THE DIAGNOSTIC SIGNIFICANCE OF LARGE ACTION POTENTIALS IN MYOPATHY

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SUMMARY

Electromyographic and histopathological studies were performed on 112 skeletal muscles in 101 subjects with myopathy. The diagnostic significance of large action potentials (LAPs) in myopathy was studied. LAPs were defined as those action potentials with a duration of over 13 ms and an amplitude of over 3 mV (peak to peak). The following results were obtained:

1. Most muscles with LAPs showed the grouped atrophy of small fibers of neuropathic change in addition to myopathic findings. Even in myopathy most LAPs reflected neuropathic change, except in thyrotoxic myopathy.

2. LAPs were not related to an increase of connective tissue increasing the impedance in volume conduction of the action potentials.

3. LAPs were frequently seen in: progressive muscular dystrophy of limb-girdle type; scapuloperoneal dystrophy; distal myopathy; oculopharyngeal dystrophy; myotonic dystrophy; polymyositis; and thyrotoxic myopathy. Other types of myopathy had few LAPs. There were two types of progressive muscular dystrophy. One had LAPs frequently and the other, rarely.

4. In myotonic dystrophy the muscles with LAPs showed scattered small angular fibers, possibly indicating neurogenic changes.

5. Interstitial myositis had LAPs more frequently than parenchymatous polymyositis. The chronic phase of polymyositis had LAPs more frequently than the acute or subacute phases.

6. In thyrotoxic myopathy the muscles with LAPs rarely showed definite changes.

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neuropathic change histopathologically. Therefore, LAPs in thyrotoxic myopathy may not indicate denervation.

Key words: EMG – Histopathology – Large action potentials – Myopathy

INTRODUCTION

In myopathy the action potentials are of low amplitude and short duration. In neuropathy they are increased in amplitude and duration; the so-called large action potentials (LAPs). However, LAPs, which are thought to be characteristic of neuropathic electromyography (EMG), sometimes appear in the EMG of myopathy (Campbell 1961; Ludin et al. 1969; Bassi et al. 1974; Mechler 1974; Takahashi et al. 1974). Whether these reflect neuropathic change is an important point in the diagnosis of myopathy.

The present paper discusses the diagnostic significance of LAPs in myopathy, comparing the appearance of LAPs with the histopathological findings in the same muscle.

MATERIALS AND METHODS

One hundred and one patients, 52 males and 49 females, aged from 6 to 76 years (mean age, 40.7 ± 16.0 years), were examined. Electromyographic (EMG) and histopathological studies were performed on 112 skeletal muscles in 101 subjects with various types of myopathy. In 9 subjects the examinations were performed on 2 different muscles in the same patient, and in one case on 3 different muscles. Twenty-two muscles in 22 subjects were examined by open-biopsy electromyography technique, recording from exposed surface muscle at open biopsy followed by excision of the muscle encompassing the exploratory needle tip for histopathological processing (open-biopsy EMG) (Warmolts et al. 1972). Histopathological examinations were more often carried out on the muscles which had LAPs associated with myopathic change in the EMG, than on the muscles which showed typical myopathic change without neuropathic change in the EMG.

The histopathological findings were evaluated in paraffin sections, and histochemical studies were performed on 45 muscles in 40 cases. The histopathological findings were classified into 3 groups. Group A showed simple myopathic changes without neuropathic change. Group B showed myopathic changes with scattered small angular fibers (Fig. 1a), indicating possible neuropathic change. Group C showed myopathic change with localized groups of small fibers or type groupings (Figs. 1b and c), indicating a mixture of myopathic and neuropathic changes.

The EMG examinations were done with a Nihonkoden MM-22A electromyograph. Concentric needle-electrodes, having an outer diameter of 0.37 mm, were used. There are several reports on normal ranges of action potentials (Petersen
Fig. 1. Histopathological findings.

a. Group B; myopathic change with scattered small angular fibers, indicating the possibility of neuropathic change. NADH-TR stain, ×250, myotonic dystrophy, 42 yr, M.

b. Group C; grouped atrophy of small fibers, indicating a definite neuropathic change. In the other part of the same muscle, myopathic change was also seen. HE stain, ×250, scapuloperoneal dystrophy, 39 yr, M.

c (see p. 164). Group C; type grouping, indicating a mixture of myopathic and neuropathic changes. ATPase stain, pH 4.2, ×100, Kearns-Shy syndrome, 29 yr, M.
et al. 1949; Yahr et al. 1950; Buchthal et al. 1954). In the present paper action potentials with a duration of over 13 ms and an amplitude of over 3 mV (peak to peak) are regarded as LAPs.

