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Muscle modifications in Parkinson’s disease: myoelectric manifestations

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Abstract

The muscle changes occurring in Parkinson’s disease (PD) may come about as a consequence of the modified pattern of motor unit activation and rigidity, which are characteristic of the disease. A tendency towards hypertrophy of type I fibers and, in some instances, atrophy of type II fibers has been observed. Fourteen patients affected by PD and 10 age-matched controls were studied in order to investigate these muscle changes. We indirectly evaluated muscle modifications by measuring muscle fiber conduction velocity (CV) and median frequency (MDF) of the power spectrum using automatic analysis of surface EMG. The tibialis anterior muscle was selected for the study of contractions electrically induced by 35 Hz pulse trains lasting 30 s; the myoelectric signal was detected using the 4-bar electrode technique described by Broman et al. (Broman, H., Bilotto, G. and De Luca, C.J. Myoelectric signal conduction velocity and spectral parameters: influence of force and time. J. Appl. Physiol., 1985, 58: 1428–1437). Muscle biopsy specimens were obtained in 4 PD patients by surgical excision at the site where the EMG recording electrode had been placed. The main difference observed between PD subjects and controls was the rate of change of MDF and CV during the course of stimulated contraction; patients with PD sustained a smaller fatigue related decrease in both parameters compared to controls. According to our histological data, this result can be explained by a type I fiber percentage which accounts for 79% of the myofiber population on average. As expected, the CV basal values correlated directly with type I fiber diameter. These data suggest that non-invasive surface EMG techniques are useful in assessing the modifications of muscle characteristics that are observed in PD patients and for analyzing some aspects of the peripheral fatigue in this disease.

Keywords: Parkinson’s disease; Muscles; Electromyography

1. Introduction

In Parkinson’s disease (PD) several skeletal muscle alterations have been documented histologically by a number of authors, although their pathogenic and clinical significance is still uncertain.

Edstrom (1970) systematically analyzed the cross-sectional area of different fiber types in skeletal muscle biopsies from patients with PD. Compared to control subjects, the biceps brachii of PD patients exhibited up to 60% atrophic type II fibers. The maximum incidence of atrophic fibers was found in patients with very severe akinesia and a long history of the disease. On the other hand, alterations in type I fibers variably occurred, mainly according to the clinical characteristics of the disease; normal size or a tendency towards hypertrophy was detectable in patients with pronounced rigidity, whereas when akinesia was prevalent and rigidity slight, reduced mean values of the cross-sectional area were sometimes found. The author attributes these modifications to the selective use of low threshold tonic motor units, while the high threshold motor units remained more often inactive, an effect due to the rigidity and akinesia (Hufschmidt et al., 1991; Wierzbicka et al., 1991; Jordan et al., 1992).

However, such alterations, rather than a consequence of the characteristics of the motor unit activation pattern in PD, could be interpreted as fairly aspecific consequences of hypomobilization, provoking disuse myofiber atrophy (Karpati and Engel, 1968; Hainaut and Duchateau, 1989).

Furthermore, alterations in skeletal muscle mitochondria have also been reported and, whether or not of
pathogenic significance for PD (Bindoff et al., 1989; Mann et al., 1992; Cardellach et al., 1993; Di Donato et al., 1993), they could affect functional characteristics of different fiber types in this disease.

On the whole, it has not been clearly established whether muscle modifications occurring in PD play a role of epiphenomena or, in turn, can be pathogenetically involved in some aspects of the clinical picture in PD, such as rigidity itself or, also, the excessive fatigability complained of by the patients.

With respect to the rigidity, Dietz et al. (1981) and Watts et al. (1986) emphasize the role of the intrinsic mechanical properties of muscle in the increase of muscle stiffness. On the other hand, Hufschmidt et al. (1991) and Meara and Cody (1992) challenge the legitimacy of attributing hypertonia to altered muscle fiber mechanical properties alone.

More interestingly, in clinical practice, PD subjects often report a subjective sensation of reduced strength and excessive fatigability (Friedman and Friedman, 1993; Van Hilten et al., 1993). The role of central and/or peripheral mechanisms of fatigue in explaining this symptom is open to several hypotheses. Some authors emphasize the role of central mechanisms, such as breakdown of the motor planning function (Marsden et al., 1982), others consider akinesia to be responsible for the phenomenon of abnormal muscle fatigue (Hallett and Khoshbin, 1980). Nevertheless, the excessive fatigability could, at least in part be explained by peripheral mechanisms related to the muscle alterations reported in PD.

