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Original article

Renal dysfunction is rare in Fukuyama congenital muscular dystrophy

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Abstract

Background: The leading cause of death in patients with Fukuyama congenital muscular dystrophy (FCMD) is congestive heart failure or respiratory dysfunction, which is same as that in Duchenne muscular dystrophy (DMD). Recent studies reported that renal dysfunction is a common complication and an increasing cause of death in advanced DMD. It can be attributable to circulatory instability or inappropriate use of drugs for treating cardiac dysfunction.

Methods: We retrospectively evaluated renal function in 38 genetically diagnosed patients with FCMD (range, 1.3–32.9 years; mean age, 13.7 ± 6.9 years) using cystatin C. We examined possible relationships of cystatin C with blood natriuretic peptide and creatinine levels along with cardiac echocardiography findings.

Results: Twenty-five patients were treated for cardiac dysfunction. Elevated cystatin C level was detected only in two, who also showed proteinuria, glycosuria, hematuria, and extremely high β2-microglobulin levels on urine tests, and were thus diagnosed with renal tubular cell damage. Because both patients were treated for intractable epilepsy with various antiepileptic drugs, including valproic acid (VPA), and had low serum carnitine levels, renal tubular cell damage was considered as an adverse effect of VPA. Unlike patients with DMD, no patient with FCMD had renal dysfunction. Such a rare occurrence of renal dysfunction can be attributable to mild cardiac dysfunction, short disease duration, and careful and early fluid management.

Conclusion: Renal dysfunction is rare in patients with FCMD; however, renal tubular cell damage should be ascertained, particularly in those undergoing VPA treatment for epilepsy.
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Keywords: Fukuyama congenital muscular dystrophy; Renal dysfunction; Creatinine; Cystatin C; Fanconi syndrome; ACE inhibitor

1. Introduction

Fukuyama congenital muscular dystrophy (FCMD), which is the second most frequently occurring muscular dystrophy in the Japanese population, is an autosomal-recessive disorder caused by *fukutin* (*FKTN*) gene mutations [1,2]. *FKTN* encodes a protein involved in α-dystroglycan (α-DG) glycosylation, which is imperative

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for linking basal lamina to cytoskeletal proteins in muscles, peripheral nerves, and brain. The combination of infantile-onset hypotonia, generalized muscle weakness, eye abnormalities, and central nervous system involvement with mental retardation and seizures associated with cortical migration defects comprise the chief characteristics of FCMD. Peak motor function is observed between the ages of 2 and 8 years, and maximal motor ability usually involves unassisted sitting or sliding on the buttocks. Most patients succumb to respiratory dysfunction, pulmonary infections, or congestive heart failure, similar to patients with Duchenne muscular dystrophy (DMD), which makes their mean life span less than 20 years.

Reports mention the utility of cystatin C (CysC), which is unaffected by muscle mass, as a tool in the assessment of renal function in patients with neuromuscular disorders, instead of creatinine concentration [3–6]. Recent studies that employed CysC discovered renal dysfunction to be a common complication of advanced DMD and the third leading cause of death in these patients [6]. Matsumura et al. reported the following observations: (1) CysC levels increased with age in patients with DMD; 17.5% and 32.4% of those aged 20–30 years and older than 30 years, respectively, showed abnormal values. (2) A weak correlation was noted between CysC and serum blood natriuretic peptide (BNP) levels and left ventricular shortening fraction (LVSF). (3) A negative correlation was noted between CysC and hemoglobin levels. (4) A relatively strong correlation was noted between CysC and blood urea nitrogen (BUN) and creatinine levels [6]. They concluded that circulatory instability due to cardiac dysfunction, inadequate fluid management, and the effect of diuretics may result in progression to renal dysfunction in patients with DMD. Villa et al. also concluded that long-term cardiac dysfunction is associated with the incidence of cardio-renal syndrome in patients with advanced DMD [5]. Because patients with FCMD also develop cardiac failure at approximately 10 years, we investigated whether renal dysfunction is also common in patients with FCMD.