RESULTS

(1) LAPs and histopathological findings in myopathy

LAPs were seen in 44 of 112 muscles (Table 1). Among these 44 muscles, 4 were group A, 14 group B and 26 group C. Most muscles with LAPs showed a mixture of myopathic and neuropathic changes histopathologically ($P < 0.01$). Four muscles with LAPs in group A were from subjects with thyrotoxic myopathy. In 68 muscles without LAPs, 51 muscles were group A, 12 group B and 5 group C. Most muscles without LAPs showed simple histopathological myopathic changes (group A). Group C without LAPs consisted of 4 muscles of patients with poly-

<table>
<thead>
<tr>
<th>LAPs</th>
<th>Histopathological findings</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>+</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>-</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>26</td>
</tr>
</tbody>
</table>
TABLE 2

LAPs AND HISTOPATHOLOGICAL FINDINGS ON OPEN-BIOPSY EMG ($\chi^2$ test: $P < 0.05$)

<table>
<thead>
<tr>
<th>LAPs</th>
<th>Histopathological findings</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>+</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

myositis and 1 muscle of a patient with Kearns-Shy syndrome. Two of the muscles from polymyositis and that from Kearns–Shy syndrome, showed the EMG findings of an associated neurogenic change, with reduction in number of neuromuscular units with no LAPs. In 1 muscle of a patient with polymyositis, LAPs were not seen in the muscle biopsied, but were present in the other muscle examined. Another muscle of a patient with polymyositis showed simple histopathological myopathic change with no neuropathic change in the EMG.

Examined with open-biopsy EMG, most muscles with LAPs showed group C type changes, which reflected a mixture of myopathic and neuropathic changes (Table 2; $P < 0.05$). Moreover, all muscles of group C had LAPs.

(2) Correlations of LAPs and connective tissue on open-biopsy EMG

In 22 muscles with open-biopsy EMG, LAPs were not related to the histopathological findings of the increase of connective tissue (Table 3; $P < 0.05$).

(3) LAPs in different forms of myopathy

LAPs were found frequently in: limb–girdle type progressive muscular dystrophy (L–G type DMP; 2 of 8 muscles); scapuloperoneal dystrophy (9 of 11 muscles); distal myopathy (1 of 5 muscles), oculopharyngeal dystrophy (3 of 5 muscles); myotonic dystrophy (4 of 10 muscles); polymyositis (16 of 47 muscles); and

TABLE 3

LAPs AND CONNECTIVE TISSUE ON OPEN-BIOPSY EMG ($\chi^2$ test: not significant)

<table>
<thead>
<tr>
<th>LAPs</th>
<th>Connective tissues(^a)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>+</td>
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<tr>
<td>+</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

\(^a\) Amount of connective tissue: -, normal amount; +, slightly increased amount; ++, markedly increased amount.
thyrotoxic myopathy (8 of 12 muscles). On the other hand, LAPs were not seen in: Duchenne type DMP (4 muscles); facioscapulohumeral type DMP (3 muscles); hypothyroid myopathy (1 muscle); steroid myopathy (1 muscle); and periodic paralysis (2 muscles). LAPs in L-G type DMP, scapuloperoneal dystrophy, distal myopathy, oculopharyngeal dystrophy and polymyositis, were associated with group C type histopathological changes. This was rarely so when LAPs were seen in myotonic dystrophy and thyrotoxic myopathy (Table 4).

