluded: thyroid function was normal and there was no history of alcohol or cardiotoxic drug exposure. Coronary angiography demonstrated right coronary dominance and angiographically normal coronary arteries. An endomyocardial biopsy was performed and the histopathological examination showed no inflammatory infiltrates or myocyte necrosis, therefore not suggestive of myocarditis and no amyloid deposition was detected on Congo Red staining. The patient had full recovery of LVEF within 1 year of updated guideline-directed medical therapy by the time; no device implantation was needed. She remained clinically stable and asymptomatic for over a decade under regular surveillance and maintaining all the HF therapy. Serial follow-up echocardiography revealed gradual progression of aortic valve disease from thickened leaflets with mild transaortic gradients (peak/mean 27/14 mmHg) in 2013, to focal calcification between the right and left coronary cusps with moderate gradients (peak/mean 37/21 mmHg) and a functional valve area of 1.2–1.3 cm^2 by 2016. LVEF remained preserved and stable throughout.

She had chronic mild hypercalcemia (ionized calcium between 2.68 and 2.80 mEq/l). A comprehensive workup was performed. The initial parathyroid hormone (PTH) level was 20 pg/ml with concurrent vitamin D insufficiency. After repletion, PTH remained within the normal range. Serum phosphate was low-normal and magnesium was always in the normal range. Serum protein electrophoresis showed no monoclonal peak, thyroid function was normal, and fine-needle aspiration of a thyroid nodule confirmed a benign follicular lesion. No occult malignancy was identified. The calcium-to-creatinine clearance ratio was repeatedly below 0.01 (ranging from 0.002 to 0.004). The patient reported a family history of hypercalcemia on the paternal side involving multiple relatives. Genetic testing for pathogenic variants in *CASR*, *GNA11*, and *AP2S1* was negative. The overall clinical and biochemical profile was consistent with the diagnosis of FHH.

A routine echocardiogram in December 2023 revealed progression of the valvular disease. The aortic valve was severely thickened and calcified with fusion of the right and left coronary cusps (functionally bicuspid), causing severe AS (peak/mean gradients of 105/69 mmHg and

functional valve area of 0.5 cm^2) with severe left chamber dilation. There was also a significant worsening of the mitral valve disease with mild annular calcification, restricted and thickened leaflets, resulting in moderate-to-severe functional regurgitation. The tricuspid valve had a dilated annulus (39 mm) with mildly thickened leaflets and mild-to-moderate regurgitation. LVEF had fallen to 41% with global hypokinesis. Given the severity of valvular disease, the patient was referred for preoperative evaluation. Coronary angiography confirmed the absence of significant coronary artery disease. Carotid ultrasound excluded hemodynamically significant stenoses, and odontological assessment excluded oral infectious foci. Pulmonary function tests revealed a mixed ventilatory defect with a severe obstructive component. She was subsequently referred for elective aortic valve intervention. In February 2024, before the planned procedure, the patient presented with acute decompensated HF—dyspnoea on minimal exertion, new-onset orthopnoea and peripheral oedema with New York Heart Association (NYHA) functional class III, markedly elevated N-terminal pro-B-type natriuretic peptide (>28,000 pg/ml) and clinical signs of systemic congestion. She underwent urgent surgical intervention: aortic valve replacement with a bioprosthesis (Perimount Magna Ease 23) and mitral (Physio 26 ring) and tricuspid (Sovering 28 band) annuloplasty. Intraoperative findings confirmed an aortic valve with extensive calcification. Following a prolonged postoperative recovery, she was discharged and enrolled in a structured rehabilitation program. At 3-month follow-up, she had returned to NYHA functional class I, with a normally functioning aortic bioprosthesis and recovered left ventricular systolic function (LVEF >50%) on echocardiography.

DISCUSSION

This case describes a rare association between FHH and premature severe AS in a 58-year-old woman with an anatomically trileaflet aortic valve that developed asymmetric calcification. The patient developed severe AS earlier than the typical age of presentation for degenerative calcific AS in trileaflet valves, which predominantly affects individuals in their seventh and eighth decades of life[3]. This premature presentation in a trileaflet valve suggests an accelerating factor beyond normal aging. While FHH is classically considered a benign condition without significant cardiovascular complications, this case suggests that sustained mild hypercalcemia may contribute to accelerated valvular calcification and earlier onset of severe AS.