The purpose of the present study was to assess these muscle fiber modifications occurring in PD and the related peripheral muscle fatigue phenomena using surface EMG. We measured muscle fiber conduction velocity (CV) together with median frequency (MDF) of the power spectrum using automatic analysis of tibialis anterior muscle surface EMGs during isometric contraction and, in some cases, related the results to muscle biopsy data obtained from the same muscle. Muscle fiber CV is defined as the propagation velocity of the depolarization zone along the membrane of a muscle fiber. MDF represents the frequency that divides the power spectrum in two regions having the same amount of power.

The study has investigated the relationship between these EMG parameters and the histochemical characterization of muscle fibers, indicating the possible consequences of muscle modifications on the previously mentioned clinical aspects of the disease, namely fatigability.

2. Methods and materials

Fourteen outpatients suffering from PD (mean age ± SD, 59.2 ± 8.1 years, all males) were referred to our laboratory (the main clinical data are reported in Table 1). All patients exhibited the akinetic hypertonc form of the disease and were being treated with L-DOPA + decarboxylase inhibitors, at dosages ranging from 250 to 750 mg/day. Ten age-matched control subjects (mean age ± SD 61.7 ± 8.2 years, all males) were also selected for the study. After careful explanation of the procedures, informed consent was obtained from all the subjects. The experimental protocol was approved by the ethical committee of our institution.

2.1. EMG

The tibialis anterior muscle was selected for this study because of the extensive data available on its histological structure (Henriksson-Larsen et al., 1985); it is also particularly suitable for CV measurements because it contains a relatively long section between motor point(s) and the distal tendon, allowing accurate positioning of the detection electrode, thus ensuring reliable estimates of CV (Roy et al., 1986). The dominant side, the right in all patients, was studied.

Each subject lay on a bed with his ankle joint at 110°. His foot was bound in an isometric brace equipped with a tension transducer. The EMG experimental phase consisted of stimulated contractions. A monopolar stimulation technique was chosen in order to improve selectivity and electrical field uniformity, especially in the deeper parts of the muscle. A rectangular sponge negative electrode (2 × 3 cm) was placed on the most proximal motor points of the muscle and a larger sponge positive electrode (8 × 12 cm) was placed on the gastrocnemius muscle. Both stimulation electrodes were dampened with tap water. The motor points of the muscle were identified as those with the lowest stimulation threshold. The stimulation electrode was moved over the motor point area until the site providing the highest muscle contraction with

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Illness duration (years)</th>
<th>HY</th>
<th>NUDS</th>
</tr>
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<td>52</td>
<td>5</td>
<td>2</td>
<td>7</td>
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<tr>
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<tr>
<td>13a</td>
<td>55</td>
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<tr>
<td>14a</td>
<td>55</td>
<td>10</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

HY, Hoehn-Yahr clinical rating scale (score range 1–5); NUDS, Northwestern University Disability Scale (score range 0–65).

Cases submitted for muscle biopsy.
tolerable sensation was found. The stimulation artifact, which detrimentally affects the myoelectric signal, was suppressed electronically by means of a technique described by Knapfitz and Merletti (1988). Stimulations consisted of 30 s pulse trains (each pulse 0.1 ms), delivered at a frequency of 35 Hz. A supramaximal stimulation, 10–15% above the level generating the maximum amplitude motor evoked potential, was applied. Stimulated contractions were induced with the subject relaxed as much as possible.

The myoelectric signal was detected with the 4 bar electrode technique described by Broman et al. (1985a). The bars, which were 10 mm long and 2 mm in diameter, were 10 mm apart. A single differential output was obtained from the 2 central bars and was used to compute the MDF. The detection technique provided 2 double-differential outputs from which the muscle fiber CV was estimated (Broman et al., 1985b). The detection electrode the MDF. The detection technique provided 2 double-differential signals were 10 mm apart. A single differential output was obtained from the 2 central bars and was used to compute the MDF. The detection technique provided 2 double-differential outputs from which the muscle fiber CV was estimated (Broman et al., 1985b). The detection electrode was attached to the skin after it had been shaved and wiped with alcohol. The 4 bars were perpendicular to the muscle fibers. The electrode was moved over the muscle in the area between the most distal motor point and the tendon and then fixed with an elastic strap in a position that showed highly correlated double differential signals during test stimulations. The 2 myoelectric signals were low pass filtered with a cutoff frequency of 480 Hz. The myoelectric signal was digitized by a 12 bit analog to digital converter and stored on the hard disk of a 386 computer. MDF and CV were computed with numerical algorithms according to the methods described by McGill and Dorfman (1984) and Merletti et al. (1992), respectively, then tabulated and plotted versus time for each stimulated contraction.

