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Renal dysfunction can be a common complication in patients with myotonic dystrophy 1

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ABSTRACT

Although renal failure can be a life-threatening complication even in neuromuscular disorders (NMDs), renal dysfunction is easily overlooked because muscle atrophy decreases the serum creatinine level. Renal function was retrospectively assessed using cystatin C (CysC) in various NMDs to clarify the differences among diseases. As is in the general population, age was correlated to CysC, and female patients showed lower CysC levels. Although elevated CysC was frequent in myotonic dystrophy 1 (DM1: MIM 160900) and motor neuron disorders, an inter-disease comparison by sex adjusted for age showed that only DM1 had a higher CysC compared to other diseases. Multivariate linear regression with the stepwise method also suggested that the number of CTG repeats had an impact on CysC levels. In two autopsy DM1 cases, nephrosclerotic changes were observed even though they were in their forties. These facts suggested a disease-specific pathomechanism for renal dysfunction in DM1. Although further study is required, renal function should be carefully monitored in patients with DM1.

1. Introduction

In patients with neuromuscular disorders (NMDs), renal dysfunction is easily overlooked because muscle atrophy decreases the creatinine (Cr) level. Thus, we should evaluate the renal function of these patients with indices not influenced by muscle volume, such as cystatin C (CysC) or beta-2-microglobulin [1,2]. We previously reported that renal dysfunction is frequent in aged patients with Duchenne muscular dystrophy (DMD) [3]. It seemed that long-term cardiac failure (low cardiac output), hypovolemia, and recurrent urinary infections can be associated with renal dysfunction [3,4]. Today, renal failure has become one of the life-threatening complications in DMD [5]. On the other hand, Ishigaki et al. reported that renal dysfunction is exceptional in patients with Fukuyama congenital muscular dystrophy (FCMD) [6]. These facts suggested that renal function can differ among diseases even in NMD. The effects of drugs such as steroids and cardioprotective agents are also unclear. To elucidate these points, we assessed renal function in various NMDs retrospectively using CysC. Consequently, we found that lgCysC is elevated in myotonic dystrophy 1 (DM1) and is related to the number of CTG repeats (CTGn). Nephrosclerotic changes were observed in autopsy DM1 cases, but their mechanism has not yet been elucidated. However, renal function should be carefully monitored in the medical management of patients with DM1.

2. Materials and methods

2.1. Patients

The subjects were patients with NMD receiving medical managements in National Hospital Organization Toneyama National Hospital from January 2012 to December 2014. The total number of subjects

Abbreviations: NMD, neuromuscular disorder; CysC, cystatin C; DM1, myotonic dystrophy 1; Cr, creatinine; DMD, Duchenne muscular dystrophy; FCMD, Fukuyama congenital muscular dystrophy; CTGn, number of CTG repeats; CMD, congenital muscular dystrophy; Dys, dystrophinopathies; MD, muscular dystrophy; MND, motor neuron disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVDd, left ventricular diastolic dimension; FS, fractional shortening; BNP, brain natriuretic peptide; TC, total cholesterol; TG, triglyceride; BUN, blood urea nitrogen; TnT, cardiac troponin T; Hb, hemoglobin; HbA1c, hemoglobin A1c; UCG, ultrasound cardiogram; eGFRcys, estimated glomerular filtration rate with CysC; lgCysC, logarithm of CysC; lgCr, logarithm of Cr; lgBUN, logarithm of BUN; lgBNP, logarithm of BNP; lgTnT, logarithm of TnT; lgTC, logarithm of TC; lgTG, logarithm of TG; lgCTGn, logarithm of CTGn; RNA, ribonucleic acid; SD, standard deviation; Amb, ambulatory; WNL, within normal limits; GFR, glomerular filtration rate.

