Regularity in the Change of Serum Creatine Kinase Level in Duchenne Muscular Dystrophy

—A Study with Long-term Follow-up Cases—

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Changes in the serum creatine kinase (CK) level according to the disease course were regressed to an exponential function $Y = A e^{-cx}$ in each case of 28 Duchenne muscular dystrophy (DMD) through a long-term follow-up study. The regression to this formula implies that DMD muscle would decay by the leaking of a certain amount of CK into the circulation in proportion to the existing muscle. The diminution coefficient "r" was significantly reduced in puberty as compared with ages around ten. The cases of rapid progression showed a high rate of CK decrement in puberty. The diminution rate of CK is suspected to reflect the difference between the rate of muscle growth and primary muscle decay.

Key Words: X-linked muscular dystrophy, CK transition with age, Statistical analysis, Exponential function

The serum creatine kinase (CK) level in Duchenne muscular dystrophy (DMD) decreases with clinical progression and age. There have been few long-term follow-up studies to investigate the characteristic of this transition. Some authors demonstrated the age-related linear decrease of the logarithm of CK level,^{1, 2)} which indicated that the transitional line could be regressed to an exponential function. The previous study³⁾ revealed that the transition of CK can be regressed to a modified exponential function $Y = L(1 + e^{-r(x-a)})$ in long-term follow-up cases, suggesting that the decreasing rate of CK is constant in any stage and that the final level converges to a certain value L. However, some cases showed a high level of L, which conflicted with the actual state. According to determine the regularity of the CK decrement, changes of the serum CK level were reanalyzed mathematically. Subsequently the obtained regression formula was

investigated in correlation with the clinical course in each case.

MATERIALS AND METHODS

The subjects were 28 cases of DMD who had been admitted to Suzuka National Hospital since the ages of 8 years or earlier (Figure 1). Diagnosis was established upon the basis of patient's history, and physical and laboratory examinations including EMG and muscle biopsy. The serum CK levels were assayed every 3 months for more than 5 years (normal value < 25 u., from 5.5 to 14 years, Mean $\pm$ SD = 10.02 $\pm$ 1.70 years).

The mathematical calculations were computed as follows. Initially, to standardize the fluctuation in short duration, the annual average of CK level was calculated. Then an attempt was made to regress the change of annual average CK level to an exponential function. The linear regression formula of the natural logarithm of annual average

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Fig. 1. Clinical course of patients. The patients were divided into groups according to the clinical course. (1) Group I: age at stage 5 $\leq$ 11.0, Group II: age at stage 5 $>$ 11.0. (2) Group A: age at stage 7 $\leq$ 15.0, Group B: age at stage 7 $>$ 15.0.

on the age was calculated:

$$y = \ln A - rx \quad 1)$$

Formula 1) was converted to an exponential function:

$$Y = A e^{-rx} \quad 2)$$

(in which Y: serum CK level, x: age, A = Y(x=0): initial value, and r: diminution coefficient)

The duration of half reduction of serum CK level ($T(1/2)$) was calculated:

$$T(1/2) = (\ln(A/(A/2)))/r = (\ln 2)/r$$

In the cases having the separate linear lines of logarithm of CK to age, the regression formula was calculated in each period. The inflexion of the regression curve was also investigated.

Statistical studies of correlation between the clinical course and the coefficients obtained or inflexion were made. The patients were divided

into groups by their clinical course. The stage of disability was evaluated according to Swinyard's classification.⁴⁾ The groups were:

1) Group I: Age at stage 5 $\leq$ 11.0 (14 cases)

Group II: Age at stage 5 $>$ 11.0 (14 cases)

2) Group A: Age at stage 7 $\leq$ 15.0 (13 cases)

Group B: Age at stage 7 $>$ 15.0 (14 cases)

Stage 5 is a condition in which patients are unable to stand and are confined to a wheelchair. In stage 7, patients are also confined to a wheelchair, and with dependence and back support. Case 13 was omitted from the classification according to age at stage 7, because he was followed up to the age of 13 and had not yet fallen into the stage 7.

