CASE REPORT

Plasma Levels of Brain Natriuretic Peptide as an Index for Evaluation of Cardiac Function in Female Gene Carriers of Duchenne Muscular Dystrophy

Katsuhito Adachi, Hisaomi Kawai*, Miho Saito, Takako Naruo, Chiyomi Kimura, Hideki Mine, Toshio Inui**, Setsuko Kashiwagi* and Masashi Akaike*

The level of plasma brain natriuretic peptide (BNP) was elevated in 8 of 15 female gene carriers of Duchenne muscular dystrophy (DMD), and the level correlated with indices of cardiac function. In one of these carriers, whose clinical course was followed for one year, the plasma BNP level was elevated before the development of cardiac symptoms, further increased with the evolution of cardiac symptoms, and then decreased after treatment for cardiac failure. These results suggest that the plasma BNP level may be useful for the early detection of cardiac dysfunction and for evaluating the efficacy of cardiac treatment in female DMD carriers.

Key words: Duchenne muscular dystrophy (DMD), female gene carrier, brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), cardiac failure

Introduction

Some female gene carriers of Duchenne muscular dystrophy (DMD) show cardiac dysfunction in addition to skeletal muscle dysfunction (1–3). We recently reported (4) a high frequency of clinical and subclinical involvement of cardiac and skeletal muscles in female gene carriers of DMD. In this study, we measured the plasma levels of brain natriuretic peptide (BNP) (5–9) and atrial natriuretic peptide (ANP) (10, 11) to investigate the potential of using plasma BNP and ANP levels as indices of cardiac dysfunction in female gene carriers of DMD.

ANP is mainly released from atrial muscle cells into the blood in response to an increase in right or left atrial pressure (10, 12). In contrast, BNP is synthesized in ventricular muscles in response to ventricular overload, and is secreted into the coronary sinuses and then into the blood (5, 12).

Patients and Methods

Fifteen female gene carriers of DMD, all of whom were mothers of patients with DMD treated as outpatients or inpatients at the National Sanatorium Tokushima Hospital, were studied. Their age ranged from 34 to 61 years (45.8 ± 8.0, mean ± SD). The diagnosis was based on finding deletions in the dystrophin gene by Southern blotting (13), mosaic staining of dystrophin in the muscle cells of skeletal muscle biopsy (14), highly elevated levels (more than 1,250 IU/l) (normal range: <125) of serum creatine kinase activity, or genetic confirmation of definite carrier based on the pedigree.

Five subjects had mild cardiac symptoms such as palpitation and feeling of precordial compression, but there was no evident manifestation of cardiac failure such as orthopnea or edema in the lower limbs. All subjects had a normal blood pressure.

The cardiothoracic ratio (CTR) was estimated on chest roentgenogram, and the left ventricular end-diastolic dimension (LVDd) and fractional shortening (FS) were determined by echocardiographic examination. The correlations of plasma BNP and ANP levels with the indices of cardiac function, CTR, LVDd, and FS, were studied, and statistically analyzed by the Mann-Whitney U-test using GB-STAT, version 4.0 (Dynamic Microsystem Inc., Silver Spring, USA). p<0.05 was considered as statistically significant.

The levels of plasma BNP and ANP were determined by immunoradiometric assay using Shionoria ANP (15) and BNP (16) Kits (Shionogi Pharmaceutical Co., Osaka) according to the manufacturer’s instructions.

From the Departments of Internal Medicine and **Neurology, National Sanatorium Tokushima Hospital and *the First Department of Internal Medicine, School of Medicine, The University of Tokushima, Tokushima

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Reprint requests should be addressed to Dr. Katsuhito Adachi, the Department of Internal Medicine, National Sanatorium Tokushima Hospital, 1354 Shikiji, Kamojima-cho, Oe-gun, Tokushima 776

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The objective of the investigation was explained to the subjects and informed consent was obtained from all of them.

Results

Plasma levels of BNP and ANP

The levels of plasma BNP ranged from 4 to 57 pg/ml (22.1 ± 15.1, mean ± SD) (Fig. 1a). The upper limit of the normal value of the plasma BNP level is 18.6 pg/ml, and there are no significant individual variations in this level in people aged 30 to 60 years (17). We found an elevated plasma BNP level in 8 (53%) of the 15 DMD carriers. Four (50%) of these eight carriers with an elevated plasma BNP level had no cardiac symptoms. On the other hand, plasma ANP levels ranged from 5 to 18 pg/ml (10.8 ± 3.8, mean ± SD), which were all normal (Fig. 1b). The upper limit of normal value of the plasma ANP level is 28.4 pg/ml, and there are no significant individual variations in this level in people aged 30 to 60 years (17).

Plasma BNP level and age

A positive correlation (r=0.53) was observed between the plasma BNP level and age (p<0.05) (Fig. 1a).

