Annals of Nuclear Medicine Vol. 19, No. 5, 411–414, 2005

Abnormal sympathetic innervation of the heart in a patient with Emery-Dreifuss muscular dystrophy

Takashi FUJITA,* Masami SHIMIZU,* Bunji KAKU,** Hounin KANAYA,** Yuki HORITA,** Yoshihide UNO,** Tsukasa YAMAZAKI,** Takio OHKA,** Kenji SAKATA* and Hiroshi MABUCHI*

**Molecular Genetics of Cardiovascular Disorders, Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University*
***Division of Cardiology, Ishikawa Prefectural Hospital*

A 33-year-old man was admitted for general malaise and vomiting. An electrocardiogram showed a complete atrioventricular block and an echocardiogram showed right atrial dilatation and normal wall motion of left ventricle (LV). Gene analysis showed nonsense mutation in the *STA* gene, which codes for emerin, and Emery-Dreifuss muscular dystrophy was diagnosed. An endomyocardial biopsy of right ventricle showed mild hypertrophy of myocytes. Myocardial scintigraphic studies with Tc-99m methoxyisobutylisonitrile (MIBI) and I-123-betamethyl-*p*-iodophenylpentadecanoic acid (BMIPP) scintigrams showed no abnormalities. In contrast, I-123 metaiodobenzylguanidine (MIBG) scintigrams showed a diffuse and severe decrease in accumulation of MIBG in the heart. Six months later, his LV wall motion on echocardiograms developed diffuse hypokinesis. These results suggest that the abnormality on I-123 MIBG myocardial scintigrams may predict LV dysfunction in Emery-Dreifuss muscular dystrophy.

Key words: Emery-Dreifuss muscular dystrophy, metaiodobenzylguanidine (MIBG), scintigraphy, *STA* gene

INTRODUCTION

EMERY-DREIFUSS MUSCULAR DYSTROPHY (EDMD) is a hereditary muscular dystrophy characterized by 3 symptoms: slow progressive muscular atrophy, muscular contractures, and cardiomyopathy with cardiac conduction disturbance.[1] EDMD occurs either as an X-linked disorder which is caused by mutation in the *STA* gene encoding emerin,[2] or as an autosomal dominant trait which is caused by mutation in *LMNA* genes encoding lamin A/C.[3] Cardiac manifestations in EDMD vary and do not correlate with the muscular atrophy or contractures.[1,4] Some patients with EDMD undergo rapid progression of cardiac disorders, left ventricular (LV) dysfunction or sudden cardiac death,[4–7] especially in patients with autosomal dominant trait EDMD. In contrast, the patients with X-linked EDMD show cardiac conduction disturbance and rarely LV dysfunction or dilated cardiomyopathy.[4] Because these cardiac disorders affect the prognosis, it is very important to detect the cardiac involvement in patients with EDMD as early as possible. Cardiac sympathetic nerve activity associates with various cardiac disorders, and we hypothesize that cardiac manifestations in patients with EDMD may relate to cardiac sympathetic nerve abnormalities. Here, we report a patient with EDMD caused by *STA* gene mutation showing abnormal sympathetic innervation of the heart detected by I-123 metaiodobenzylguanidine (MIBG) myocardial scintigraphy.

Received September 8, 2004, revision accepted January 21, 2005.

For reprint contact: Takashi Fujita, M.D., Molecular Genetics of Cardiovascular Disorders, Division of Cardiovascular Medicine, Graduate School of Medical Science, Kanazawa University, 13–1 Takara-machi, Kanazawa 920–8640, JAPAN.

CASE REPORT

A 33-year-old man was referred to our clinic for general malaise and vomiting on July 18, 2002. A first-degree atrioventricular block had been found for the first time by electrocardiography (ECG) at 18-years of age, and again

at 20-years of age (Fig. 1). However, he had not undergone treatment because of the lack of symptoms. Physical findings were almost normal except for a slight weakness and atrophy of the biceps brachii muscle (manual muscle test IV/V). Electrocardiography revealed a complete atrioventricular block at admission (Fig. 1).

