CASE REPORT

Dilated cardiomyopathy and progressive familial intrahepatic cholestasis

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Accepted 9 February 2014

SUMMARY

This case is of a 29-year-old man with progressive familial intrahepatic cholestasis type 1 also known as Byler's disease. At the age of 21, our patient developed non-ischaemic dilated cardiomyopathy. Cardiac MRI demonstrated global wall thinning, with significant areas of myocardial fibrosis in the mid and epicardial walls from base to apex on postgadolinium late contrast enhanced images. No shared genetic loci between dilated cardiomyopathy and Byler's or cholestatic liver disease have yet been found. This presents the first documented case of non-ischaemic dilated cardiomyopathy, with evidence of mid wall fibrosis, in association with an established diagnosis of progressive familial intrahepatic cholestasis type 1 since childhood.

BACKGROUND

Dilated cardiomyopathy is a common diagnosis seen in young patients with heart failure. Causes could be genetic, postinfectious, ischaemic and certainly idiopathic in some cases. Dilated cardiomyopathy had been linked to certain illnesses. However, no definite literature is available to link progressive familial intrahepatic cholestasis and dilated cardiomyopathy. This case supports the need for lateral thinking in finding the cause of dilated cardiomyopathy in the young.

CASE PRESENTATION

We present the case of a 29-year-old man with progressive familial intrahepatic cholestasis type 1. Our patient is the eldest of four affected siblings from a large family of a travelling background. His presentation was in early infancy with recurrent episodes of severe sepsis, prolonged diarrhoea and failure to thrive. Onset of jaundice was at 6 months and cholestasis has persisted since. Severe pruritus, unresponsive to conventional therapies, has been a predominant symptom. Our patient displays extrahepatic features common to progressive familial intrahepatic cholestasis type 1 including short stature, sensorineural deafness, secretory diarrhoea and elevated sweat electrolyte concentration. Features of fat-soluble vitamin deficiency are also evident, including bowing of the limbs and peripheral neuropathy. He is of normal intelligence.

Bilirubin concentration in this man is persistently elevated (between 100 and 200 mmol/L), although may be significantly higher during intercurrent illness. Consistent with progressive familial intrahepatic cholestasis type 1, serum γ -glutamyltransferase

and cholesterol are normal. Hepatic synthetic function remains relatively preserved with a normal serum albumin and prothrombin time.

Diagnosis of progressive familial intrahepatic cholestasis type 1 was confirmed in childhood by liver histology, which demonstrated canalicular cholestasis with few interlobular bile ducts. Hepatocellular architectural changes were evidenced by periportal biliary hepatocyte metaplasia.

Aged 21, our patient presented acutely with shortness of breath, bipedal oedema and paroxysmal nocturnal dyspnoea. A transthoracic echocardiography demonstrated dilated cardiomyopathy with moderate left atrial dilation, left ventricular end-diastolic dimension of 5.9 cm and moderate functional mitral regurgitation. Left ventricular ejection fraction at this time was 45%. He proceeded to right and left heart catheterisations, which were unremarkable. A diagnosis of primary dilated cardiomyopathy was made and he was started on appropriate treatment including ACE inhibitor, diuretics and aldosterone antagonists.

Despite remaining symptomatically and clinically stable, the left ventricle continued to dilate (left ventricular end-diastolic dimension of 6.4 cm) and the left ventricular ejection fraction deteriorated to 25%. The patient was referred for cardiac MRI before consideration for implantable cardioverter-defibrillator implantation. Cardiac MRI was performed based on standard Society of Cardiovascular Magnetic Resonance protocols.

Cardiac MRI confirmed non-ischaemic dilated cardiomyopathy with mild functional mitral regurgitation and extensive mid wall fibrosis. In figures 1 and 2, cine and postgadolinium images of Byler's associated dilated cardiomyopathy, the short axis steady-state free precession cine images (figures 1A–C and 2A–C) demonstrate global wall thinning. Areas of mid wall high signal are noted in the cine images confirmed as myocardial fibrosis on postgadolinium late contrast enhanced images (figures 1D–F and 2D–F). Regions of fibrosis are noted in the mid and epicardial walls from base to apex. Given these findings the patient was referred for implantable cardioverter-defibrillator implantation.

One month after the cardiac MRI, while awaiting outpatient implantable cardioverter-defibrillator insertion, he suffered a ventricular fibrillation cardiac arrest and was successfully resuscitated with no neurological deficits. An implantable cardioverter-defibrillator was subsequently implanted during the acute admission and was then discharged after full in-hospital recovery.

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To cite: James S, Waterhouse D, McDonald K, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-202950

Figure 1 Cine and postgadolinium images of Byler's associated dilated cardiomyopathy: short axis steady-state free precession cine images (A–C) demonstrate global wall thinning. Areas of mid wall high signal are noted in the cine images confirmed as myocardial fibrosis on postgadolinium late contrast enhanced images (D–F). Regions of fibrosis are noted in the mid and epicardial walls from base to apex.

Figure 2 Cine and postgadolinium images of Byler's associated dilated cardiomyopathy: areas of mid wall high signal are noted in the cine images (A–C) confirmed as myocardial fibrosis on postgadolinium late contrast enhanced images (D–F). Regions of fibrosis are noted in the mid and epicardial walls from base to apex.

INVESTIGATIONS

It is emphasised that this patient has established diagnosis of progressive familial intrahepatic cholestasis type 1 since childhood with relevant hepatological investigations (not available to us) performed in a paediatric hospital prior to transferring to adult care to the hepatology unit.