In Suzuka National Hospital, the average CK level of the last six months prior to death was 80.7 ± 23.3 u. in 23 DMD cases. The age at CK of 80.7 u. was evaluated in each cases.

RESULTS

The transitional change of CK in DMD was significantly regressed to an exponential function $Y = A e^{-rx}$. Most of cases demonstrated a significantly separate regression formula by F-test crossing in their early teens except for cases 13, 17 and 26, i.e., rapid declining line at ages around ten and moderate line in puberty (Figure 2). Then, the regression lines were analyzed in the two period of both rapid and moderate decline of the CK level. The mean coefficients of correlation in the rapid and the moderate period were 0.98108 and 0.82087, respectively.

The coefficient in the moderate period were significantly reduced compared with those in the rapid period. Although no significant differences in coefficients were noted in the rapid period between the groups divided by the clinical course, in the moderate period, the groups of rapid progression evidenced smaller initial value and diminution coefficients than those with slow progression. $T(1/2)$ elongated to 4.99 ± 1.77 years in the moderate period compared with that of 2.11 ± 0.35 years in the rapid period. The groups of rapid progression showed smaller $T(1/2)$ than those of slow progression in moderate period (Table 1). Also, rapid progress groups tended to exhibit earlier ages of inflexion, the point of the

Fig. 2. Application of regression curve for transition of CK level. (A) Correlation of annual average of CK in logarithmic scale with age. (B) Regression curve of annual average of CK level with age. (C) Regression curve and actual CK level.

Table 1. Coefficients obtained and T(1/2)

Rapid period					
	N	ln A	r	T(1/2)	rs
Total	28	9.694 ± 0.793	0.349 ± 0.085	2.11 ± 0.35 years	0.98108 ± 0.01678
Group I	14	9.565 ± 0.777	0.369 ± 0.092	1.99 ± 0.49	0.98100 ± 0.01271
Group II	14	9.822 ± 0.809	0.329 ± 0.078	2.22 ± 0.52	0.97936 ± 0.02004
Group A	13	9.686 ± 0.863	0.377 ± 0.095	1.97 ± 0.49	0.98284 ± 0.00983
Group B	14	9.719 ± 0.776	0.325 ± 0.075	2.24 ± 0.51	0.97903 ± 0.02190
Moderate period					
	N	ln A	r	T(1/2)	rs
Total	25	$6.933 \pm 1.059^*$	$0.151 \pm 0.050^*$	$4.99 \pm 1.77^*$	0.82078 ± 0.20395
Group I	13	$6.936 \pm 1.059^*$	$0.178 \pm 0.052^*$	$4.03 \pm 1.36^*$	0.80668 ± 0.21858
Group II	12	$6.929 \pm 0.928^*_{@}$	$0.120 \pm 0.048^*_{@}$	$5.99 \pm 2.15^*_{@}$	0.83625 ± 0.18668
Group A	12	$6.998 \pm 0.928^*$	$0.180 \pm 0.042^*$	$4.14 \pm 1.30^*$	0.78819 ± 0.21978
Group B	13	$6.959 \pm 0.929^*_{@@}$	$0.119 \pm 0.055^*_{@@}$	$5.99 \pm 2.26^*_{@@}$	0.85104 ± 0.18398

Mean $\pm$ SD, *: significantly changed compared with the steep declining period ($p < 0.01$),

@: significantly changed compared with Group I ($p < 0.02$) and

@@: significantly changed compared with Group A ($p < 0.02$) by t-test.

line intersection, with smaller CK levels (Table 2). The difference of ages between initiation of stage 5 and inflexion was 1.64 ± 0.97 years.

Table 3 shows the calculated age as CK at 80.7 u. The cases in the rapid progress groups

were evaluated to reach this level at earlier ages.