FHH is typically characterized by a benign clinical course with normal longevity and minimal complications[1]. The chronic hypercalcaemic state therefore preceded the development of aortic valve calcification and severe AS by several decades, establishing an unequivocal temporal sequence between exposure and outcome. Large cardiovascular studies of FHH patients have not demonstrated increased cardiovascular risk, with one cross-sectional study of 50 FHH patients finding no differences in blood pressure, arterial stiffness, or cardiovascular disease compared to controls[9]. However, the literature on valvular calcification specifically in FHH remains limited. This lack of data contrasts with the well-established relationship between other calcium metabolism disorders and accelerated valve calcification.

The plausibility of this association is reinforced by examining conditions that share biochemical overlap with FHH. Studies of chronic kidney disease demonstrate that hypercalcemia and hyperphosphatemia promote accelerated valvular calcification through mechanisms involving altered balance between promoters and inhibitors of calcification[8]. Additionally, elevated serum calcium and phosphate levels themselves have been independently associated with increased risk of PHPT[10], which shares biochemical overlap with FHH, has shown conflicting associations with aortic valve calcification in the literature. One study found that PTH levels independently predicted aortic valve calcification area even after adjustment for traditional cardiovascular risk factors however, some studies show no significant association[11]. The existence of established relationships between these analogous calcium metabolism disorders and valvular calcification lends further credibility to a similar association in FHH.

The mechanisms by which FHH may promote accelerated aortic valve calcification likely involve multiple pathways. Chronic hypercalcemia increases calcium availability for deposition in valvular tissues. Experimental studies demonstrate that elevated extracellular calcium promotes osteogenic transformation of valvular interstitial cells (VICs) through activation of signalling pathways[12]. The initiation phase of calcific aortic valve disease involves valvular endothelial injury, inflammation, and lipid deposition, while the propagation phase is characterized by a self-perpetuating cycle of calcification driven by osteoblastic transformation of VICs[6]. The asymmetric calcification that created a functionally bicuspid valve in this patient would itself accelerate disease progression through abnormal hemodynamic stress with high-frequency unsteady shear stress that promote pro-inflammatory signalling and extracellular matrix remodelling[12]. This creates a cycle where initial calcification changes valve geometry, which in turn accelerates further calcification.

The only effective therapy for severe symptomatic AS is valve replacement, either surgical or transcatheter, while no medical therapies have proven efficacy in slowing or reversing calcific aortic valve disease progression. FHH generally requires no specific treatment. Rigorous control of modifiable cardiovascular risk, factors such as hypertension, dyslipidaemia and diabetes is recommended, particularly in younger patients where these factors may accelerate progression[5].

Taken together, the evidence assembled in this case — the clear temporal precedence of lifelong hypercalcemia, the

robust biological mechanisms linking calcium to valvular osteogenic transformation, the graded population-level relationship between serum calcium and AS risk, the parallels with analogous calcium metabolism disorders, and the coherence with established pathophysiological understanding — provides reasonable support for the hypothesis that chronic hypercalcemia in FHH may have contributed to accelerated aortic valve calcification in this patient. Definitive causality cannot be established from a single case report, and the most significant limitations are the absence of replication across FHH cohorts and of direct experimental evidence. This case underscores the need for prospective studies that systematically assess valvular calcification in FHH cohorts, particularly with long-term echocardiographic follow-up, to determine whether periodic monitoring should be considered in this population. This case is also noteworthy for the unusual occurrence of two distinct episodes of HF separated by a decade: the first resulting from idiopathic cardiomyopathy with complete recovery, and the second from severe AS. It illustrates both the progressive nature of valvular disease and the rare development of HF from two different and independent aetiologies in the same patient.

CONCLUSION

This case highlights a potential association between FHH and accelerated valvular calcification leading to premature severe AS. Although FHH typically follows a benign clinical course, chronic hypercalcemia may warrant long-term cardiovascular surveillance, particularly for valvular calcification. Further studies are needed to determine whether systematic cardiovascular screening, particularly echocardiographic surveillance for valvular calcification, should be recommended in patients with FHH.

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