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Genetic dilated cardiomyopathy with inflammation in an infant that responded to immunosuppressive therapy evaluated using cardiovascular magnetic resonance

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Brief Report

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Abstract

Cardiovascular magnetic resonance T1 and T2 mapping reflects inflammation, fibrosis, and myocardial oedema. However, its application in infants remains uncertain. Herein, we report a three-month-old boy with dilated cardiomyopathy successfully treated with steroids. Cardiovascular magnetic resonance was useful for diagnosis based on the elevated native T1, T2, and extracellular volume and evaluation of response to immunosuppressive therapy in infantile inflammatory dilated cardiomyopathy.

Introduction

Cardiovascular magnetic resonance has become increasingly important when evaluating myocardial inflammation complementary to the diagnostic accuracy and risk of endocardial myocardial biopsy because of its noninvasiveness and its ability to image the entire myocardium.[1] In 2018, the updated Lake Louise Criteria for cardiovascular magnetic resonance in myocardial inflammation suggested a "two out of two" approach, combining oedema-sensitive cardiovascular magnetic resonance images (T2-weighted images or T2 mapping) with at least one additional T1-based tissue characterisation technique or late gadolinium enhancement to increase its specificity when detecting myocardial inflammation.[2] However, there are few reports of its application in children and none regarding infants. Regarding treatment, some studies of endocardial myocardial biopsy samples from patients with virus-negative, chronic inflammatory cardiomyopathy suggest that the immunosuppressive therapy with predonisone and azathioprine can improve cardiac function.[3,4] Furthermore, short-term effects of immunosuppressive therapy in genetic cardiomyopathy are reported based on its vulnerability to inflammation.[5] We report a case of genetic dilated cardiomyopathy in an infant diagnosed using cardiovascular magnetic resonance based on the updated Lake Louise Criteria, who responded well to steroids.

Case presentation

A male infant weighing 2,816 g at 38 weeks gestational age was born through vaginal delivery without asphyxia after an uneventful pregnancy. He was the second child of a family with no history of cardiovascular diseases. Two days post-birth, the infant was admitted to our neonatal ICU due to a heart murmur. Echocardiography showed a small ventricular septal defect. He had no signs of heart failure and was discharged medication free at one month of age. After discharge, his weight gain was within normal range. At a routine outpatient visit at three months of age, cardiac enlargement with a cardiothoracic ratio of 61% was noted on a chest radiography. There was no obvious prior infection. Echocardiography showed left ventricular enlargement with left ventricular end-diastolic dimension of 180% of normal, left ventricular ejection fraction of 28%, impaired contractility, and mild mitral regurgitation. Blood testing showed elevated brain natriuretic peptide 250 pg/mL, elevated troponin T 0.086 ng/mL, and slightly elevated C-reactive protein 0.32 mg/dL. He was treated for heart failure with diuretics, angiotensin converting enzyme inhibitor, and beta-blocker, but imaging findings did not improve and brain natriuretic peptide remained unchanged at 212 pg/mL. Cardiac catheterisation and endocardial myocardial biopsy were not performed due to concerns about complications, and cardiovascular magnetic resonance was selected. It revealed a left ventricular end-diastolic volume of 256% vs. normal and left ventricular ejection fraction of 20%. The ratio of pulmonary to systemic blood flow was 1.3 and mitral regurgitation was 17%. Late gadolinium enhancement was not clear, and the global T2 signal intensity ratio was >2.0 in mid-apical (Fig. 1). The global left ventricular native T1 values (mean) were 1131 ± 60 msec, markedly higher than those measured in healthy patients less than one year old at our institution. The extracellular volume mapping was also