Table 4 shows the data of multiple regression analysis of diminution coefficient, CK level and inflexion to the ages of the stages. In the estimation of clinical course by the age of stage 5 in the

Table 2. Inflexion of the regression curve

	N	Age of inflexion	CK level at inflexion
Total	25	12.20 ± 1.23 years old	247.8 ± 106.3 u.
Group I	13	11.62 ± 0.98	207.1 ± 75.0
Group II	12	$12.83 \pm 1.45^*$	291.8 ± 132.3
Group A	13	11.66 ± 0.87	203.0 ± 71.5
Group B	12	$12.70 \pm 1.50^{**}$	$290.8 \pm 126.7^{**}$

Mean $\pm$ SD, *: significantly changed compared with Group I ($p < 0.05$),
 **: significantly changed compared with Group A ($p < 0.05$) by t-test.

Table 3. Calculated age at CK of 80.7 u.

Groups	Evaluated by the coefficient of the Rapid period		Evaluated by the coefficient of the Moderate period	
Total	15.5 ± 2.3 y.o.	(N=28)	20.1 ± 3.8 y.o.	(N=25)
Group I	14.5 ± 1.6	(N=14)	18.0 ± 3.3	(N=13)
Group II	$16.7 \pm 2.4^*$	(N=14)	$22.7 \pm 2.7^*$	(N=12)
Group A	14.4 ± 1.8	(N=13)	17.7 ± 2.6	(N=12)
Group B	$16.5 \pm 2.4^{**}$	(N=14)	$22.6 \pm 3.3^{**}$	(N=13)

Mean $\pm$ SD, *: significantly large compared with Group I ($p < 0.01$) and
 **: significantly large compared with Group A ($p < 0.01$) by t-test.

Table 4. Data of multiple regression analysis of coefficient obtained, CK level and inflexion to the ages of the stages

Regression formula	R ²	Total number	Number of cases with an error of		
			1.0	0.5	0.25 year
Rapid Period					
Age (Stage 5) = 2.23 ln CK(9) − 4.74 r − 1.15	0.6672*	28 ¹⁾	8	5	7
Age (Stage 7) = 1.83 ln CK(9) − 3.72 r + 4.95	0.5294*	24 ²⁾	8	3	4
Inflexion					
Age (Stage 7) = 2.30 ln CK + 0.56 Age − 4.71	0.4276*	23	5	4	5

CK(9); annual average CK of 9 years. *; $p < 0.01$ by F-test

1) Because of cases 1, 13, 17 and 22 did not yet fall into the stage, total number is 24.

2) Because of 4 cases above and case 26 who did not show the inflexion, total number is 23.

rapid period, 20 of 28 cases were statistically evaluated to show an error of less than a year in actual age, and 15 of 24 cases were also estimated likewise for stage 7. As much as 14 of 23 cases were estimated to have developed into stage 7 in the data of inflexion with an error of less than a year.

In case 23, who had been observed from the age of 4 to 18, three separate regression lines were demonstrated, i.e., a flat rather increasing line in the middle of the first decade, a steep declining curve until the mid-teens, and a moderate one hereafter (Figure 3).

DISCUSSION

In this study, the transitional changes of CK level were significantly regressed to an exponential function $Y = A e^{-rx}$ in long-term follow-up DMD cases. Two separate curves were demonstrated in most cases, i.e., rapid declining curve at ages around ten and a moderate one in puberty. From the analysis of the regression formula, the cases of rapid progression tended to exhibit earlier ages of inflexion with smaller CK level than those of slow progression as well as a more rapid rate of CK decrement in puberty.

The exponential formula $Y = A e^{-rx}$ has the same characteristics as decay equation of atomic nucleus, which, therefore, suggests that the muscle

will degrade by leaking a certain amount of CK into the general circulation in proportion to the existing muscle volume. However, the fluctuation of serum CK in DMD is well known to be caused by many conditions including muscle exercise.^{5, 6} It is uncertain to what extent these factors would play a role in regulating the serum CK level and CK changes would be essentially caused by the breakdown of muscle. In any case, in spite of the fluctuation, this serum enzyme activity falls with progression of illness and probably in proportion to muscle volume. To standardize the fluctuation, the annual average of CK level was used for the calculation in this study.