Muscle fiber CV is computed as \( \frac{\text{MDF}}{\text{CV}} \), where \( t \) is the inter-electrode distance and \( t \) is the mean value of the delay between the 2 double differential signals. MDF is the frequency satisfying the following equation:

\[
\int_0^{\text{MDF}} P(f) \, df = \int_0^{\text{CV}} P(f) \, df
\]

where \( P(f) \) is the power spectrum. The MDF and the CV values collected from PD subjects and controls showed a curvilinear trend over time, which could be modeled with either a least-square exponential curve of the type

\[
y = A \exp(-Bt) + C
\]

or a least-square polynomial curve of the type

\[
y = at^2 + bt + c
\]

The fatigue indices were obtained from these least square regression curves using models described by Merletti et al. (1991). We defined a normalized fatigue index (FI) as \( 100A/B(A+C) \) for curve 1 and \( 100b/c \) for curve 2, where: (i) \( AB \) is the value of the slope of the exponential regression curve for \( t = 0 \), and \( A + C \) is the y axis intercept (initial value); (ii) \( b \) is the value of the slope of the polynomial curve for \( t = 0 \), and \( c \) is the initial value. Nonparametric tests were used to estimate statistically: (1) the significance of differences in parameter modifications between the subjects with PD and controls by means of the Mann-Whitney test for independent samples; (2) relationships between different parameters by means of the Spearman rank correlation test.

In all statistical tests the difference was considered to be significant at the \( P < 0.05 \) level.

2.2. Muscle biopsy

Muscle biopsy specimens were obtained from the tibialis anterior muscle under local anesthesia in 4 patients (cases 11, 12, 13 and 14 in Table 1).

Surgical excision was performed at the site where recording electrodes had been placed for the EMG study. Biopsy specimens were frozen in liquid nitrogen-chilled isopentane for the histochemical study. Serial transverse frozen sections, 10 \( \mu \)m thick, were stained with hematoxylin and eosi, modified Gomori trichrome, routine ATPase and ATPase with preincubation at pH 4.6 and 4.2, reduced nicotinamide dehydrogenase tetrazolium reductase (NADH-TR) and cytochrome c oxidase (COX). For each of 5 different fields per case, serial sections were studied to determine fiber type in at least 500 fibers.

Morphometric study was performed using a micro-metric optical method at a magnification of 250×. Fiber type percentages, as well as atrophy and hypertrophy factors and diameter variability coefficients were determined according to the criteria set out by Dubowitz and Brooke (Dubowitz, 1985).

In particular, atrophy and hypertrophy factors of type I and II fibers were calculated, for each subject, as follows:

(a) For the atrophy factors we multiplied the number of fibers with diameter between 30 and 40 \( \mu \)m by 1, the number between 20 and 30 \( \mu \)m by 2, the number between 10 and 20 \( \mu \)m by 3 and the number of fibers <10 \( \mu \)m by 4. We obtained a factor by adding all these products together, dividing the sum by the total number of examined fibers and multiplying by 1000.

(b) A similar calculation was made for the hypertrophy factors, assigning a score of 1 for each fiber between 80 and 90 \( \mu \)m, a score of 2 for each fiber between 90 and 100 \( \mu \)m, a score of 3 for each fiber between 100 and 110 \( \mu \)m and a score of 4 for each fiber between 110 and 120 \( \mu \)m.

A diameter variability coefficient was determined by the formulae: standard deviation \( \times \) 1000\text{mean fiber diameter} and was considered normal when less than 250.

Results were compared to data on normal tibialis anterior both from the literature (Helliwell et al., 1987) and from 2 age-matched male subjects in our laboratory (C1 and C2).
Table 2
EMG and histological data of PD patients with muscle biopsy

<table>
<thead>
<tr>
<th>Case</th>
<th>EMG parameters</th>
<th>Muscle biopsy</th>
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<tbody>
<tr>
<td></td>
<td>Basal CV (m/s)</td>
<td>Final CV (m/s)</td>
</tr>
<tr>
<td>11</td>
<td>3.65</td>
<td>2.50</td>
</tr>
<tr>
<td>12</td>
<td>2.27</td>
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<td>13</td>
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</tr>
<tr>
<td>14</td>
<td>5.74</td>
<td>5.02</td>
</tr>
<tr>
<td>PDa</td>
<td>4.35 ± 1.4</td>
<td>3.26 ± 0.2</td>
</tr>
<tr>
<td>Controlsb</td>
<td>4.62 ± 0.5</td>
<td>3.93 ± 0.7</td>
</tr>
<tr>
<td>C1</td>
<td></td>
<td></td>
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<tr>
<td>C2</td>
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<td>c</td>
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aPD overall average values (n = 14).
bControl average values (n = 10). C1 and C2 are controls 1 and 2 from our laboratory.
cNormal values from Helliwell et al. (1987).