2. Patients and methods

We retrospectively evaluated renal function using CysC in patients who had been genetically diagnosed with FCMD during their regular evaluation at Tokyo Women's Medical University from January 2013 to June 2014. Serum CysC values were measured using latex-coagulating nephelometry (LZ TEST 'EIKEN' cystatin C, Eiken Chemical, Tokyo, Japan) on the HITACHI LABOSPECT 008 in the clinical laboratory of Tokyo Women's Medical University. In patients older than 18 years, eGFRcys was assessed using the forecasting formula from the Japanese Clinical Practice of Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012 as follows: eGFRcys of male patient $(\mathrm{ml/min/1.73\ m^2}) = (104 \times \mathrm{CysC}^{-1.019} \times 0.996^{\mathrm{age(years)}}) - 8$, and eGFRcys for female patients $(\mathrm{ml/min/1.73\ m^2}) = (104 \times \mathrm{CysC}^{-1.019} \times 0.996^{\mathrm{age(years)}} \times 0.929) - 8$ [8]. The clinical history of patients, which included respiratory support initiation, such as non-invasive positive pressure ventilation or tracheostomy with invasive ventilation, cardiac function, gastrostomy intervention, and medication for epilepsy, was retrospectively evaluated. Cardiac dysfunction was defined by LVSF <27%, and/or LV Tei index >0.5. SPSS 20.0 (Tokyo, Japan) was used for statistical analyses. Data were summarized using descriptive statistics, including means, standard deviations (SD), medians, ranges, frequencies, and percentages. The possible relationships of CysC with hemoglobin (Hb) level, BUN, creatinine, and BNP, as well as echocardiography results were examined using Pearson correlation coefficients. The data were divided into five groups with respect to age (<5, 5–9, 10–14, 15–19, and >20 years), and differences in mean values were assessed by multiple comparison and one-way analysis of variance. Statistical significance was set at $p < 0.05$.

2.1 Ethical considerations

This study was approved by the Medical Ethics Committee of Tokyo Women's Medical University (approval number 4705).

3. Results

3.1. Patients' background and data

The clinical data of 38 patients genetically diagnosed with FCMD (range, 1.3–32.9 years; mean age, 13.7 ± 6.9 years) were analyzed (Table 1). Twenty-nine patients had a homozygous founder 3-kb insertion mutation in the *FKTN* gene, and nine had a compound heterozygous mutation. Male and female patients were equal in number. Cardiac dysfunction was detected in 66% of patients (25/38); gastrostomy was performed in 34% of patients (13/38), and the other patients were put on oral diet. Regarding the treatment for cardiac dysfunction, b-blocker (carvedilol) was the most frequently used (36.8%), followed by angiotensin-converting enzyme (ACE) inhibitors such as enalapril maleate (18.4%) and cilazapril hydrate (5.3%). The dose of enalapril maleate was 2.5 mg/day for younger children and 5.0 mg/day for older patients; the dose of cilazapril hydrate was 0.5 mg/day. Antiepileptic drugs (AEDs) were administered in 50% of patients (19/38), and three medications were administered in 13% of patients with intractable seizures. The mean CysC level was 0.70 ± 0.17 mg/l

Table 1
Patients' background and data. The clinical data of 38 patients genetically diagnosed with FCMD (range, 1.3–32.9 years) were analyzed. Abnormally elevated CysC levels were noted in two patients.

	n = 38
Age (years), mean ± SD (range)	13.5 ± 6.8 (1.3–32.9)
M:F	19:19
NPPV initiation, n (%)	15 (39.4)
Cardiac dysfunction, n (%)	25 (65.8)
Cardiac dysfunction treatment	
Carvedilol, n (%)/dose (mg/day)	14 (36.8)/1.25–20
Candesartan, n (%)/dose (mg/day)	1 (2.6)/2.0
Enalapirl maleate, n (%)/dose (mg/day)	7 (18.4)/2.5–5
Cilazapril hydrate, n (%)/dose (mg/day)	2 (5.3)/0.5
Diuretics, n (%)/dose (g/day)	3 (7.9)/furosemide 10 mg/day, spironolactone 5 mg/day
Gastrostomy initiation, n (%)	13 (34.2)
AED treatment, n (%)/≧3 kinds, n (%)	19 (50.0)/5 (13.1)
Elevated CysC level, n (%)	2 (5.3)
CysC level, mean ± SD (mg/l)	0.70 ± 0.17 (0.47–1.34)
BUN, mean ± SD (mg/dl)	8.7 ± 3.2 (2–17.9)
Cr, mean ± SD (mg/dl)	0.07 ± 0.02 (0.03–0.14)
Hemoglobin (Hb), mean ± SD (g/dl)	12.8 ± 1.4 (9.8–15.4)

(range, 0.47–1.34 mg/l), and abnormally elevated CysC level.(>0.95 mg/l) was noted in two patients (5.3%).

