

# Thyrotoxic Myopathy (Peculiarities on Clinical Diagnosis by Specific Pattern of Muscle Weakness and Atrophy without Reduction of Strength in Quadriceps Muscles and Some Remarks on Cause of Muscle Weakness)

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## Abstract

Data on 263 patients (47 males and 216 females) with thyrotoxic myopathy (TM) have been studied. 151 patients were under the Kazakov's personal observation and 112 cases were taken from the literature. The quantitative evaluation of frequency, level of weakness (and atrophy) of some muscles, the description of topography of muscular lesions at different phases of TM have been presented. An original pattern of muscular weakness and atrophy was established which allow to reveal myopathy at its early stage, even with the absence of obvious signs of thyrotoxicosis. This permits to reasonable respect thyrotoxicosis in many cases. The weakening of hormonal control of cAMP-dependent processes is probably the basic cause of muscular weakness and structural changes in skeletal muscles in thyrotoxic myopathy (TM).

**Keywords :** Thyrotoxic myopathy, thyrotoxicosis, skeletal muscle, pattern of muscle involvement, terminal motor innervation, motor unit potentials, cycle AMP system in muscle.

## INTRODUCTION

With hyperthyroidism in the pathological process might involve different sections of the neuromuscular system. Thyrotoxic myopathy (TM) occurs more often among other thyrotoxic neuromuscular disorders. Quite controversies opinions exit on the frequency of affections of some muscles, topography of muscle weakness, the period of development of myopathy from the onset of thyrotoxicosis, the dependence of myopathy signs on the severity and duration of thyrotoxicosis (1-6). Pathogenesis of TM unknown and the mechanism of the muscle weakness remain obscure (7,8).

The aim of present paper was to clarify some specific of the clinical picture, the frequency and level of weakness and atrophy of some muscles, the sequence

of involvement of some muscles into pathological process, the pattern of muscular weakness in mild, moderate and severe forms of TM, and its some endocrinological aspects; to precise role of lower motor neurons, skeletal muscle and disorders of the cyclic nucleotide system into pathogenesis of muscle weakness in human TM.

## PATIENTS AND METHODS

In studying TM we have used both personal observations (151 patients) and case histories taken from the literature (112 patients). A total of 263 patients (47 males and 216 females) have been studied.

Basing on data of the state of strength and function of muscles the criteria were developed for designation of the three stages of TM. This permitted to divide

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the patients (both in personal observations and cases taken from the literature) into 3 groups: with mild, moderate and severe myopathy. Among the personal observations 60.3, 28.5 and 11.2% patients had mild, moderate and severe degree of myopathy respectively and the average age in each group was 43.5, 45.8 and 53.8 years respectively. Among the observations from literature mild, moderate and severe TM was in 13.4, 31.3 and 55.3% patients, respectively and the average age in each group was 52.6, 47 and 51.4 years respectively. The duration of thyrotoxicosis (by objective history) varies from one month to 21 years: from 1 to 11 months in 10.4 and 54.1% patients, from 1 to 5 years – in 45 and 36.7%, from 6 to 10 years- in 11.9 and 4.1 %, over 11 years - in 2.6 and 5.1 % patients respectively by personal and literature data. Among patients examined personally 11.2, 27.2, 57.6 and 4% had minimal, mild, moderate and severe signs of thyrotoxicosis respectively and among patients from the literature 26.8, 27.7, 36.6 and 8.9 % had latent, mild, moderate and severe thyrotoxicosis respectively.

The diagnosis of thyrotoxicosis was established basing on the clinical picture and was confirmed by the study of thyroid gland function (level thyroid-stimulating hormone, total thyroxin, triiodothyronine, uptake of <sup>131</sup>iodine, antithyroglobulin and antithyroidperoxidase antibodies levels and thyroid ultrasonogram in some patients) at the department of Endocrinology First Pavlov State Medical University of St. Petersburg.

To reveal the muscular weakness and establish the time of appearance of dysfunction of individual muscles and muscular groups we used a special test inquiry for subject under study. Along with neurological examination, the function and trophicity of muscle were thoroughly studied by methods [9 - 11]. The modified tests [12] have been used also. The muscular strength was measured manually by method [13].

To compare data on the frequency of weakness and frequency of atrophy of individual muscles the quantitative evaluation (in %) of these changes in the personal as well as in observations from literature was performed.

The processing of results of manual study of muscles and case history data obtained from 263 TM patients was made differently for personal observations and

cases taken from the literature by using punch cards K-5.

Histological studies of the sternohyoideus muscle taken during subtotal subfascial resection of thyroid gland (14) were conducted in 63 women with diffuse toxic goiter aged from 25 to 60 years. 38 of them had TM: 26 had a mild form, 11- moderate and 1- severe. 25 patients had thyrotoxicosis without muscular weakness. 23 women aged from 23 to 55 years with nodular non-toxic goiter were under control. Endotracheal anesthesia was used. Biopsies were fixed in 10-12% formalin solution, 20% neutral formalin and Zenker- formol solution and 96° alcohol. Longitudinal and transverse celloidin, paraffin and frozen sections were used. Muscles were stained with hematoxylin and eosin (HE), by the Van Gieson method, the Mallory method, with sudan III-IV, iron-hematoxylin and by the Bielshowsky-Gros-Lavrentyev silver method for nerve fibers and nerve endings [15]. Morphological changes, internal (central) sarcolemmal nuclei included, were assessed in each biopsy on 7 to 8- $\mu$ m -thick celloidin transverse section, in 100 fibers taken from three separate microscopic fields. The percentage of changed fibers was calculated. The minimal diameter of about 8-90 fibers of the sternohyoideus muscle was measured by method [16] in each biopsy with an ocular micrometer by scanning the preparation from one end to the other, using 8- $\mu$ m -thick transverse cryostat sections stained for succinat dehydrogenases and mitochondrial  $\alpha$ -glycerophosphate dehydrogenase with the use of phenasine-metosulphate by method [17].