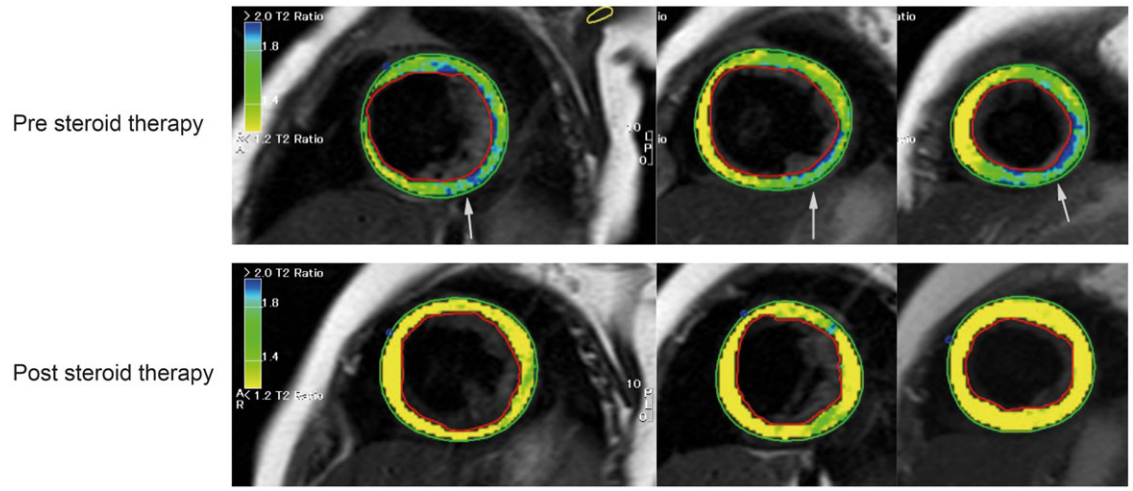

Figure 1. Colour map of signal intensity ratio (SIR) of myocardium compared to skeletal muscle in T2-enhanced Dark Blood image. The SIR is elevated (>2.0) in the mid to apical inferior-lateral region of the myocardium (indicated by the arrows), and steroid therapy reduces the SIR to less than 2.0.

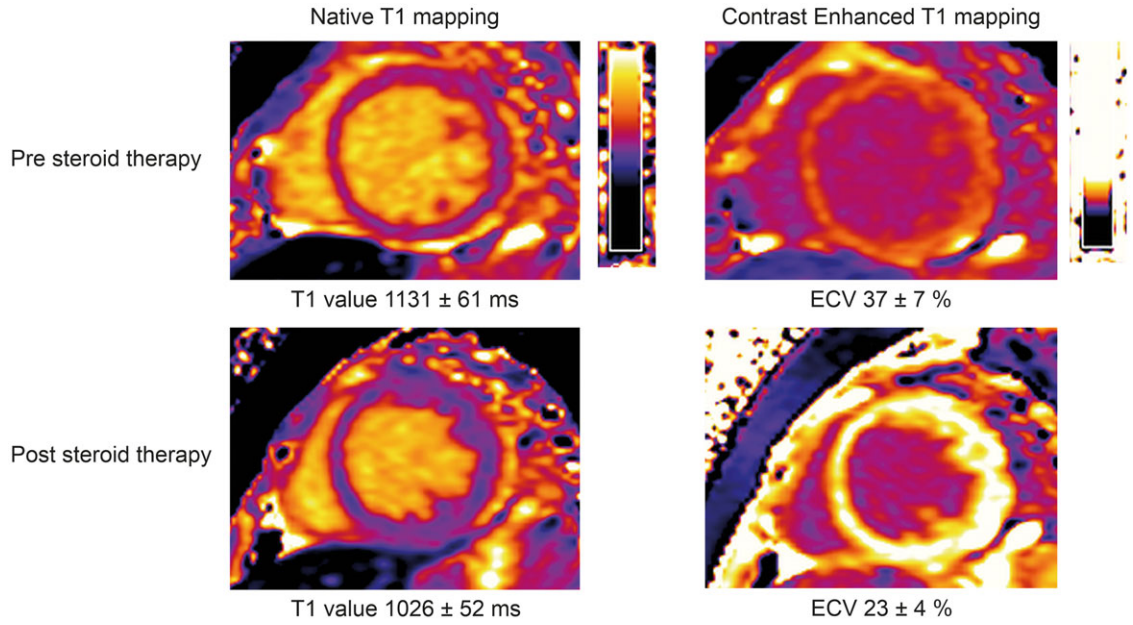

Figure 2. T1 mapping images before and after contrast and extracellular volume fractions. The global left ventricular native T1 values (mean) were elevated at 1131 ± 60 msec and the extracellular volume mapping (ECV) was also high at 37 ± 7%. After steroid induction, cardiovascular magnetic resonance showed a normalised native T1 value (mean) of 1026 ± 52 msec, ECV (mean) 23 ± 4%.