3.2. Correlation between CysC and BUN, creatinine, Hb, and cardiac dysfunction markers

No correlation was noted between CysC and BUN levels ($r = -0.40$, $p = 0.810$) (Fig. 1(a)) and between CysC and Hb levels ($r = -0.036$, $p = 0.829$) (Fig. 1(b)). However, a moderately significant correlation was found between CysC and creatinine levels ($r = -0.455$, $p = 0.004$) (Fig. 2). No correlation was found between CysC and each cardiac dysfunction marker, such as BNP ($r = 0.042$, $p = 0.802$) (Fig. 3(a)) and LVSF ($r = -0.155$, $p = 0.358$) (Fig. 3(b)).

3.3. Comparison of mean creatinine values among groups divided by age

Patients with FCMD showed no increase in CysC with age ($p = 0.180$) (Fig. 4). On the contrary, a clear decrease was observed in creatinine levels with age in patients with FCMD, and a statistically significant difference was noted among each group ($p = 0.000$) (Fig. 5).

3.4. Detailed data of two patients with FCMD with abnormal CysC levels

Twenty-five patients (66%) were treated for cardiac dysfunction, but elevated CysC level was detected in

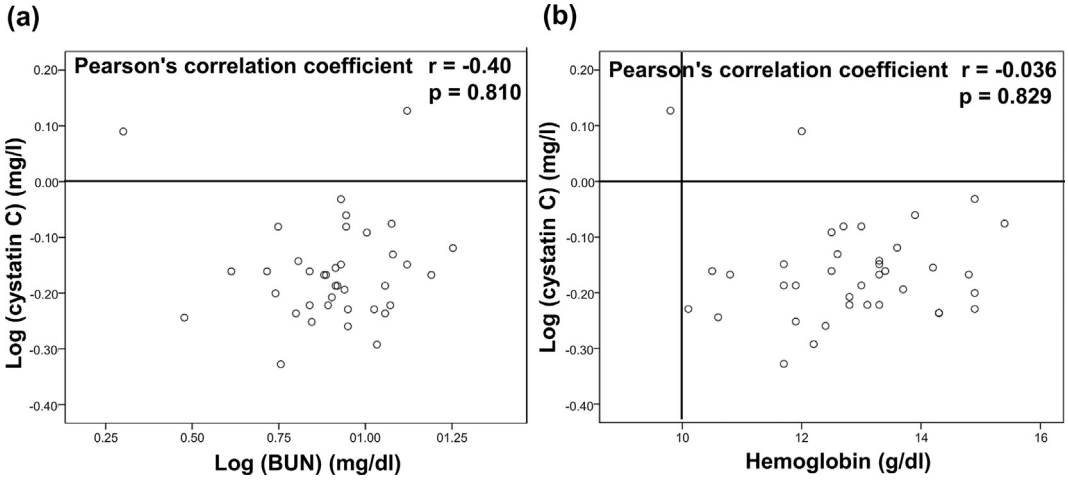

Fig. 1. (a) Correlation between CysC and BUN levels. (b) Correlation between CysC and hemoglobin levels. Each bar indicates the upper limit of normal value. No correlation was found between CysC and BUN or hemoglobin levels.

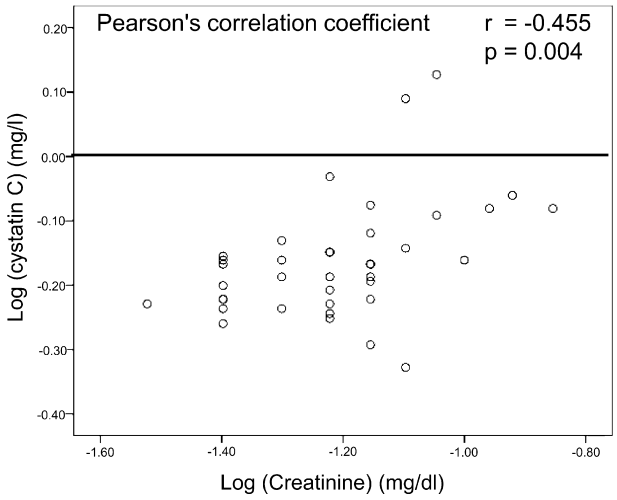

Fig. 2. Correlation between CysC and creatinine level. A moderately significant correlation was found between CysC and creatinine levels.