Plasma levels of creatine kinase, potassium, lysozyme, and angiotensin converting enzyme were 151 IU/*l*, 3.8 mEq/*l*, 6.9 μg/d*l*, and 12.3 IU/*l*, respectively. Plasma levels of adrenaline, noradrenaline, and dopamine were within normal limits. A chest X-ray film showed no pulmonary congestion and no cardiomegaly, and the cardiothoracic ratio was 39.8%. Transthoracic echocardiography disclosed right atrial dilatation, but neither asynergy nor hypertrophy of the LV walls was seen. Coronary arteriography showed no significant stenosis. Left ventriculography showed normal LV wall motion, and LV ejection fraction was 72.4%. Electrophysiological studies showed a very low atrial voltage and an A-H block (H-V time = 80 msec, maximum sinus node recovery time = 1,300 msec). Endomyocardial biopsy of the right ventricle showed slight hypertrophy of the myocytes and a biopsy of the biceps brachii muscle showed roughly round necrotic, separating muscle fibers of various sizes.

After informed consent was obtained in accordance with the guidelines of the Bioethical Committee on Medical Research of the School of Medicine of Kanazawa University, DNA was isolated from the peripheral white blood cells of the patient and his parents. The results of their *STA* gene analyses are shown in Figure 2. The proband and his mother had a nonsense mutation W226X (TGG→TAG) in the *STA* gene.

The patient underwent Ga-67, Tc-99m methoxyisobutylisonitrile (MIBI), I-123 betamethyl-*p*-iodophenylpentadecanoic acid (BMIPP), and I-123 MIBG myocardial scintigraphic studies for ruling out sarcoidosis and for evaluations of the possible existence of myocardial ischemia, metabolic disorder, and sympathetic nerve abnormalities. The former two scintigrams showed no abnormalities. In contrast, I-123 MIBG scintigrams showed a diffuse and severe decrease in accumulation of I-123 MIBG in the heart as shown in Figure 3.

The patient underwent a DDD pacemaker implantation, but atrial pacing failed to stimulate the right atrium because of increased pacing threshold. The pacemaker setting was then changed from the DDD to the VVI mode. After this procedure, the patient had no symptoms for six months. But when we examined him by transthoracic echocardiography again six months later, LV wall motion on echocardiograms showed diffuse hypokinesis (LV ejection fraction = 34.6%). At this time an angiotensin II receptor blocker was prescribed to prevent progression of the LV remodeling. The patient has had no cardiac symptoms and the LV function has been preserved to the same degree for 2 years.

DISCUSSION

In this report, we demonstrated that the uptake of I-123 MIBG in a patient with EDMD was decreased severely and diffusely in spite of normal LV function, and that the LV function decreased 6 months later. These results suggest that the decreased uptake of MIBG might precede the abnormality of LV function.

The mechanism of decreased cardiac accumulation of MIBG in patient with EDMD is unknown. MIBG is an analogue of norepinephrine, and is taken up by uptake-1 and uptake-2 mechanisms, and is stored in the presynaptic terminals of sympathetic nerves. In an autopsy study of patients with EDMD, no abnormalities of the spinal cord or ventral spinal roots were found.[8] In addition, the patient was young and showed no disorders of the central nervous system such as Parkinson disease. Accordingly, a diffuse and severe decrease in accumulation of MIBG in the heart suggests an abnormality in the cardiac sympathetic nerve terminals in the patient. Cardiac manifestations such as sinus bradycardia, atrioventricular block, and atrial standstill in patients with EDMD[4] may support our hypothesis because a decrease in cardiac sympathetic nerve activity leads to suppression of the cardiac conduction system. On the other hand, the *STA* gene encodes emerin, which is a ubiquitous protein located on the cytoplasmic surface of the inner nuclear membrane.[9] In the patient, neither MIBI nor BMIPP scintigraphies showed any abnormalities. It is not known at all how an abnormal nuclear protein affects cardiac sympathetic nerve terminals in a heart that has normal coronary blood flow and fatty acid metabolism. To our knowledge, I-123 MIBG myocardial scintigraphic findings in patients with EDMD caused by *STA* gene mutation have not been reported to date. On the other hand, a homozygous mutation in the *LMNA* gene, another EDMD-related gene, revealed a reduction of axon density, axonal enlargement, and the presence of nonmyelinated axons.[10] Emerin shows a similar distribution as lamins in the heart,[11] and some abnormalities in cardiac sympathetic nerve may develop in EDMD patients with *STA* gene mutations. In addition, abnormal accumulation of MIBG was noted in myocardial scintigraphy in patients with Becker muscular dystrophy.[12] Although the mechanism is unknown, abnormalities in the cardiac sympathetic nervous system may also occur in patients with muscular dystrophy. Further investigations regarding cardiac sympathetic nerve abnormalities in patients with EDMD are necessary in the future.