In the present study, the reduced diminution rate of CK was observed in puberty as compared with ages around ten, and there could be some speculations on the alteration of the rate. This alteration might be caused by loss of walking ability, but this is not likely because of the differences in ages between the initiation of non-ambulatory status and the change of diminution coefficient. Again, this alteration could be due to the change of muscle metabolism between before and during puberty. Endocrinological changes might cause metabolic alteration of muscle. And, it is necessary to take into account the increased growth rate of residual muscle in puberty. The increasing rate of muscle strength in back stretch-

Fig. 3. Transitional change of serum CK level in case 23, who had been followed from the age of 4 to 18. (A) Actual CK level. (B) Correlation of annual average of CK level with age. Three separate lines were demonstrated.

ing is higher than in puberty than younger ages,⁷⁾ which implies the alteration of muscle growth rate in the early teens. Therefore, in DMD, the increased growth rate of residual muscle could well delay the progression of muscle wasting. The previous report demonstrated that those patients with lean and small body weight shows the rapid progression and those with growing well in puberty tended to progress moderately. In mathematical terms, the participation of muscle growth in CK transition could be expressed as follows. If the growth coefficient of muscle is assumed to be "k", the formula for muscle volume (M) is:

$$M = m e^{kx} \quad 3)$$

(m; initial volume of muscle)

When the muscle growth is not taken into consideration, the formula of CK change is assumed to be:

$$Y' = A' e^{-r'x} \quad 4)$$

The apparent formula of CK transition in the present study is:

$$\begin{aligned} Y &= A e^{-rx} \propto M \times Y' \quad 2) \propto 3) \times 4) \\ &= m e^{kx} \times A' e^{-r'x} \\ &= mA' e^{-(r' - k)x} \end{aligned}$$

Then, if the muscle growth coefficient "k" is larger than the actual CK diminution coefficient "r'", the serum CK level increases. And if "k" is smaller than "r'", CK will be diminished. Furthermore, in case of these coefficients showing the same value, the serum CK level will show a plateau.

Although the initial value "A" plays a significant role in the equation, it does not indicate the CK value at birth, for the regression is effective in the period in which the apparent diminution coefficient remains at a certain value.

In the period of infancy, in spite of the histological findings of muscular degeneration,⁸⁾ the DMD child shows increasing muscle volume and locomotive activity. For the high-growth period throughout life, muscle growth is high enough to cover up the muscle decay in infancy. And, in the second half of the first decade, the relatively higher rate of muscle degeneration seems to cause the rapid progression of illness with an abrupt drop of the serum CK level.

Since the report of Ebashi,⁹⁾ high level of CK in DMD has been well-known, and, after the rise in infancy, it remains at a high level with great fluctuation until the later ages of the first decade followed by an abrupt decrease at around ten.¹⁰⁾ The wide ranging fluctuation of the serum CK level is commonly observed in this disease by various causes, but the serum level decreases with clinical progression and age in long-term observation. As a whole, linear decrease of logarithm of CK in age was noted by some authors.¹⁻³⁾ Brooke and colleagues²⁾ demonstrated a steep decrease of logarithm of the serum CK level in ages around ten followed by a moderate decrease in puberty as a whole in short-term follow-up cases. But, there have been few reports of long-term follow-up studies to investigate the characteristic of CK transition.

In this study, the serum CK level of DMD was revealed to decrease with age, not at random but regularly, and it was demonstrated that the rate of the decrement reflected the progression of the illness. These results seem to be worthwhile to investigate the mechanism of muscle wasting in DMD. And multiple regression analysis demonstrated a statistical significant correlation of diminution coefficient, inflexion and CK level as to the age of the stages. A similar study with more cases will be beneficial to predict the clinical course and to estimate the effects of the treatment.

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