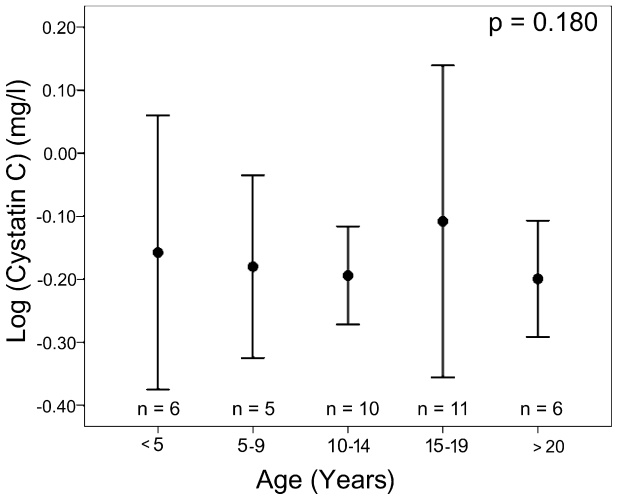

Fig. 4. Comparison of mean values of CysC among groups divided by age. Patients with FCMD showed no increase in CysC with age, similar to patients with DMD.

only two. Patients 1 and 2 showed CysC levels of 1.34 and 1.23 mg/l, respectively. Their eGFRCys were estimated at 63.5 and 64.8 ml/min/1.73 m^2. Only one patient was treated with an ACE inhibitor but not with a high dose. These two patients also showed proteinuria, glycosuria, hematuria, and extremely high β2-microglobulin levels on urine tests, and they were thus diagnosed with renal tubular cell damage. Because both patients were treated for intractable epilepsy with numerous AEDs, including valproic acid (VPA), and had low serum carnitine levels, renal tubular cell damage was speculated to be an adverse effect of VPA. One patient's condition improved after reducing the VPA dose, but the other patient developed Fanconi syndrome (Table 2).

4. Discussion

Researchers have extensively focused on renal dysfunction as the third leading cause of death in patients with advanced DMD [6,7]. A recent study that utilized CysC proved the presence of cardio-renal syndrome in patients with DMD, showing the frequent occurrence of renal dysfunction with left ventricular dysfunction among patients with DMD, and the strong correlation between CysC and eGFR and left ventricular ejection fraction (LVEF) following the onset of systolic dysfunction [5]. Because circulatory instability due to cardiac dysfunction was speculated to result in renal dysfunction in patients with DMD, cardio-renal syndrome

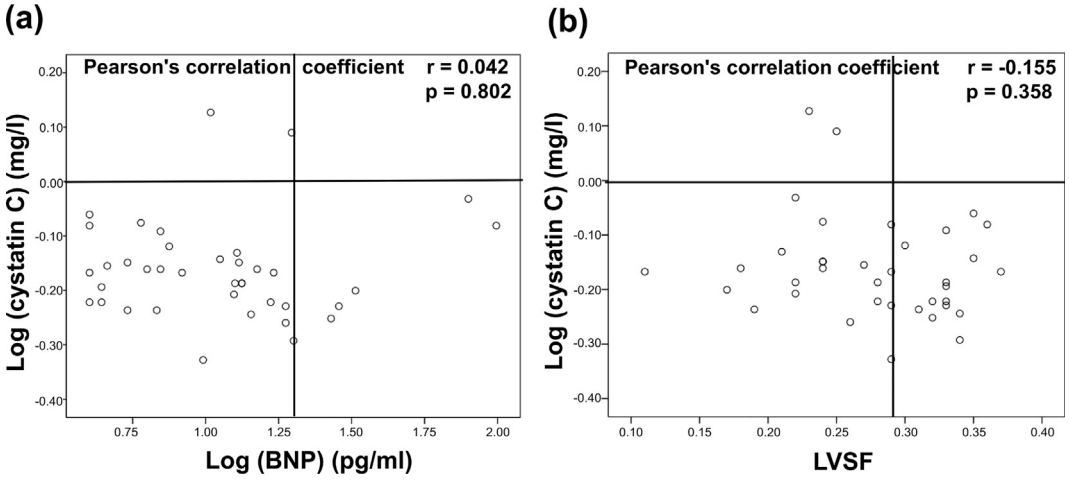

Fig. 3. (a) Correlation between CysC and BNP level. (b) Correlation between CysC and LVSF. Each bar indicates the upper limit of the normal value. No correlation was found between CysC and BNP or LVSF.