(4) LAPs in DMP
Most DMP with LAPs showed a mixture of myopathic and neuropathic changes and belonged to group C histopathologically, that is, 13 of 15 muscles (86.7%). Most DMP without LAPs showed simple myopathic changes and belonged to group A histopathologically, that is, 19 of 21 muscles (90.5%). In DMP, LAPs were related to muscles in which the histopathological findings suggested neurogenic changes. There were 2 types of DMP; one had LAPs frequently and the other, rarely. The former were L-G type DMP, scapuloperoneal dystrophy, distal myopathy and oculopharyngeal dystrophy. The latter were Duchenne type and facioscapulohumeral type DMP. However, the number of examined muscles was too small for definite conclusions to be made in distal myopathy and facioscapulohumeral type DMP. Duchenne type DMP frequently showed typical myogenic change in the EMG and the number of examined muscles with Duchenne type DMP was small.
LAPs in myotonic dystrophy

LAPs were frequently found in myotonic dystrophy, that is in 4 of 10 muscles (40%). However, all muscles with LAPs showed scattered small angular fibers histopathologically, namely, group B type.

LAPs in polymyositis

LAPs were present in 16 of 47 muscles from subjects with polymyositis (34.0%). Most of these (12 of 16) showed a mixture of myopathic and neuropathic changes and belonged to group C. Most muscles without LAPs showed simple myopathic changes and belonged to group A, that is 18 of 31 muscles (58.1%). Therefore, LAPs in polymyositis were generally related to findings showing histopathological neuropathic changes.

Polymyositis was classified into 2 groups histopathologically; interstitial myositis, that is, interstitial lesions primarily affecting the connective tissues and the vessels; and polymyositis, that is, parenchymatous lesions resulting in a primary degeneration of the muscle fibers. The latter was further divided into 2 groups: the chronic phase, examined more than 6 months after the onset; and the acute or subacute phases, examined less than 6 months after the onset. In interstitial myositis, LAPs were seen in 7 of 11 cases (63.6%). In the chronic phase of polymyositis, LAPs were seen in 8 of 24 cases (33.3%). In the acute or subacute phases of polymyositis, no LAPs were seen (Table 5). These differences are statistically significant (P < 0.02).

LAPs in thyrotoxic myopathy

In thyrotoxic myopathy, LAPs were seen in 8 of 12 muscles examined (66.7%), but only in 1 muscle was there a mixture of myopathic and neuropathic histopathological changes. Most muscles with LAPs showed simple myopathic changes (group A; 4 muscles) or scattered small angular fibers (group B; 3 muscles). The relationship between LAPs and the histopathological findings in thyrotoxic myopathy was not statistically significant (Table 6). In thyrotoxic myopathy, LAPs might appear without organic neuropathic change.

<table>
<thead>
<tr>
<th>LAPs</th>
<th>Acute or subacute&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Chronic&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Interstitial&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>0</td>
<td>8</td>
<td>7</td>
<td>15</td>
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<tr>
<td>−</td>
<td>9</td>
<td>16</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>24</td>
<td>11</td>
<td>44</td>
</tr>
</tbody>
</table>

<sup>a</sup> The acute or subacute phases of polymyositis; examined within 6 months after the onset.
<sup>b</sup> The chronic phase of polymyositis; examined more than 6 months after the onset.
<sup>c</sup>Interstitial myositis; interstitial lesions primarily affecting the connective tissues and the vessels.
TABLE 6
LAPs AND HISTOPATHOLOGICAL FINDINGS IN THYROTOXIC MYOPATHY (χ² test: not significant)

<table>
<thead>
<tr>
<th></th>
<th>Histopathological findings</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>A</td>
<td>B</td>
</tr>
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<td>−</td>
<td>A</td>
<td>B</td>
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<tr>
<td>Total</td>
<td>A</td>
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DISCUSSION

There are at least 4 possible explanations for LAPs in myopathy (Mechler 1974). (1) Fibrosis might destroy or damage a part of the terminal motor nerve fibers (Campbell 1961). (2) The amplitude and duration of the surviving motor units could be increased by the low volume conduction of connective tissue (Campbell 1961). (3) The "collateral sprouting" hypothesis of Coërs (1965) provides another possible explanation. He found degenerative neural phenomena such as swelling of end-plates and of subterminal nerve fibers, and sprouting of terminal nerve fibers in myopathy. The sprouting branches could develop functionally effective contacts with muscle fibers which had lost their innervation. It was clear that the increase in the number of muscle fibers innervated by a single axon augmented the muscle fiber pool of the active motor unit and this must be reflected in the EMG. (4) The "sick motoneurones" hypothesis of McComas et al. (1971b) provides another possible explanation. They showed that the number of motor units from the extensor digitorum brevis muscles was decreased in myopathy. The theory that LAPs appear because of the increase of connective tissue which augments the impedance in volume conductor, means that LAPs do not indicate neuropathic change but can appear even in simple myopathy. However, our results showed that LAPs were not always related to increased connective tissue and that most muscles with LAPs showed a mixture of myopathic and neuropathic histopathological changes. It therefore seems unlikely that LAPs would appear in simple myopathy without neuropathic changes.

