Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Prevalence and clinical features of Fabry disease in Japanese male patients with diagnosis of hypertrophic cardiomyopathy

Toru Kubo (MD, FJCC)[a,*], Yuri Ochi (MD)[a], Yuichi Baba (MD)[a], Takayoshi Hirota (MD)[a], Katsutoshi Tanioka (MD)[a], Naohito Yamasaki (MD)[a], Makoto Yoshimitsu (MD)[b], Koji Higuchi (MD)[b], Toshihiro Takenaka (MD, FJCC)[b], Kimiko Nakajima (MD)[c], Tadayasu Togawa (PhD)[d], Takahiro Tsukimura (PhD)[d], Shigetoshi Sano (MD)[c], Chuwa Tei (MD, FJCC)[b], Hitoshi Sakuraba (MD)[e], Hiroaki Kitaoka (MD, FJCC)[a]

[a] Department of Cardiology, Neurology and Aging Science, Kochi Medical School, Kochi University, Kochi, Japan
[b] Division of Cardiac Repair and Regeneration, Graduate School of Medicine and Dental Sciences, Kagoshima University, Kagoshima, Japan
[c] Department of Dermatology, Kochi Medical School, Kochi University, Kochi, Japan
[d] Department of Functional Bioanalysis, Meiji Pharmaceutical University, Tokyo, Japan
[e] Department of Clinical Genetics, Meiji Pharmaceutical University, Tokyo, Japan

ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form 23 April 2016
Accepted 24 May 2016
Available online xxx

Keywords:
Fabry disease
Hypertrophic cardiomyopathy
Prevalence

ABSTRACT

Background: The prevalence of Fabry disease (FD) in Japanese patients presenting with unexplained left ventricular hypertrophy (LVH) has remained unclear.
Methods: We measured plasma α-galactosidase A activity in 177 men with a diagnosis of hypertrophic cardiomyopathy (HCM) (maximum LV wall thickness ≥15 mm).
Results: Two patients (1.1%) showed very low α-galactosidase A activity [0.0 and 0.3 nmol/hr/ml (normal range: 3.6–17.6 nmol/hr/ml)], and a clinical diagnosis of cardiac variant of FD was finally made. One patient was a 55-year-old man who came to our hospital because of abnormal results of electrocardiography and showed concentric LVH in echocardiography. A missense mutation, R112L, was identified. The other was a 74-year-old man who had been diagnosed with HCM at the age of 60 years in another hospital and was referred for evaluation of repeated hospitalization for heart failure. Although echocardiography revealed asymmetric septal hypertrophy (ASH) with interventricular septal wall thickness of 16 mm and posterior wall thickness of 11 mm and reduced LV ejection fraction with hypokinetic posterior wall motion, his echocardiographic findings at the initial diagnosis of HCM were not ASH but concentric LVH with normal LV systolic function. A splicing mutation, IVS4+919G>A, was identified.
Conclusions: The prevalence of FD in Japanese male patients with a clinical diagnosis of HCM was found to be 1.1%. These patients showed late onset and concentric LVH at initial presentation.

Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder that results from a deficiency of α-galactosidase A (α-Gal A) activity [1,2]. This enzymatic defect leads to the progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide and globotriaosylsphingosine (lyso-Gb3), throughout the body and causes multisystemic problems including neurological, ocular, skin, renal, and cardiac manifestations in classic type of FD. The majority of patients with this disease have cardiac involvement that is mainly manifested as left ventricular hypertrophy (LVH). Since Nakao et al. reported a 3% prevalence of an atypical variant of FD in male patients with LVH [3], a cardiac variant of FD with late-onset isolated cardiac manifestation has been recognized. Cardiac involvement of FD is associated with significant morbidity and early death due to heart failure or ventricular arrhythmias [1,4]. Since disease-specific enzyme replacement therapy (ERT) is now available for FD, correct diagnosis is important [5–7]. However, there has been no report since the report by Nakao et al. on the prevalence of FD in Japanese patients presenting with unexplained LVH.

* Corresponding author at: Department of Cardiology, Neurology and Aging Science, Kochi Medical School, Kochi University, Oko-cho, Nankoku-shi, Kochi 783-8505, Japan. Tel.: +81 88 880 2352; fax: +81 88 880 2349.
E-mail address: jm-kubotoru@kochi-u.ac.jp (T. Kubo).

http://dx.doi.org/10.1016/j.jjcc.2016.05.014

The aim of this study is to determine the prevalence of FD in a Japanese cohort of male patients with a clinical diagnosis of hypertrophic cardiomyopathy (HCM) by using α-Gal A screening.

Methods

Subjects

We performed clinical evaluation including measurements of plasma α-Gal A activity in 177 consecutive unrelated male patients with HCM between May 2003 and March 2014.

The diagnosis of HCM was based on echocardiographic demonstration of unexplained LVH, i.e. maximum LV wall thickness ≥ 15 mm. Patients with the dilated phase of HCM who showed previous documentation of unexplained LVH by echocardiography (maximum LV wall thickness ≥ 15 mm) were included in this study. Informed consent was obtained from all patients or their parents in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School (approval number: 14-34).