high at 37 ± 7% (Fig. 2). The cardiovascular magnetic resonance findings suggested inflammation in dilated cardiomyopathy according to the updated Lake Louise Criteria, as anomalous coronary arteries and secondary cardiomyopathies were ruled out. Based on the evidence in adult inflammatory dilated cardiomyopathy, prednisolone 2 mg/kg/day (45 mg/m^2/day) was introduced after obtaining parental consent. Two weeks later, brain natriuretic peptide improved to 25.8 pg/mL. Cardiovascular magnetic resonance performed two months after steroid induction showed a normalised native T1 value (mean) of 1026 ± 52 msec, extracellular volume mapping (mean) of 23 ± 4% (Fig. 2), and global left ventricular T2 signal intensity ratio all improved to <2.0 (Fig. 1). After tapering steroids, his condition did not worsen. Genetic testing later revealed a heterozygous nonsense mutation in the filamin-C gene.

Discussion

This is the first infant case wherein updated Lake Louise Criteria, including T1 mapping, was useful for diagnosis and evaluating the efficacy of steroid in dilated cardiomyopathy. The short-term efficacy of immunosuppressive therapy in the treatment of infantile hereditary dilated cardiomyopathy was also demonstrated.

T1 and T2 mapping in cardiovascular magnetic resonance reflect inflammation, fibrosis, and oedema in acute and chronic myocardium. It can facilitate the objective assessment of

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myocardial inflammation or diffuse fibrosis and is useful for early diagnosis and treatment of myocardial diseases. In adult dilated cardiomyopathy, the current literature clearly demonstrates the diagnostic and prognostic significance of diffuse myocardial fibrosis as measured using cardiovascular magnetic resonance T1 mapping.[6] Normal T1 and T2 values have not been noted in infants so far, and few reports have applied it to infant dilated cardiomyopathy. In a study of paediatric cardiomyopathy, the extracellular volume mapping of dilated cardiomyopathy was significantly higher than in the control group and exceeded the upper limit of normal in the majority of patients and the T1 index was higher compared to previously published data.[7] The report speculates that this may be due to the fact that myocardial remodelling progresses more rapidly in younger age groups. Ishikawa et al. reported normal T1 and extracellular volume mapping values for normal children under one year old at our institution.[8] In this case, T1 and extracellular volume mapping values were remarkably higher than those measured in that report. This suggests that even infants show higher T1 values in dilated cardiomyopathy than the normal group. Given the challenging clinical management of infant dilated cardiomyopathy with unfavourable outcomes, non-invasive imaging modalities of myocardial tissue may be very valuable.

Studies of endocardial myocardial biopsy samples from adult patients with virus-negative, chronic inflammatory cardiomyopathy suggest that immunosuppressive therapy can improve cardiac function.[3] Evidence for immunosuppressive therapy in paediatric dilated cardiomyopathy is sparse. A study of 43 dilated cardiomyopathy patients aged 10 months to 15 years with myocarditis on myocardial biopsy showed improvement in clinical, cardiovascular, and pathologic inflammatory findings in the prednisolone plus azathioprine or cyclosporine group.[4] Moreover, genetic mutations in structural proteins reportedly result in vulnerable myocardium to pathogens, and the short-term efficacy of immunosuppressive therapy for hereditary genetic cardiomyopathy is also reported.[5] In this case, because the safety of azathioprine in infants is not established, prednisolone alone was administered at doses considered reasonable based on other paediatric immune disorders. This resulted in improvement of cardiovascular magnetic resonance findings and brain natriuretic peptide.

Conclusion

Cardiovascular magnetic resonance, including T1 mapping, was very useful for diagnosis based on updated Lake Louise Criteria and for evaluation of response to immunosuppressive therapy with steroids in genetic dilated cardiomyopathy.

Data availability. The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Author contribution. Hiromitsu Shirouzu wrote the original draft. Yuichi Ishikawa supervised the manuscript. Nobuhiko Kann managed the data.

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Competing interests. The authors declare none.

Ethical standards. Written informed consent was obtained from the parents of the patient for the publication of this case report and any accompanying images.

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