Case Report

Rare case of familial restrictive cardiomyopathy : a case report

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Familial restrictive cardiomyopathy is an extremely rare disease affecting the heart. The exact incidence and genetic associations are not well delineated. It generally presents with a restrictive filling pattern on echocardiography with normal or near normal systolic function. We present the case of a 29 year old male who had features of biventricular failure. Echocardiography, cardiac MRI and catheterisation data confirmed the diagnosis of restrictive cardiomyopathy. Other investigations ruled out secondary causes of a restrictive physiology and the strong family history clinched the diagnosis in favour of a familial restrictive cardiomyopathy. Familial restrictive cardiomyopathy heralds a grave prognosis. A heart transplant appears to be the only modality of therapy which offers long term sustained resolution of symptoms. Our patient is currently waiting for the availability of a suitable donor for a heart transplant.

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As per the definition of the AmericanHeart Association (AHA), "Primary restrictive non-hypertrophied cardiomyopathy is a rare form of heart muscledisease and a cause of heartfailure that is characterized by normal or decreased volume of bothventricles associated with biatrial enlargement, normal LV wall thickness and AV valves, impaired ventricular fillingwith restrictive physiology, and normal (or near normal) systolic function"[1]. However in a series of 94 patients, Ammash *et al* reported systolic dysfunction in 16%[2]. Data about the exact burden of restrictive cardiomyopathy (RCM) is largely unavailable.However, an epidemiologic survey carried out in Japanese hospitalsnationwide, estimated a prevalence of 0.2 per 100,000 inhabitants[3].

RCM can be classified as primary/idiopathic or acquired[4]. What is common to primary/idiopathic or acquired RCM though,is the restrictive ventricular physiology. However, the causes of this disorder are widely heterogeneous.Distinguishing primary/idiopathic RCM from other diseasesmanifesting secondarily as restrictive ventricular physiology is especially important as it influences subsequent therapy and long-term prognosis. We describe here a rare case of familial idiopathic RCM presenting with biventricular systolic dysfunction.

Case Report

A 29 year old non-diabetic, non-hypertensive male presented with complaints of insidious onset, steadily progressive exertional dyspnoea for the past four months which had worsened over the past six days. He had a history of palpitations at a young age for which he was put on metoprolol 50 mg. His father had a sudden cardiac death at the age of 25-26 years of age and his younger sister had recently succumbed to a massive ischaemic stroke at the age of 25 years (Fig 3A).

Physical examination revealed bilateral pitting pedal oedema, raised jugular venous pressure with a positive Kussmaul's sign, a heart rate of 100/minute, blood pressure of 92/60 mm of Hg and respiratory rate of 28/minute. His cardiac apex was in the left 5th intercostal space on the left mid-clavicular line, a left ventricular S3 was heard and there were fine crepitations at both the lung bases. Hepatomegaly with mild ascites was also noted.

Routine blood panels were unremarkable except for raised liver enzymes and a deranged INR. Chest skiagram was reflective of pulmonary congestion (Fig 1A). There was evidence of marked biatrial enlargement on the electrocardiogram (Fig 1B) and echocardiography corroborated the same (Fig 2B). A restrictive ventricular inflow pattern (Fig 2C) along with generalised wall hypokinesia and a compromised left ventricular systolic function was detected. Average Global longitudinal strain was -4.5 % and right ventricular systolic function was also reduced (Fig 2A).

A diagnosis of RCMwith biventricular failure was made. Cardiac catheterisation confirmed the diagnosis with characteristic square root sign and elevated right atrial and right ventricular pressures. A search for potential causes of his conditiondid not turn up any evidence in favour of secondary causes of restrictive physiology such as amyloidosis, haemochromatosis, sarcoidosis or eosinophilic myocarditis. Cardiac MRI suggested the possibility of cardiac amyloidosis owing to relative apical sparing on late gadolinium enhancement (Fig 2D). However, in view of no other supportive evidence for amyloidosis, a diagnosis of idiopathic RCM was considered significantly more likely. Further elaboration of the strong family history also yieldedan echocardiographic image of his recently deceased younger sister, which showed prominent biatrial enlargement (Fig 3B). Based on all the clinical, biochemical and imaging evidence, a final diagnosis of familial idiopathic RCM was made.