In DMP, many LAPs were seen in L-G type DMP, scapuloperoneal dystrophy and oculopharyngeal dystrophy. However, in Duchenne type DMP, LAPs were not seen. Most muscles with Duchenne type DMP showed a typical myogenic EMG and histopathological pattern. There are therefore 2 types of DMP, one frequently associated with neuropathic change and the other, rarely. There are at least 3 possible explanations for neuropathic change in DMP: (1) DMP is essentially a neurogenic disorder, and myopathic changes merely a secondary product as McComas et al. (1971b) suggested. (2) DMP is essentially a myogenic disorder, but some kinds of myopathy are associated with neural degeneration. (3) DMP
is essentially a myogenic disorder, and neuropathic change is a secondary effect or an accidental complication. Muscles which showed LAPs with myopathic change in EMG were more often examined by muscle biopsy than those showing typical myopathic change alone in the EMG, so it is difficult from our results to conclude which hypothesis is correct. It may be suggested that in slowly progressive myopathy, such as L-G type DMP, motor nerves might be damaged as a secondary effect of muscle degeneration.

There are several reports of myotonic dystrophy with peripheral nerve disturbance (McComas et al. 1971a; Bassi et al. 1974; Panayiotopoulos et al. 1976, 1977). In this study, no case of myotonic dystrophy with LAPs showed simple myopathic change histopathologically. LAPs in myotonic dystrophy may therefore reflect neuropathic change, and scattered small angular fibers may also indicate neuropathic change (Dubowitz et al. 1973). Some authors believe that muscle changes in myotonic dystrophy are neuropathic (McComas et al. 1971a; Bassi et al. 1974), while others believe that "myopathic" and "neuropathic" changes are independent processes (Panayiotopoulos et al. 1976, 1977).

In the EMG of polymyositis, denervation potentials have often been seen. There are some reports on polymyositis with LAPs, claimed as indicating "neuromyositis" (McEntee et al. 1965). Coërs (1956) divided polymyositis into interstitial and a parenchymatous type. We found LAPs frequently in interstitial myositis, perhaps because peripheral nerves may be disturbed by angiitis in the interstitium. In addition, LAPs were seen occasionally in the chronic phase of parenchymatous polymyositis, but not seen in the acute or subacute phases. Mechler (1974) found LAPs in the chronic phase of polymyositis. In the acute or subacute phases of polymyositis, motor nerves might not be damaged. In the parenchymatous type, muscle fibers are chiefly disturbed by an autoimmune reaction and peripheral nerves may be spared.

Ramsay (1965) reported that myopathic changes in the EMGs of proximal muscles were found in 92.6% of patients with thyrotoxicosis. Thereafter, Ludin et al. (1969) reported that in 8 of 13 patients with thyrotoxicosis, EMGs demonstrated neurogenic lesions in the distal muscles of the lower extremities, and they assumed that the signs of neurogenic lesions were the expression of a subclinical polyneuropathy. Moreover, McComas et al. (1974) found loss of operational motor units in 20 patients with thyrotoxicosis and the reversible nature of the postulated motoneurone dysfunction was demonstrated by increased motor unit counts in 6 patients studied again after treatment of their thyrotoxicosis. In the present study, most muscles with LAPs in thyrotoxic myopathy did not show a mixture of myopathic and neuropathic histopathological changes. LAPs in thyrotoxic myopathy do not always indicate denervation. It is possible that functional rather than organic disturbance such as reinnervation occur, because the EMG findings improve in parallel with the improvement of symptoms.
REFERENCES


