Study on Relationship between the Muscular Pathology and Prognosis in the Motor Neuron Disease

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In order to investigate the mode of progression in motor neuron disease (MND), and find if there is any correlation between the muscular pathology and prognosis of the disease, activity index (ACT), atrophy factor of type I muscle fibers (A1), and type II (A2), hypertrophy factor of type I muscle fibers (H1), and type II (H2) and grouping factors were analyzed. Thirty-five patients with MND were evaluated whether there were any factors correlated to the severity of ACT. Among various factors, A1 showed the most significant change to the severity of ACT. Therefore, it was suggested that A1 was best correlated with the rate of prognosis of the disease process. Probably involvement of the motor neuron innervating type I muscle fibers takes place in the earlier stage than that of the neurons of type II, or there might be some difference of innervation ratio between type I and type II fibers. Further investigation is necessary to evaluate the relationship between the actual prognosis of these patients and their ACT by follow up study.

Key Words: Muscle biopsy, Activity index, Atrophy factor, Statistical analysis

Motor neuron disease (MND) is the devastating disorder of the central nervous system characterized by involvement of both upper and lower motor neurons. The average survival span of this disorder is said to about three years after onset. Histology of muscle biopsy specimens has been shown to be a useful and reliable tool in the evaluation of patients with neuromuscular disorders.

It is well known that there is basically two different types of muscle fibers in human being and they have a different metabolic and electrophysiological characteristics. Muscle biopsy specimens from patients with MND show a variety of histologically demonstrated abnormalities, including atrophy of fibers and grouping of their fibers.

But, only few reports have been concerned with the muscle pathology and their prognosis and the relationship between muscle histologic finding and their prognosis is not well known.

In this paper, we report the results of computer analysis of our own data derived from skeletal muscle biopsy specimens from 35 patients with MND from 1969 to 1985.

MATERIALS AND METHODS

1. Patients

The clinical records of 35 patients (23 men and 12 women) with MND seen as our department between 1969 and 1985 were comprehensively reviewed. Each of the 35 patients had a clinical diagnosis of MND established from the history, physical examination, electromyographic studies, and muscle biopsy. All patients had both upper and lower motor dysfunction.

2. Histological analysis

All muscle biopsies were undergone in the quadriceps femoris using standard methods described by Dubowitz and Brooke and cryostat sections were made from fragments immersed isopentane and liquid nitrogen. The type I muscle fibers were defined as either high activity of NADH-TR or weak reaction of standard ATPase stain (pH 9.4), and type II muscle fibers were defined as either weak activity of NADH-TR or strong reaction of standard ATPase stain. The muscle specimens were measured at X100 magnifications directly from the microscope in each type of 100 muscle fibers.

For the purpose of this study, we evaluated the following items.

mean fiber diameter
percent of fiber atrophy factor
hypertrophy factor
fiber-grouping — The maximal numbers of contigu-
ous muscle fibers in the NADH-TR or ATPase-stained sections, provided that a contiguous fibers touches two or more fibers of its own muscle fibers.

3. Clinical analysis

The following items were also evaluated.

Age — The patient’s age in years at the time of muscle biopsy.

Sex — Male or female

Duration — The period in years from onset of symptoms referable to MND until the time of muscle biopsy.

Severity — A numerical score from 1 to 4 based on the patient’s levels of activity.

1: little or no interference with work and daily activities.

2: moderate interference with work and daily activities, but ambulatory and able to earn a living.

3: severe interference with daily activities, but ambulatory and able to earn a living.

4: totally dependent on others.

Activity Index — The severity (numerical score) divided by duration (in year).

Strength of muscle — The scale form 0 to 5 (according to Manual Muscle Testing).

Duration — The period in years from onset of symptoms referable to MND until the time of muscle biopsy.

Symptoms referable to MND until the time of muscle biopsy.

Percent of type I fibers

Hypertrophy factor of type II fibers

Atrophy factor of type I fibers

Atrophy factor of type II fibers

Mean diameter of type I fibers

Mean diameter of type II fibers

Percent of type II fibers

Percent of type H fibers

Grouping of type II fibers

Grouping of type I fibers

SEX: Severity of disease

ACT: Activity Index

S: Strength of muscle on which biopsy was done.

For clarity, Table 1 lists all the items considered in this study.

4. Statistical analysis

Our statistical consults, using program SAS version 5, compared each items with every each others, calculatory Spearman and Kendall correlation coefficients and probability values for the each correlations.

RESULTS

Table 2 illustrates a summary of histologic findings. The mean fiber diameter of both type I and II muscle fibers were reduced from normal mean of about 60 μ. It seems equal involvement of both muscle fiber types. The distribution of type I and type II muscle fibers was normal, with about one third type I and two thirds type II muscle fibers respectively, and each of them exhibited normal percent of fiber distribution. For the atrophy and hypertrophy factors (A1, A2, H1, H2), it has been said that normal upper value of A1 is 150 in male, 100 in female respectively, A2 is 150 in male, 200 in female respectively, H1 is 150 in male, 400 in female respectively, H2 is 400 in male, 150 in female respectively. 10 As the A1 and A2, only few muscle specimens remain within normal values (A1 in Biopsy 3, 4, 7, 19, 25, 29, 31 and A2 in Biopsy 4, 7, 19).

As for H1 and H2, many of muscle specimens remain within normal values.

The value of type II fiber grouping (G2) was more higher than that of type I fiber grouping.