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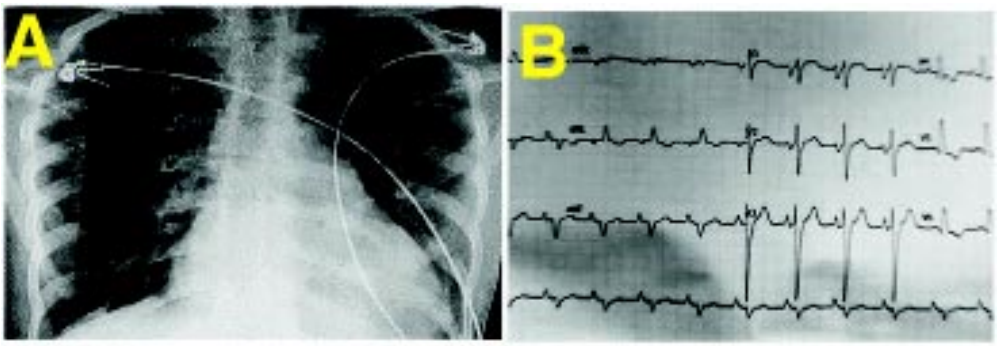

Fig 1 — Chest skiagram and electrocardiogram of patient. (A) Chest skiagram showed evidence of pulmonary congestion. (B) Electrocardiogram revealed marked biatrial hypertrophy and repolarisation abnormalities

He was treated with standard heart failure therapy upon which his condition showed some improvement. Currently he has been put on the heart transplant registry and is awaiting a suitable donor.

Discussion

Initial discovery of a familial form of RCM was in 1998[5]. Genetic counselling, family history, and evaluation of clinical reportsof family members are part of the clinical genetic workup for patientsdiagnosed with RCM[6]. Familial RCM demonstrates autosomaldominantinheritance in the majority of cases. However, even an extensive search of the medical literature did not turn up any reference of familial restrictive cardiomyopathy in the Indian sub-continent. To the best of our knowledge, our patient represents the first reported case of familial restrictive cardiomyopathy from India.

The family history of our patient was significant for sudden cardiac death of his father at a young age of 25-26 years, presumably due to a fatal arrhythmia. His sister's ischemic stroke was likely cardioembolic in origin. Biatrial enlargement seen in her echocardiographic image suggests that she might have been suffering from the same restrictive physiology that her brother currently suffers from. However, the unavailability of information about a full diagnostic and imaging work up prevents us from confirming that assumption about his sister with absolute certainty. Fortunately, the young children of our patient and his deceased sister are yet to be substantially affected by the disease process as their current echocardiographic and doppler studies are essentially normal. They will be closely followed up through successive years.

The TNNI3 gene that encodes the thin filament troponin I is the most commondisease gene responsible for RCM[7]. Mutations in thetroponin T2 gene (TNNT2) are less common in RCM and may alsocause HCM and DCM[8]. Other sarcomeric genes involved in RCMinclude ACTC1, MYL3, MYH7, TTN, TPM1, MYL3, and MYL2[9-13]. Recent reports have described mutations in Z-disc protein-encodinggenes, including