3. Results

3.1. EMG

No significant differences in mean basal values between the PD patients and controls were observed for either CV or MDF parameters (Table 2). The mean final values were significantly higher for both CV and MDF in the PD group.

The tibialis anterior fibers showed a smaller reduction in both parameters for PD patients compared to controls (Table 2). The Mann-Whitney test showed that MDF and CV FI were significantly lower in the PD group. MDF FI was higher than CV FI both in PD patients and in con-

Fig. 1. CV and MDF mean absolute values during the fatigue protocol in normals (N) and PD (P) subjects.
trols. No significant relationship was detected between FIs and clinical scores in PD patients.

Fig. 1 presents the time course of CV and MDF mean absolute values in the control and PD groups, and Fig. 2 contains a plot of these same values for the 4 PD patients who underwent muscle biopsy.

No significant difference was found between patients and controls in mean initial values of contractile force (7.3 ± 2.5 versus 7.0 ± 3.5 N, respectively) or force decrease during the stimulated contraction (−0.8 ± 0.7 versus −0.6 ± 0.3 N, respectively).

3.2. Muscle biopsy

Prevalence of type I fibers in case 14 (Table 2) was found. Atrophy and hypertrophy factors were within the normal range for both type I and II fibers, with the exception of case 11 (increased type II hypertrophy factor: 2750) and case 14 (increased type I atrophy and hypertrophy factors: 186 and 686, respectively). Normal values: (i) type I, atrophy factor <160 from Helliwell et al. (1987), C1 72 and C2 94; hypertrophy factor <400, C1 106, C2 122; (ii) type II, atrophy factor <160, C1 44, C2 32; hypertrophy factor <2000, C1 744, C2 680, respectively.

The mean diameter calculation showed a tendency (value beyond 1 SD of control mean) towards hypertrophy for type I fibers in cases 12,13 and 14, and for type II fibers in case 11, towards atrophy for type II fibers in case 13. Small clusters of markedly atrophic fibers of both types were present in case 14 (Fig. 3). The diameter variability coefficient was greater than normal (<250) in cases 12 (264) and, especially, 14 (348) for type I fibers, as well as in cases 12 (312) and 13 (347) for type II fibers.

Analysis of the spatial distribution of the different fiber types showed a certain degree of fiber type grouping (Fig. 3), more evident for type I fibers, with homotypic groups as large as 30–35 fibers in some instances.

In case 14, a unique central NADH-TR-hyporeactive core, sometimes with targetoid appearance, was observed in about 40% of type I fibers (Fig. 3). In the other cases peripheral hyperreactive rims or central hyporeactive cores were detected in rare fibers on NADH-TR and COX oxidative stains.

Correlations between mean all fiber diameter and basal MDF or CV values in the biopsied cases were not significant. However, when only type I mean diameter was considered, the correlation was significant with basal CV (r = 0.8), and borderline with MDF. With respect to EMG FIs (Table 2), an inverse correlation was found between percentage of type I fibers and CV FI (r = −0.7), while the negative r value between type I percentage and MDF FI was borderline. No correlation was found between MDF or CV FIs and fiber diameter.

Finally, if single cases are considered, it should be noted that case 14, with the highest percentage and diameter of type I fibers, was also the subject with highest basal CV and lowest CV FI (Table 2).

4. Discussion

The presence of muscle alterations in PD has been corroborated further by the findings reported in this study. However, although our histological data with regard to the type I fiber modifications are similar to those reported by Edstrom (1970) in the brachial biceps muscle, they are at partial odds with his observations on type II fibers, which in our study also appeared to be normo- or hypertrophic. These discrepancies may depend on the functional characteristics of the muscle examined in this study, the tibialis anterior, a non-postural muscle which would change differently from the brachial biceps, but also on other possible causes such as the duration of the disorder and the degree of disability. Similar differences for type II fiber modifications have also been reported to exist among muscles in the presence of upper motor neuron lesions, where both atrophy and hypertrophy have been reported (Edstrom, 1970; Jakobsson et al., 1991).
On the other hand, the use of the described electrophysiological techniques has enabled us to analyze these muscle fiber modifications in a noninvasive and detailed fashion, while at the same time allowing exploration of some functional aspects associated with peripheral fatigue phenomena.