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was 586 including 31 with genetically or histologically diagnosed congenital muscular dystrophy (CMD), 156 with genetically or immunohistochemically certified DMD, 114 with genetically or immunohistochemically confirmed Dys (Becker muscular dystrophy: 94, female dystrophinopathy: 20), 141 with genetically or clinically (typical clinical signs) and electrophisiologicaly (myotonic discharges) diagnosed DM1, 84 with genetically or histologically diagnosed other MD (facioscapulohumeral muscular dystrophy: 47, limb-girdle muscular dystrophy: 37), and 60 with genetically or clinically, histologically, and electrophisiologicaly diagnosed MND (amyotrophic lateral sclerosis: 36, spinobulbar muscular atrophy: 3, spinal muscular atrophy: 21) (Table 1). In DMD/Dys, prednisolone, ACEIs/ARBs, and beta-blockers were given in 27/5, 105/60, and 86/27 patients, respectively. Most patients took prednisolone on alternate days, and the mean dose was 0.222 ± 0.106 mg/kg/day. The average CTGn of 110 genetically diagnosed DM1 patients was 916.6 ± 562.7 (100–2900).

Renal pathology was checked in two autopsy DM1 cases. Case 1 was a 47-year-old man who died from bradycardic heart failure. His CTGn exceeded 2000. He complained of weakness since 12 years of age, was started on non-invasive ventilation at 34 years of age, and received a tracheostomy at 42 years of age. He developed bradycardic atrial flutter at 44 years of age and became bedridden. Although pacemaker implantation was recommended, he refused it. His LVDd was 46 mm and FS was 31% eight months prior to his death. He showed mild elevation of BNP (26.5 mg/mL) and hyperlipidemia (TC 256 mg/dL, TG 206 mg/dL), but there were no apparent renal dysfunction (BUN 20.5 mg/dL, Cr 0.13 mg/dL). Unfortunately, CysC was not checked in this patient. Case 2 was a 42-year-old man who died of pneumonia. His CTGn was 400. He developed weakness and myotonia at 10 years of age and started using wheel-chair at 35 years of age. Although he developed respiratory failure at 33 years of age, he refused mechanical ventilation. His LVDd was 38 mm, FS was 35%, BNP was 11.6 pg/mL, and TnT was 0.041 ng/mL. He also showed hyperlipidemia (TC 266 mg/dL, TG 80 mg/dL) without renal dysfunction (BUN 6.8 mg/dL, Cr 0.1 mg/dL). CysC five months prior to his death was also normal (0.75 mg/L).

2.2. Methods

Laboratory data such as CysC, Cr, BUN, BNP, TnT, Hb, TC, and TG were extracted from medical records. In patients with DM1, CTGn and HbA1c were also extracted. From UCG data within four months of laboratory examination, LVDd and FS were obtained. In cases over 18 years of age, eGFRcys levels were also assessed using the equations from the Japanese Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012 as follows: eGFRcys of male subjects (mL/min/1.73 m^2) = $(104 \times CysC^{-1.019} \times 0.996^{age\ (y)}) - 8$; eGFRcys of female subjects (mL/min/1.73 m^2) = $(104 \times CysC^{-1.019} \times 0.996^{age\ (y)} \times 0.929) - 8$ [2].

Student's *t*-test was used to assess differences in age, lgCysC, and CTGn for continuous data. Spearman's rank-correlation coefficient was used to investigate correlations between two variables. Inter-disease comparisons of lgCysC and eGFRcys were done by analysis of covariance using age as a covariate. The Bonferroni correction was used to assess differences in lgCysC among diseases or age groups for multiple comparisons. Sex differences in eGFRcys were assessed by analysis of covariance using age as a covariate. In dystrophinopathies (DMD and Dys), comparisons of lgCysC between patients treated with or without steroids, ACEIs/ARBs, and beta-blockers were done by analysis of covariance using age, sex, and FS as covariates. Formulae for lgCysC were estimated by multivariate linear regression with stepwise methods (entered if the *p*-value was <0.05) using sex, age, LVDd, FS, lgCr, lgBUN, lgBNP, lgTnT, Hb, lgTC, and lgTG as independent variables. In DMD and Dys, the dose of prednisolone, with or without of ACEIs/ARBs and beta-blockers, was added as independent variables. In DM1, HbA1c and lgCTGn were added as independent variables. In MND, lgTnT, LVDd, and FS were excluded as independent variables since cardiac assessments were not included as routine examinations in these patients. Statistical analyses were done with SPSS Statistics version 22®.