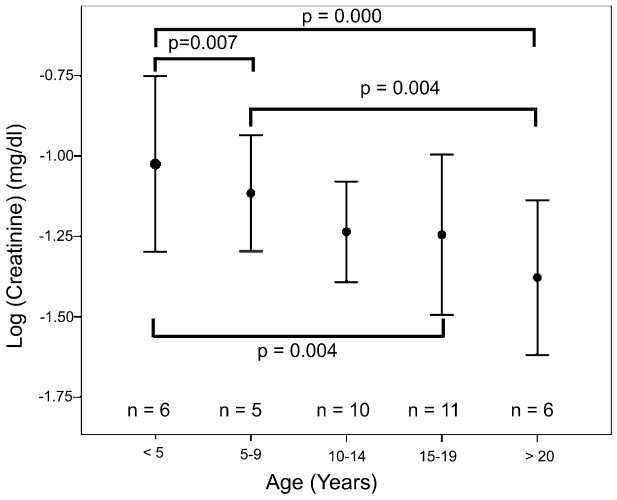

Fig. 5. Comparison of mean values of creatinine among groups divided by age. A clear decrease was found in creatinine levels with age in patients with FCMD, and a statistically significant difference was found among each group.

may also occur in patients with other muscular dystrophies that develop cardiomyopathy, such as FCMD. Matsumura et al. assessed renal function by evaluating CysC in patients with various neuromuscular disorders and found that the frequency of renal dysfunction differed among muscular dystrophies. They reported that renal dysfunction can frequently occur in patients with myotonic dystrophy 1 (DM1) and DMD, but they could not find a patient who showed elevated CysC levels among 31 patients with several kinds of congenital muscular dystrophy [9].

Several hypotheses have been considered for renal dysfunction in patients with each muscular dystrophy. The presumed factors for renal dysfunction in DM1 are very specific to the disease's characteristics; that is, premature senility in renal pathology, glucose intolerance, or hyperlipidemia. In DMD, decreased preload due to cardiac dysfunction, fluid discontinuation, increased or prolonged use of diuretics, or diarrhea are speculated to cause cardio-renal syndrome following renal hypoperfusion [6,9]. Motoki et al. concluded that chronic decrease in oral intake is one of the predisposing factors for renal dysfunction in patients with DMD. They suggested the importance of nutritional management in the prevention of renal dysfunction by the early introduction of gastrostomy in patients with DMD [10].

Even though patients with FCMD also have cardiac dysfunction, none of the patients with FCMD in this study progressed to cardio-renal syndrome, except for two patients who developed renal tubular cell damage, which probably resulted due to the administration of AEDs. No correlation was noted between CysC and BNP levels or LVSF in FCMD, which are markers of cardiac dysfunction, whereas cardio-renal association was suggested in DMD, which showed that LVSF had a certain effect on the logarithm of CysC [6,9]. Cardiac dysfunction is reported to be significantly milder in patients with FCMD than in patients with DMD, whereas skeletal muscle involvement is significantly worse in patients with FCMD [11]. Different from DMD [6], no relationship was noted between CysC and anemia in this study. Thus, the risk of cardio-renal or cardio-renal-anemia syndrome in patients with FCMD seems to be lower than that in patients with DMD.

In addition, renal dysfunction due to adverse effects of drugs such as ACE inhibitor or angiotensin II receptor blocker (ARB) is an important issue [12–14]. Ishikawa et al. warned about the risk of renal dysfunction

Table 2
Detailed data of two FCMD patients with abnormal Cys C levels.

	Patient 1	Patient 2
Age (years)/sex	19/M	18/F
CysC (mg/l)	1.34	1.23
eGFRcys (ml/min/1.73 m^2)	63.5	64.8
BUN (mg/dl)/Cr (mg/dl)	13.2/0.09	2/0.08
Serum P (mg/dl)	3.0	1.9
Urinalysis	Pro 1+/Glu 2+/Hem 3+	Pro 2+/Glu 4+/Hem 1+
U-β2MG (μg/l)/U-NAG (U/l)	64,300/7.8	71,400/24.6
FKTN 3 kb insertion/phenotype	Heterozygous/typical	Heterozygous/typical
Respiratory support/age	NPPV 8 years	NPPV 15 years LTS18 years
Cardiac dysfunction onset (age)/treatment	17 years/enalapril maleate (5 mg)	14 years/carvedilol
LVSF/BNP (pg/ml)	0.23/10.4	0.25/19.7
Gastrostomy initiation (age)	15 years	13 years
Epilepsy/treatment	Intractable/VPA, CZP, TPM, LVT	Intractable/VPA, CBZ, LVT
VPA concentration (μg/ml)	80–90	70–90
Treatment for renal tubular damage	Reduced VPA dose	Discontinued VPA Carnitine intake
Outcome	Improved	Fanconi syndrome