Table 2. Histologic data

<table>
<thead>
<tr>
<th>Type</th>
<th>% of Fibers</th>
<th>Atrophy Factor</th>
<th>Hypertrophy Factor</th>
<th>Grouping Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>30%</td>
<td>50%</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Type II</td>
<td>70%</td>
<td>50%</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Type I</td>
<td>40%</td>
<td>60%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Type II</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Type I</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Type II</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

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The clinical data were shown in the Table 3, the mean age of biopsy was performed 55 years, the range 26 to 73 years. The series including 23 men and 12 women whose duration of illness varied from a half year to 6 years (average 1.5 years). The severity of the disease varied in these patients from level 2 to 4, with an average level of 2.7. The value of Activity Index (ACT) varied from 0.5 to 8.0, with an average level of 3.0.

The average score of Manual Muscle Testing (MMT) was 3.4. The Table 4 showed a statistically significant of individual items of each others either Spearman or Kendall correlation coefficients and probability values. For example, the relation between mean fiber diameter of type I muscle fibers (D1) and atrophy factor of type I muscle fibers (Al) was statistically significant (p < 0.001) both of Spearman and Kendall correlation coefficients and probability values. It is important if there is any significant correlation between histological analysis and clinical analysis. From this consideration, only Al showed statistically significant with clinical items, DUR and ACT both of Spearman and Kendall probability values. From this correlation, it is obvious that preservation of type I muscle fibers relate to a more benign course of MND, and type II muscle fibers are not an important in refractory to the progression of the disease process. The strength of muscle on which biopsy was done not correlated to the prognosis of MND, and also fiber grouping were not reflect the prognosis of MND.

### Table 4. Positive correlation of items

<table>
<thead>
<tr>
<th>Items</th>
<th>Spearman</th>
<th>Kendall</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 with D2</td>
<td>0.311</td>
<td>0.049</td>
</tr>
<tr>
<td>D1 with A1</td>
<td>-0.693</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D1 with H1</td>
<td>0.465</td>
<td>0.005</td>
</tr>
<tr>
<td>D1 with A2</td>
<td>-0.462</td>
<td>0.003</td>
</tr>
<tr>
<td>D1 with H2</td>
<td>0.601</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1 with DUR</td>
<td>-0.471</td>
<td>0.004</td>
</tr>
<tr>
<td>A1 with ACT</td>
<td>0.446</td>
<td>0.007</td>
</tr>
<tr>
<td>A2 with H1</td>
<td>-0.374</td>
<td>0.027</td>
</tr>
<tr>
<td>H1 with H2</td>
<td>0.590</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>H1 with G1</td>
<td>0.346</td>
<td>0.043</td>
</tr>
<tr>
<td>H1 with ACT</td>
<td>0.943</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### DISCUSSION

We found that the diameter of both type I and type II muscle fibers were reduced, 48.9 μ in type I muscle fiber diameter and 47.6 μ in type II muscle fiber diameter respectively.

It is conceivable that type II muscle fibers are more susceptibly involved than type I muscle fibers, because the mean diameter of type II muscle fibers were more reduced than those of type I muscle fibers, but the type II muscle fibers does not influence concerning the prognosis of MND. For the percent of muscle fiber distribution, they exhibited the normal distribution, about one third type II muscle fiber.

It has been said that MND does not display the disproportion of both or either muscle types against the cases with congenital fiber type dis-

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G1.

ALS: amyotrophic lateral sclerosis

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Among the various items, especially clinico-pathological correlation, only ACT and DUR correlated with pathological items, atrophy factor of type I muscle fibers, means that the state of type I muscle fibers were considered to correlate with degree of progression of disease and suggests that type I muscle fibers play an important role in determining the prognosis of MND, but type II muscle fibers did not.

According to Brooke and Engel, type I muscle fibers correlated the activity of the disease. Patten also mentioned that involvement of type I muscle fibers is more important in relation to activity of MND. These datas seems to be support our results.

Both of type I and type II grouping factors in our study did not reflect the influence of prognosis of MND. The grouping of muscle fibers indicates the presence of reinnervation. Dubowitz and Brooke suggested that fiber type grouping may represent a compensatory mechanism of denervated muscle in MND and therefore such grouping may be a favorable histologic finding, but they did not evaluate their suggestion systematically or statistically.

Butler mentioned that presence of grouping in patients with MND had the less severe form of disease and also suggested that grouping may be of prognostic significance.

But, the fiber grouping did not influence concerning the prognosis in our data. MND restlessly progress occurring with denervation and reinnervation, and we attempted whether there are any factors concerning the prognosis of MND, and it was obvious that state of type I muscle fibers correlate with progression and duration of illness. But, there should be several dissolved questions are existed. First, problem of diameter between male and female, there are no restricted normal range of atrophy factor and hypertrophy factors for age. Second, about 90% of patients with MND exhibit the type I muscle atrophy and those of 60% display type II muscle atrophy, and nearly 0% of patients with MND was seen with hypertrophied type I muscle fibers and those of 30% exhibit hypertrophied type II muscle fibers. These meant, in the cases with MND, type I muscle fibers more susceptibility atrophied than type II muscle fibers, and retrospectively, our datas might be expectable results from above suggested documents.

In summary, both of muscle fibers are involved in the MND process, and degree of atrophy of type I muscle fibers the best correlate to the severity of this disease.

The data suggests that alteration of type I muscle fibers are an important in determining the rate of progression and duration of the illness. Furthermore, analysis of type I muscle fibers may be an important role for the thinking of pathogenesis of MND.

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REFERENCES