On pathological examination, hematoxylin-eosin, periodic acid-Schiff, periodic acid methenamine silver and Masson trichrome stains were done, and two renal specialists reviewed them.

The protocol of this study was approved by the ethics review board of National Hospital Organization Toneyama National Hospital.

3. Results

According to the diseases, there were marked differences in patient profiles. The sex ratio was skewed in DMD and Dys. Mean ages were lower in CMD and DMD and higher in MND. In terms of motor function, more than half of the patients were bed-ridden in CMD, DMD, and MND,

Table 1
Patients' profiles.

		CMD	DMD	Dys	DM1	MD	MND
N (M/F)		31 (13/18)	156 (156/0)	114 (94/20)	141 (72/67)	84 (37/47)	60 (32/28)
Age (y)	Mean ± SD	18.8 ± 9.0	21.2 ± 10.6	37.4 ± 17.0	42.8 ± 14.2	44.3 ± 19.3	55.0 ± 19.3
	(min–max)	(3.9–43.0)	(2.2–50.5)	(3.5–86.3)	(1.7–73.1)	(5.8–85.8)	(8.4–79.2)
Motor	Amb/sit/bed	4/7/20	24/52/80	80/25/9	89/46/6	48/33/3	11/15/34
CysC (mg/L)	Mean ± SD	0.617 ± 0.128	0.724 ± 0.342	0.780 ± 0.262	0.840 ± 0.259	0.257 ± 0.148	0.828 ± 0.304
	WNL/high	31/0	142/14	102/12	103/38	77/7	45/15
eGFRcys	Mean ± SD	142.1 ± 28.7	132.8 ± 37.6	113.6 ± 27.5	99.6 ± 27.0	110.3 ± 24.9	92.9 ± 30.2
	(N)	(13)	(87)	(103)	(136)	(74)	(52)
LVDd (mm)	Mean ± SD	35.5 ± 5.4	42.0 ± 7.8	46.5 ± 7.8	40.6 ± 5.2	41.2 ± 6.4	
	(N)	(28)	(152)	(102)	(113)	(68)	
FS (%)	Mean ± SD	29.1 ± 7.0	24.9 ± 9.4	27.8 ± 7.9	33.2 ± 7.5	35.7 ± 5.4	
	(N)	(28)	(153)	(103)	(113)	(68)	
Cr (mg/dL)	Mean ± SD	0.12 ± 0.05	0.14 ± 0.11	0.47 ± 0.22	0.54 ± 0.19	0.41 ± 0.18	0.29 ± 0.190
BUN (mg/dL)	Mean ± SD	10.78 ± 4.87	11.86 ± 6.08	13.66 ± 4.79	12.57 ± 5.13	12.86 ± 4.00	14.13 ± 7.17
BNP (pg/mL)	Mean ± SD	11.50 ± 13.82	20.16 ± 21.96	17.81 ± 22.51	17.11 ± 19.54	21.16 ± 50.28	26.08 ± 57.05
TnT (ng/mL)	Mean ± SD	0.029 ± 0.024	0.056 ± 0.052	0.023 ± 0.039	0.028 ± 0.018	0.058 ± 0.055	
	(N)		(155)	(111)		(82)	
Hb (g/dL)	Mean ± SD	13.61 ± 0.99	13.94 ± 1.41	14.58 ± 1.81	13.70 ± 1.82	14.17 ± 1.56	13.06 ± 1.64
TC (mg/dL)	Mean ± SD	164.2 ± 24.8	154.0 ± 30.7	177.8 ± 35.6	194.9 ± 41.6	188.8 ± 35.8	180.8 ± 43.8
	(N)						(55)
TG (mg/dL)	Mean ± SD	73.9 ± 32.7	97.0 ± 72.9	145.1 ± 111.4	155.1 ± 109.9	111.3 ± 68.8	113.7 ± 62.5
	(N)		(155)				(56)
HbA1c (%)					5.63 ± 1.01		
					(136)		

The numbers of patients examined are shown in parentheses when all patients did not have data.