In patients with EDMD, cardiac manifestations such as arrhythmia that results in sudden cardiac death or dilated cardiomyopathy that results in severe heart failure affect the prognosis. For these cardiac disorders, medical treatment and/or pacemaker implantation is necessary[13]; a few cases that have severe heart failure need heart transplantation.[14] If the abnormalities on I-123 MIBG myocardial scintigrams precede the abnormalities of the conduction

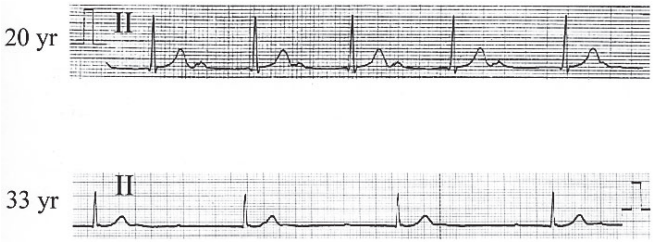

Fig. 1 Electrocardiograms of the patient at 20 years of age (*upper*) and 33 years of age (*lower*). Upper: P-Q interval is prolonged and the P wave voltage is 0.15 mV. Lower: The P wave voltage is decreased (0.05 mV) and a complete atrioventricular block is shown.

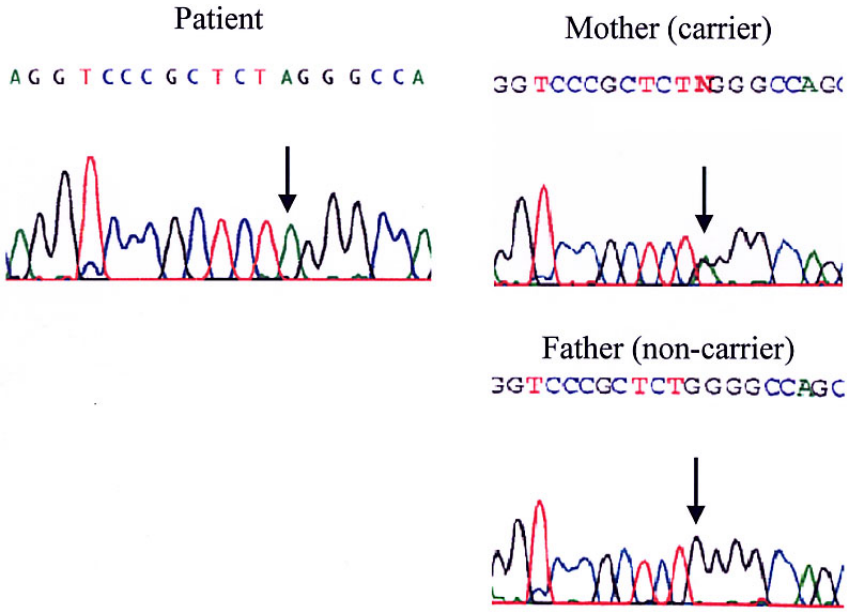

Fig. 2 Sequence analysis of the *STA* gene. A mutation W226X (TGG→TAG, shown with *arrows*) is seen in the proband and his mother