He then had the following cardiology investigations in our cardiology unit at the first onset of heart failure, summarised as follows:

1. First transthoracic echocardiography: showed dilated cardiomyopathy with moderate left atrial dilation, left ventricular end-diastolic dimension of 5.9 cm and moderate functional mitral regurgitation. Left ventricular ejection fraction at this time was 45%.
2. Right and left heart catheterisation: showed normal coronary arteries with normal intracardiac pressure study.
3. Follow-up transthoracic ECG (after maximal disease modifying therapies): the left ventricle continued to dilate (left ventricular end-diastolic dimension of 6.4 cm) and the left ventricular ejection fraction deteriorates to 25%.
4. Cardiac MRI: showed non-ischaemic dilated cardiomyopathy with mild functional mitral regurgitation and extensive mid wall fibrosis. In [figures 1](#) and [2](#), cine and postgadolinium images of Byler's associated dilated cardiomyopathy, the short axis steady-state free precession cine images ([figures 1A–C](#) and [2A–C](#)) demonstrate global wall thinning. Areas of mid wall high signal are noted in the cine images confirmed as myocardial fibrosis on postgadolinium late contrast enhanced images ([figures 1D–F](#) and [2D–F](#)). Regions of fibrosis are noted in the mid and epicardial walls from base to apex.

DIFFERENTIAL DIAGNOSIS

In elucidating the cause of this patient's cardiomyopathy, we had considered the following diagnoses, which were clarified by the cardiac investigations.

1. Ischaemic cardiomyopathy: in this patient, the right and left heart catheterisations showed normal coronaries with no obstructive lesions to account for potential coronary artery disease. Certainly the cardiac MRI did not show any evidence of subendocardial or transmural late gadolinium enhancement and myocardial scarring to suggest infarcts.
2. Infiltrative cardiomyopathy such as amyloidosis or sarcoidosis: amyloidosis and sarcoidosis fibroses are specific with certain typical appearances post late gadolinium enhancements, which was not evident in the cardiac MRI.
3. Primary dilated cardiomyopathy: the findings from the transthoracic ECG and cardiac MRI fit this diagnosis. The classical patchy mid-wall fibrosis with the absence of subendocardial or transmural late gadolinium enhancement lead to the diagnosis of primary dilated cardiomyopathy.

TREATMENT

The treatment of primary dilated cardiomyopathy is mainly supportive. Heart failure treatments are more successful in the 21st century and helped to maintain normal life in patients with improvement in prognosis. For this patient, he was initiated on optimal medical therapies such as ACE inhibitor, diuretics and aldosterone antagonists to stabilise his heart failure symptoms. He also later needed an implantation of life-saving implantable cardioverter-defibrillator after suffering a cardiac arrest which he had recovered from. It is also importance to engage the

patient in a disease modifying programme such as ambulatory heart failure unit for continued monitoring.

OUTCOME AND FOLLOW-UP

Three years on, the patient is doing well and attending regular review within a disease modifying programme in an ambulatory heart failure unit. His ejection fraction improved and maintained at 35% with implantable cardioverter-defibrillator in situ with no further cardiac arrests.

DISCUSSION

This is the first description of extensive mid wall fibrosis in a case of dilated cardiomyopathy in a patient with progressive familial intrahepatic cholestasis. The presence of mid wall fibrosis is a recognised risk factor for major adverse cardiac events, including malignant arrhythmia.^{1 2} Progressive familial intrahepatic cholestasis is a heterogeneous group of autosomal recessive liver disorders with varying phenotypes, always resulting from hepatocellular cholestasis, presenting in infancy and resulting in death from liver failure.

A definite link between cholestatic liver disease and focal cardiac fibrosis leading to dilated cardiomyopathy has not been reported in the literature. There exist, however, theories on how liver failure and cardiac failure constitute a clinical continuum. Models include impaired hepatic metabolism of systemic vasodilators,^{3 4} autonomic neuropathy⁵ and an increase in proinflammatory cytokines with secondary effects on cardiomyocytes.

A case has been described in the literature of mitochondrial dysfunction in Byler's disease secondary to vitamin E deficiency, which developed from fat-soluble vitamin malabsorption. Pathology revealed combined hepatocyte and cardiomyocyte mitochondrial changes.⁶ Effect of hypovitaminosis E on the Purkinje cardiomyocytes has previously been observed, with mitochondrial mineralisation leading to macrophage invasion, phagocytosis and fibrosis.⁷

The precise mediator of mid wall fibrosis in patients with chronic cholestasis has not been identified. No shared genetic loci between dilated cardiomyopathy and Byler's or cholestatic liver disease have yet been found. The current understanding is that fibrosis in Byler's disease represents an interplay between intracellular dysregulation and systemic alterations in homeostasis.

Learning points

- ▶ Always consider the patient's medical history as part of a diagnosis.
- ▶ Dilated cardiomyopathy in the young is usually genetically related; either as part of a disease process or independent.
- ▶ Successful treatments are available to delay the progression of dilated cardiomyopathy and prevent cardiac arrest.

Acknowledgements We would like to acknowledge the valued input of the patient for allowing us to present this case, Prof A McCormick for his perspective on the case from the hepatologist's point of view and Prof J Dodd for allowing us to use the image.

Contributors SJ and DW wrote and edited the main body of work. RH selected the figures and images and KM reviewed the final work.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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