Both patients were treated for intractable epilepsy with numerous AEDs, including VPA, and had low serum carnitine levels.

due to ACE inhibitor, especially for patients with severe chronic heart failure associated with DMD [15]. They also recommended administering the appropriate dose of ACE inhibitor under careful monitoring in such cases to avoid the adverse effects. Although there was no detailed description on the adverse effects of drugs in the previous reports focused on renal dysfunction in patients with DMD or DM1 [6,9], there was a possibility that renal dysfunction could be caused by adverse effects of drugs in some cases, and not only owing to cardio-renal syndrome. In our study, the dose of ACE inhibitor or ARB was not high, which ultimately implies relatively mild cardiac dysfunction, contributing to the prevention of renal dysfunction.

The secondary reason for the rare occurrence of renal dysfunction in patients with FCMD can be careful fluid management started from the early stage. The nutritional management of patients with FCMD is usually controlled by caregivers from childhood because these patients also have intellectual issues and poor upper-limb function due to muscle weakness and joint contractures. Moreover, tube feeding or gastrostomy is instituted in their early teens because of dysphagia. Dysphagia is the most serious challenge faced by patients with FCMD, which can be life-threatening. We retrospectively studied dysphagia and therapeutic interventions in patients who were genetically diagnosed with FCMD [2]. All patients with severe form required tube feeding from infancy, and >50% underwent gastrostomy before 10 years. In typical form patients, dysphagia emerged on average at age 10 (7–14) years. After gastrostomy, the body weight of the patients was maintained using appropriate diet instead of limiting fluid intake, and the frequency of aspiration episodes was significantly decreased to decrease fluid intake.

In patients with DMD, dysphagia occurs in the late-advanced stage, and they are strongly willing to control their fluid management, depending on their situation. Some patients with DMD have fluid intake restriction for reducing the number of times of toilet use, which can induce dehydration. In patients with DMD, inadequate fluid management may cause circulatory instability, which can result in progression to cardio-renal syndrome. On the contrary, most patients with FCMD experience good fluid management throughout their life by their caregiver, unlike patients with DMD.

Two patients with intractable epilepsy that was treated with various AEDs developed renal tubular cell damage. More than 50% of patients with FCMD exhibit febrile seizures and/or epilepsy [2]. Most patients experience seizures that are controllable with just one AED, but some have intractable seizures that must be treated with three medications. Carbamazepine and VPA have been the agents that have been most frequently used for treating seizures associated with FCMD. Both patients were treated with VPA and showed significantly low serum carnitine concentrations. Secondary carnitine deficiency has been established as the cause for renal proximal tubular dysfunction with Fanconi syndrome in handicapped patients administered with VPA and/or elementary diet [16,17]. VPA causes secondary carnitine deficiency using carnitine at the mitochondrial transport, and carnitine deficiency can induce mitochondrial dysfunction in renal tubules [16]. Handicapped patients receiving elementary diet can also easily develop carnitine deficiency. Attention should be paid to possible secondary renal tubular cell damage in patients with FCMD, particularly in those treated with a relatively high dose of VPA for epilepsy and those receiving carnitine-deficient elementary diet via tube feeding. These patients were noted to have VPA-induced renal tubular dysfunction because of increased CysC levels, but the CysC levels of both patients were relatively low compared with that in patients with renal failure due to glomerular dysfunction. Simple qualitative measurement of urine was more useful in detecting VPA-induced Fanconi syndrome.

Different from patients with DMD, creatinine decreased with age in patients with FCMD, which may correlate with muscle mass. A moderately significant correlation was noted between creatinine and CysC, and both increased in patients with renal dysfunction. Creatinine levels were also useful in predicting renal abnormalities if the level abnormally increased compared with the usual level although it was within normal range.

CysC level did not increase with age in patients with FCMD in this study; however, it was the limitation of this study. The average age of the patient population was rather young, although the severity of complications and disability were as serious as those in patients with advanced DMD. Age was reported to have a certain effect on IgCysC in other muscular dystrophy groups similar to the general population, except for patients with congenial muscular dystrophy including those with FCMD [9]. Because this study was a single-center, retrospective study, further research, particularly focusing on elderly patients, is warranted.

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