CV and MDF parameters have been shown to be indirect measurements of the diameter of muscle fibers and an indirect means for inferring the fiber type constitution of a muscle. Hakansson (1956) documented a direct relationship between action potential CV and muscle fiber circumference in isolated frog muscle fibers. Broman et al. (1985a) reported that CV has a positive correlation with both limb circumference and muscle force, considering that the fiber diameter of high threshold motor units is on the average greater than that of lower threshold motor units, the relationship between muscle CV and fiber type diameter is considered further. Andreassen and Arendt-Nielsen (1987) showed that muscle fiber CV in the tibialis anterior muscle was highly correlated with such contractile properties of the motor unit as twitch torque, rise time and half relaxation time so that it could therefore be included in the family of interrelated size parameters.

CV is also related to other factors such as the pH of interstitial and intracellular fluids (Brody et al., 1989), the ion concentration in different compartments and to the motor unit firing rate (Miller and Rinzel, 1981; Morimoto and Masuda, 1984). During prolonged contraction in normal subjects, the CV values decrease; this is an electrical manifestation of fatigue (Hakansson, 1956; Naeije and Zorn, 1982; Sadoyama et al., 1983; De Luca, 1984; Arendt-Nielsen and Mills, 1985; Broman et al., 1985a; Andreassen and Arendt-Nielsen, 1987; Merletti et al., 1990). This decrease, which is related to alterations in muscle membrane excitability, has a different time course in phasic and tonic fibers, the decrease in the tonic fibers being slower.

With respect to the second parameter investigated, MDF is influenced by muscle fiber diameter and fatigue phenomena and is generally accepted as one of the power spectrum parameters most suitable for tracking spectral compression due to localized muscle fatigue (Stulen and De Luca, 1981). MDF modifications during stimulated contraction are strictly related to reductions in CV (Hakansson, 1956; Naeije and Zorn, 1982; Sadoyama et al., 1983; De Luca 1984; Arendt-Nielsen and Mills 1985; Broman et al., 1985a; Andreassen and Arendt-Nielsen, 1987; Merletti et al., 1990), although other factors, such as lengthening of the depolarization zone, contribute to its decrease (Gydikov et al., 1984), which thus usually ap-
pairs greater than the associated reduction in CV (Merletti et al., 1990).

Taking these considerations into account, electrophysiological data obtained by means of the stimulated fatigued protocol, can be partly interpreted on the basis of the histological muscle changes documented in our PD patients. In fact, the main difference revealed between the PD subjects and controls involves the rate of CV and MDF change during stimulated contraction, which was smaller in PD patients. Such findings correlate with the percentage of type I fibers and fit with the tendency towards hypertrophy of these more fatigue-resistant fibers, revealed in 3 of the 4 patients in this study who had muscle biopsies. Hypertrophy of type I fibers could indicate that these fibers are over-utilized as a consequence of PD.

These results suggest that type I fiber modifications seem to be important in explaining CV and MDF changes during fatiguing stimulated contractions.

The physiologic prevalence of type I fibers in the tibialis anterior, where they represent about two thirds of the total population (Henriksson-Larsén et al., 1985; Helliwell et al., 1987), provides a suitable test bed for this hypothesis, as it highlights the effects of the observed diameter modifications of type I fibers. This conclusion is further supported by the significant relationships between type I fiber mean diameter and basal CV values. Only in case 11 did the reduced tendency to fatigue appear to be engendered by hypertrophy of type II fibers alone.

The meaning of reduced peripheral fatigability as deduced from CV and MDF parameters in PD tibialis anterior appears an intriguing question. In a previous study of biceps brachii and brachio-radialis muscles in subjects affected with PD, similar data were obtained during voluntary contractions (Rossi et al., 1993), thus not excluding some central mechanism of motor unit recruitment as an explanation for these results. With respect to their clinical relevance, a reduction of FI compared to controls, together with the lack of significant differences in force during stimulated contraction, even if limited to only 30 s, prevents us assigning pathogenic significance to these histological muscular modifications as a cause of abnormal fatigue phenomena in PD. On the contrary, there is evidence that these phenomena are brought about by central movement alterations, such as akinesia and rigidity (Hallett and Khoshbin, 1980).

Nevertheless, we cannot exclude the existence of a muscular cause of reduced motor performance during longer exercises, which involves oxidative metabolism, particularly in view of the mitochondrial alterations reported by Bindoff et al. (1989) and Cardellach et al. (1993) in PD skeletal muscle.

In conclusion, our study confirms the occurrence of unusual histological muscular alterations in PD some of which can be revealed qualitatively and quantitatively by means of noninvasive EMG procedures based on CV and MDF measurements.

Acknowledgements

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