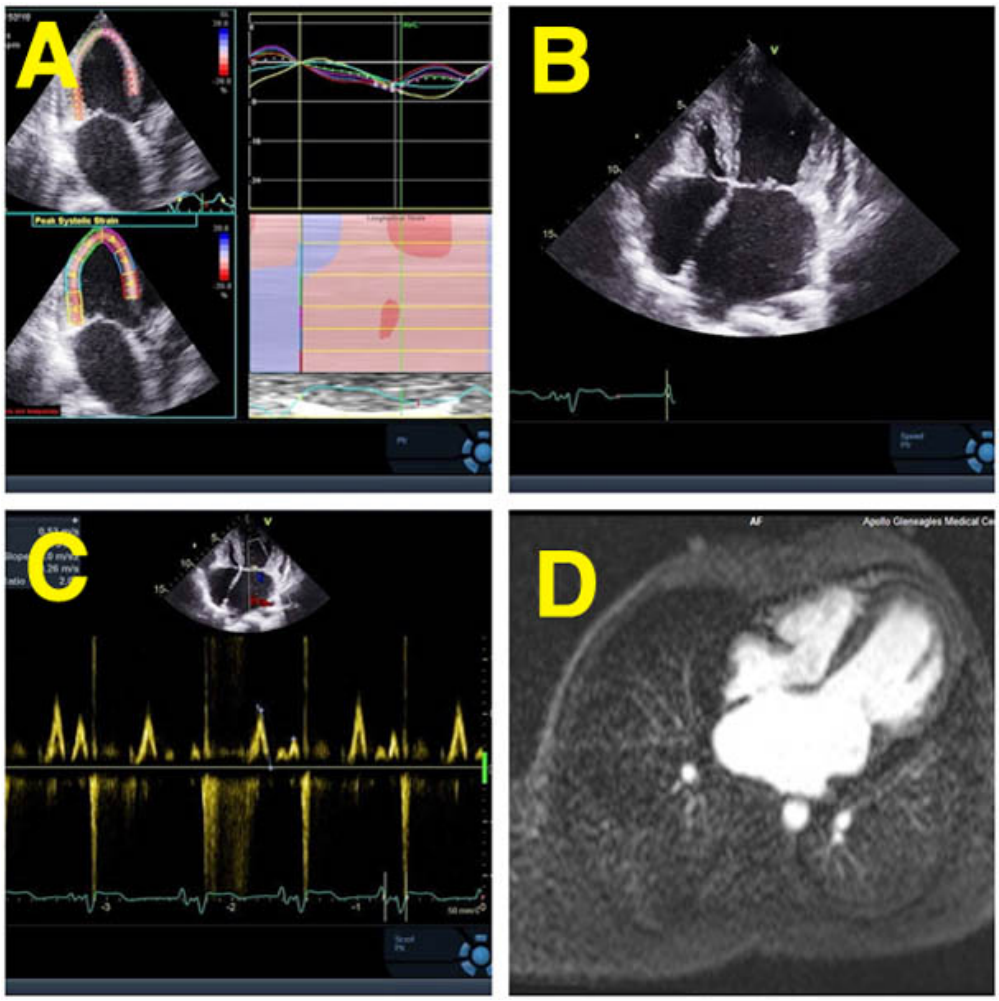

Fig 2 — Systolic dysfunction with average global longitudinal strain = -4.5%.
(B) Massive biatrial enlargement. (C) Restrictive ventricular physiology with E/e' = 2.0. (D) Cardiac MRI showed a lack of late gadolinium enhancement in the apical region, thus favouring cardiac amyloidosis over familial RCM.

MYPN, FLNC, and BAG3, in patients with RCM[14-17]. Pending genetic testing data for our patient and his family, accurate characterisation of the culprit genes responsible for his RCM will not be possible. Also, information from an endomyocardial biopsy will be sought during subsequent follow-up of our patient. The absence of such data is acknowledged as a limitation of this report.

Interestingly, our patient did not have any evidence of skeletal myopathy at presentation. Certain series have found a progressive non-wasting skeletal myopathy in individuals who survived into the 5th decade.18Whether the same holds true for our patient remains to be seen in the due course of time. In the interim period, he is being prepared for a heart transplantation, which is by far the most definitive long-term treatment for this condition.

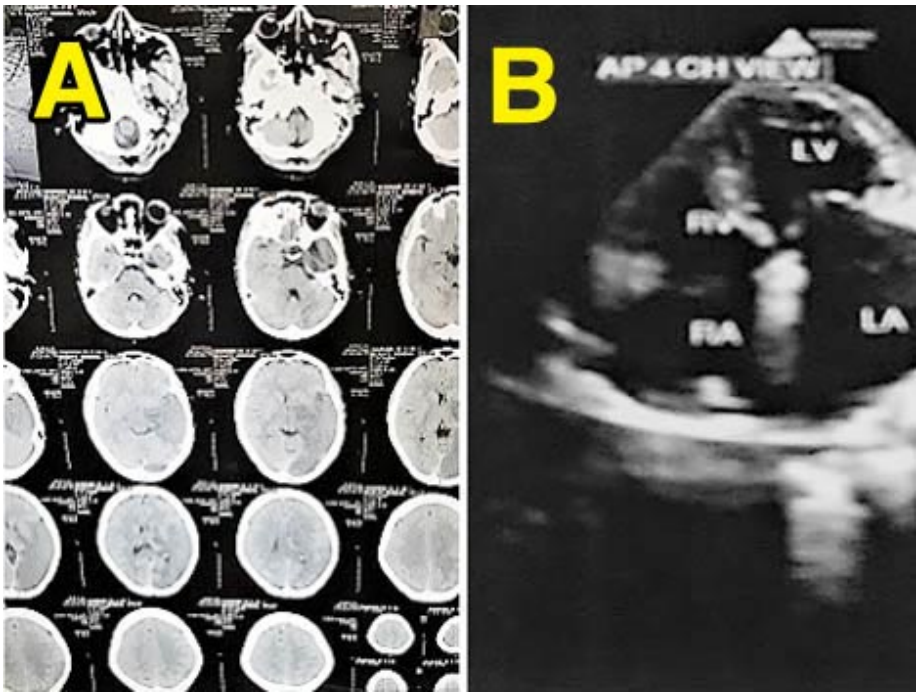

Fig 3 — Sister's available imaging reports. (A) CT brain showing left parieto-occipital infarct. (B) Still echocardiographic image showing biatrial enlargement

Conclusion

Familial idiopathic RCM is an exceedingly rare clinical entity. Given the grave prognosis that it portends, cardiac transplantation often turns out to be the only long-term therapeutic option[2]. The challenge lies in identifying such patients early, optimising their treatment protocols and proactively screening the entire family for evidence of latent cardiac compromise.

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