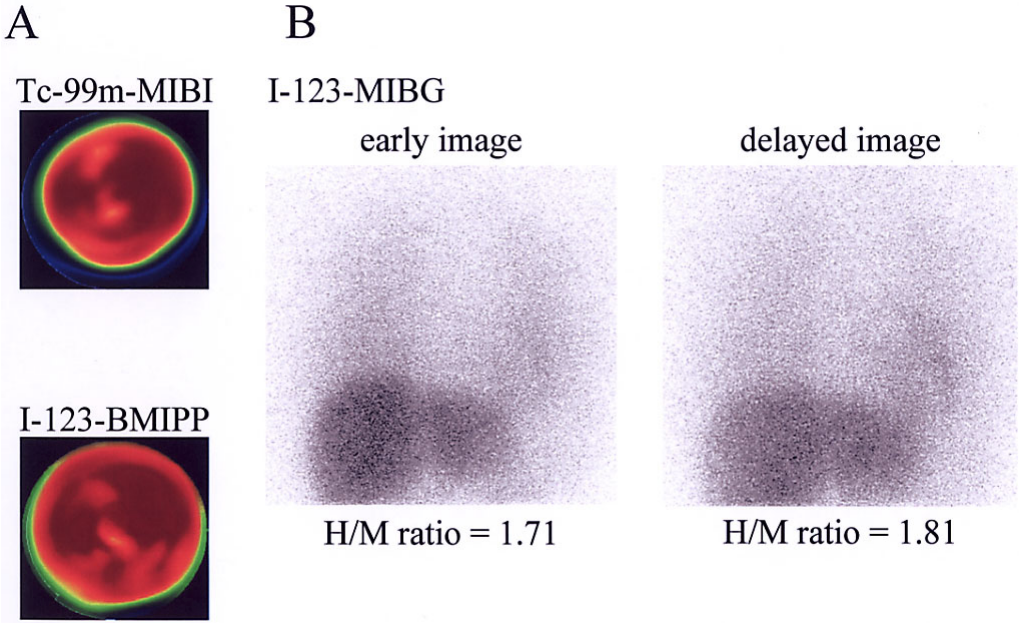

Fig. 3 A: Tc-99m MIBI (*upper*) and I-123 BMIPP (*lower*) scintigrams show no abnormalities. B: I-123 MIBG scintigrams. Both early image (*left*) and delayed image (*right*) show a diffuse and severe decrease in accumulation of MIBG in the heart. Heart/Mediastinum accumulation ratios of early and delayed images are 1.71 and 1.81, respectively.

system and/or LV function, I-123 MIBG myocardial scintigraphy may be useful for prediction and management of cardiac involvement in patients with EDMD.

REFERENCES

1. Emery AEH, Dreifuss FE. Unusual type of benign X-linked muscular dystrophy. *J Neurol Neurosurg Psychiatry* 1966; 29: 338–342.
2. Bione S, Maestrini E, Rivella S, Mancini M, Regis S, Romeo G, et al. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. *Nat Genet* 1994; 8: 323–327.
3. Bonne G, Di Barletta MR, Varnous S, Becane HM, Hammouda EH, Merlini L, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. *Nat Genet* 1999; 21: 285–288.
4. Boriani G, Gallina M, Merlini L, Bonne G, Toniolo D, Amati S, et al. Clinical Relevance of Atrial Fibrillation/Flutter, stroke, pacemaker implant, and Heart Failure in Emery-Dreifuss Muscular Dystrophy. *Stroke* 2003; 34: 901–908.
5. Funakoshi M, Tsuchiya Y, Arahata K. Emerin and cardiomyopathy in Emery-Dreifuss muscular dystrophy. *Neuromusc Disord* 1999; 9: 108–114.
6. Fatkin D, MacRae C, Sasaki T, Wolff M, Porcu M, Frenneaux M, et al. Missense mutations in the rod domain of the lamin A/C gene as cause of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999; 341: 1715–1724.
7. Vohanka S, Vytopil M, Bednarik J, Lukas Z, Kadanka Z, Schildberger J, et al. A mutation in the X-linked Emery-Dreifuss muscular dystrophy gene in a patient affected with condition cardiomyopathy. *Neuromuscul Disord* 2001; 11: 411–413.
8. Hara H, Nagara H, Mawatari S, Kondo A, Sato H. Emery-Dreifuss muscular dystrophy. An autopsy case. *J Neurol Sci* 1987; 79: 23–31.
9. Cartegni L, Di Barletta MR, Barresi R, Squarzoni S, Sabatelli P, Maraldi N, et al. Heart-specific localization of emerin: new insights into Emery-Dreifuss muscular dystrophy. *Hum Mol Genet* 1997; 6: 2257–2264.
10. De Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat JM, Tazir M, Kassouri N, et al. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot-Marie-tooth disorder type 2) and mouse. *Am J Hum Genet* 2002; 70: 726–736.
11. Manilal S, Sewry CA, Pereboev A, Man N, Gobbi P, Hawkes S, et al. Distribution of emerin and lamins in the heart and implications for Emery-Dreifuss muscular dystrophy. *Hum Mol Genet* 1999; 8: 353–359.
12. Kaminaga T, Matsumura K, Hatanaka H, Shimizu T. Abnormality of the myocardial sympathetic nervous system in a patient with Becker muscular dystrophy detected with iodine-123 metaiodobenzylguanidine scintigraphy. *Clin Nucl Med* 2001; 26: 701–703.
13. Buckley AE, Dean J, Mahy IR. Cardiac involvement in Emery Dreifuss muscular dystrophy: a case series. *Heart* 1999; 82: 105–108.
14. Merchut MP, Zdonczyk D, Gujrati M. Cardiac transplantation in female Emery-Dreifuss muscular dystrophy. *J Neurol* 1990; 237: 316–319.