Plasma BNP level and cardiac function

The cardiothoracic ratio (CTR) ranged from 40 to 60% (50.5 ± 5.4, mean ± SD). A CTR of greater than 50% was found in 7 (46%) of the 15 DMD carriers. Four (57%) of these seven carriers with an increased CTR also had an elevated BNP level. A positive correlation (r=0.48) was observed between the plasma BNP level and CTR (p<0.05) (Fig. 2).

LVDd ranged from 42.6 to 58.4 mm (49.0 ± 5.6, mean ± SD) [normal range: 40–50 (18)]. It was elevated in 8 (53%) of the 15 DMD carriers. Five (65%) of these eight carriers with an enlarged LVDd also had an elevated BNP level. There was a positive correlation (r=0.54) between the plasma BNP level and LVDd (p<0.05) (Fig. 3a).

FS ranged from 13.5 to 41.1% (25.9 ± 7.9, mean ± SD) [normal range: 27–3 (18)]. It was decreased in 8 (53%) of the 15 DMD carriers. Four (50%) of these eight carriers with a low FS also had an elevated BNP level. There was a negative correlation (r=−0.48) between the plasma BNP level and FS (p<0.05) (Fig. 3b).

Cardiac symptoms, indices of cardiac dysfunction, and plasma BNP levels in one DMD carrier

A 62-year-old Japanese woman with a 25-year-old DMD son had a high serum creatine kinase activity (140 IU/l) and deletions in the dystrophin gene. She had no hypertension, diabetes mellitus, or abnormal electrocardiographic findings. She had no history of cardiac disorders. At the age of 61 years (July 1994), her plasma BNP level was high (43 pg/ml), while FS was low (17.2%). At age 62, she felt palpitation and her plasma BNP level was high (60 pg/ml). She also had left ventricular enlargement. Upon treatment with an angiotensin-converting enzyme (ACE) inhibitor (lisinopril, 5 mg/day), the
Figure 3. a) Correlation between the plasma BNP level and the LVDd. A positive correlation was observed. *Patients with cardiac symptoms; BNP as in Fig. 1. b) Correlation between the plasma BNP level and FS. A negative correlation was observed. *Patients with cardiac symptoms; BNP as in Fig. 1.

cardiac symptoms improved, the BNP level decreased to 27 pg/ml, LVDd decreased, and FS increased. There was no increase in the plasma ANP level throughout this period (Fig. 4).

Discussion

The main causes of death in patients with DMD are respiratory failure and heart failure (19), which have been attributed to a deficiency of dystrophin in the skeletal muscle and in the myocardium (20, 21). Skeletal muscle weakness (1) and cardiac manifestations (2, 3) have been observed in some DMD female gene carriers, and these conditions are also believed to result from an abnormal expression of dystrophin in the skeletal muscle and in the myocardium (4).

Cardiac dysfunction is one of the main causes of death in some female carriers (22) as well as in DMD patients (19). Therefore, early detection and treatment of cardiac dysfunction is important not only for DMD patients but also for female gene carriers.

We previously reported (11) that plasma levels of ANP are
a useful index of cardiac function in patients with DMD. Furthermore, we recently reported that an elevation of the plasma BNP level more sensitively reflects mild or latent left ventricular dysfunction in patients with DMD compared to the plasma ANP level (9).

In comparing plasma BNP levels with those of ANP in DMD carriers, BNP levels were elevated in about half of the DMD carriers, while none of the carriers showed elevated ANP levels. These findings suggest that plasma BNP levels more accurately reflect cardiac dysfunction than plasma ANP levels in DMD carriers.

With regard to the relationship between plasma BNP levels and cardiac function, BNP levels were positively correlated with CTR, which is a simple index of cardiac load. This indicates that plasma BNP levels may be useful as an index of cardiac load in DMD carriers with or without cardiac symptoms or dysfunction. Moreover, since the plasma BNP level was also positively correlated with LVDd, which reflects left ventricular load, the BNP level may also be a useful indicator of left ventricular load in DMD carriers. The observed negative correlation between the BNP level and FS, which reflects left ventricular contractility, indicates that BNP levels become elevated in response to left ventricular dysfunction in DMD carriers. These findings suggest that the plasma BNP level may be a useful index of cardiac dysfunction in DMD carriers with or without cardiac manifestations.

The positive correlation between age and the plasma BNP level indicates that older DMD carriers have a greater load on the cardiac muscle. This finding highlights the importance of paying attention to cardiac function in older DMD carriers.

In a DMD carrier whose cardiac function was followed for more than one year, the slightly elevated plasma BNP level that was found before the appearance of cardiac symptoms further increased after the development of symptoms, and then declined after treatment with an ACE inhibitor, which shows that ACE inhibitors are effective in reducing cardiac load and latent cardiac dysfunction.

Cardiac dysfunction in DMD carriers has not received as much attention as that in DMD patients. However, the present results show that female gene carriers often exhibit cardiac dysfunction, including latent cardiac dysfunction. Therefore, we believe that long-term evaluation of the plasma BNP level may be useful for detecting cardiac dysfunction and for estimating the efficacy of treatment in DMD carriers.

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References