Clinical evaluation

Evaluation of patients included medical history, clinical examination, 12-lead electrocardiography, and M-mode, two-dimensional (2-D) and Doppler echocardiography. Maximum LV wall thickness was defined as the greatest thickness in any single segment. Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were measured from M-mode and 2-D images obtained from parasternal long-axis views, and fractional shortening [%FS = (LVEDD − LVESD)/LVEDD × 100] was calculated.

Measurements of α-Gal A and lyso-Gb3

Peripheral venous blood samples were collected from all of the patients for measurement of plasma α-Gal A activity. The activity was determined using the method previously described at Kagoshima University [3]. The normal range was 3.6–17.6 nmol/hr/ml.

We measured lyso-Gb3 in plasma samples from two patients with low α-Gal A activity. The measurement of lyso-Gb3 was carried out by high-performance liquid chromatography (HPLC) according to the method described previously [8]. The normal range was <2 nmol/l.

Genetic analysis

We performed genetic analysis for the two patients with low α-Gal A activity. Peripheral blood samples were taken, and they were frozen and stored at −20 °C. Deoxyribonucleic acid (DNA) was extracted and in vitro amplification of genomic DNA was performed using polymerase chain reaction (PCR) as previously described. Oligonucleotide primers were used to amplify exons (exon 1 to exon 7) and the middle of intron 4 for specific splicing defect mutation (IVS4+919G>A) of the *GLA* gene. Information on primer sequences and PCR conditions is available upon request. Sequencing was performed using a BigDye Terminator Cycle Sequencing Kit from Applied Biosystems Inc. (Waltham, MA, USA), and the sequences were analyzed on an Applied Biosystems PRISM 3100-Avant Genetic Analyzer in accordance with the manual of the manufacturer.

Results

Clinical characteristics of study population

We studied 177 men with a clinical diagnosis of HCM. Table 1 shows the clinical characteristics of the HCM patients in the present study. The patients were aged from 15 to 87 years (mean age, 62 ± 13 years) and the mean age at diagnosis of HCM was 56 ± 14 years. Maximum LV wall thickness was 19 ± 4 mm.

Table 1
Clinical characteristics of study patients.

	HCM (n = 177)
Age at the study (years)	62 ± 13 (15–87)
Age at diagnosis of HCM (years)	56 ± 14 (15–87)
Maximum LV wall thickness (mm)	19 ± 4 (10–33)
Interventricular septal wall thickness (mm)	15 ± 4 (7–29)
Posterior wall thickness (mm)	12 ± 2 (7–23)
LV end-diastolic diameter (mm)	48 ± 6 (32–69)
LV end-systolic diameter (mm)	29 ± 7 (16–56)
Fractional shortening (%)	40 ± 9 (15–59)
Left atrial diameter (mm)	45 ± 7 (30–69)

Data are shown as mean ± SD (range). HCM, hypertrophic cardiomyopathy; LV, left ventricular.

Patients with FD

Fig. 1 shows the distribution of plasma α-Gal A activity across all the subjects in the study. We found very low plasma α-Gal A activity in two patients (1.1%) [0.0 and 0.3 nmol/hr/ml (normal range: 3.6–17.6 nmol/hr/ml)] and a clinical diagnosis of cardiac variant of FD was finally made. The clinical characteristics of these two patients and the results of genetic analysis are shown in Table 2. The mutations we identified were absent in at least 100 healthy individuals.

One patient (Patient no. 1) was a 55-year-old man who came to our hospital because of abnormal results of electrocardiography conducted by a group medical examination. He had no history of any symptoms or diseases. Electrocardiography showed LVH with ST-T change and a relatively short PR interval of 133 ms (Fig. 2a). He had no symptoms and showed concentric LVH with wall thickness of 18 mm in echocardiography (Fig. 2b). Cardiovascular magnetic resonance (CMR) imaging revealed concentric hypertrophy with late gadolinium enhancement in the basal lateral wall (Fig. 2c). Fig. 2d shows the pathology of a skin biopsy. Electron-microscopic findings in the skin lesion showed the characteristic lamelatted dense bodies in the endothelial cells at the dermis. Plasma lyso-Gb3 level was high and missense mutation R112L was

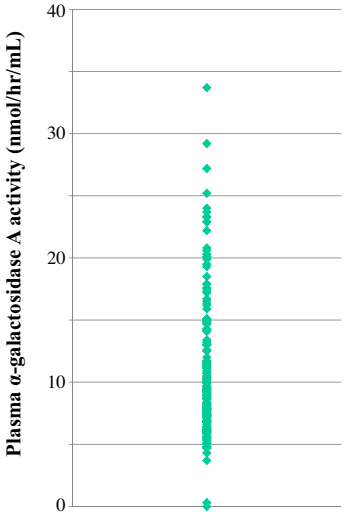

Fig. 1. The distribution of plasma α-galactosidase A activity across all subjects in the study.

Please cite this article in press as: Kubo T, et al. Prevalence and clinical features of Fabry disease in Japanese male patients with diagnosis of hypertrophic cardiomyopathy. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.05.014