Electromyography (EMG) studies were in 26 TM patients (23 women and 3 men) aged from 26 to 62 years. 16 of them had mild myopathy, 8- moderate and 2-severe. 13 women and 2 men aged from 29 to 57 years who had not disease of neuromuscular system were under control. For the EMG examination a Medacor two-channel electromyography and concentric electrodes were used. Each muscle (biceps brachii and vastus lateralis) was searched for spontaneous activity at rest and motor unit potential (MUP) are samples at minimal voluntary contraction from some different places. The following EMG criteria have been evaluated: pattern at maximal voluntary contraction, spontaneous activity, number of polyphasic potentials and mean amplitude and mean duration of at least 20 MUPs.

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Conduction velocity of motor fibres of ulnar nerve, indices of terminal and residual latency, and duration of M-reply and repetitive transmission studies (muscle action potential of abductor digiti minimi muscle evoked by repetitive stimulation of ulnar nerve at different frequencies) were measured by methods [18, 19].

Statistical analysis of the data was done with a Hewlett-Packard N 9845S computer using standard programs with evaluation of parametric criteria and histogram plotting.

### RESULTS

#### Clinical specific features of the TM. Frequency, degree of muscle weakness and pattern of muscle weakness (and atrophy) in different stages of the disease

In TM patients the weakness of the muscles iliopsoas (in 96%), gluteus maximus (78, 8%), interossei palmaris and lumbricales (74.9%), neck flexors (65.5%), biceps brachii (62.2%), deltoideus (42.3%), trapezius and serratus anterior (31.1%) and rectus and obliques abdominis (21.1%) is more often being revealed (table 1, personal observations). In cases from the literature the muscles of the iliopsoas and gluteus maximus (together) (in 96.7%), upper arm (70.5%), deltoideus (65.5%), shoulder girdle (79.4%), rectus and obliques abdominis (41%) more also often affected. More often weakness of some muscles as compared to the personal observations seems to be caused than, that many investigators included into the notion "affection of the muscle" its "weakness and/or atrophy".

In the majority of patients only mild and moderate weakness of some muscles was discovered independently on the severity of myopathy (table 2). The degree of myopathy is determined by the change in the percentage of mildly and moderately weakened muscles and frequency of their weakness and not by the increase in the paresis level (for the exception of some muscles) (table 1, 2). No paralysis was found in patients under investigation. In cases taken from the literature paralysis of some muscle was rarely described.

In the literature there are controversies opinions about the relationship between the frequency (and level) of

weakness and atrophy of muscles in TM patients. We studied this problem taking into consideration the anatomical regions and muscular groups. Muscles of shoulder girdle (trapezius, serratus anterior), shoulder (supraspinatus and infraspinatus), upper arm (triceps) and thighs (quadriceps and adductors) reveal more often atrophy than weakness, or atrophy of muscles over the level their weakness. In contrast, other muscular groups (mimic, neck flexors, interossei palmaris, rectus and obliques abdominis, iliopsoas and gluteus maximus) weakness were often revealed than atrophy, or muscular weakness prevails over the level of their atrophy (table 1).

The other TM specificity is the excessive folded skin over the affected muscles. More often it is observed in shoulder girdle, thighs (more often in quadriceps) and especially upper arms (more often in triceps). In TM patients this sign is caused rather by the atrophy of subcutaneous fat than of muscles.

The clinical picture of the TM reveals other specific features: frequent (in 40% personal patients) affection of mimic muscles (frontals and orbicularis oculi, pars orbitalis) in a mild and moderate level, the preservation or increase of deep reflexes, the absence of muscle pseudohypertrophies and terminal atrophies, tendon and muscular retractions, abnormal postures of separate body segments (classical "winging" of the scapulae, sloping shoulders, "sunken" chest, pronounced of lumbar lordosis).

For diagnostics of neuromuscular disease it is insufficient to know only the frequency of weakness and atrophy of some muscles, though this sign is sufficiently valuable if it reflects some phases of the disease. The topography (pattern) of muscle involvement of great importance also.

The examination patients (151 men) were divided into five groups according to the topography of muscular weakness. The cases taken from the literature (112 observations) were divided into three groups to the topography of muscular affections (weakness and/or atrophy).

In the first group (55 personal patients -36.4%) muscles of pelvic girdle, hands and/or neckflexors suffered mostly. This group was formed mostly of patients with mild myopathy (51 men i.e. 56% out

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**Table 1.** *Freqesncy of weakness in some muscles and muscles groups depending on the degree of Thyrotoxic Myopathy and Freqesncy of Atrophy in these muscles in 151 patients ( 91-with mild Myopathy, 43-with moderate and 17- with severe Myopathy*

| Name of muscle, muscle groups  | Degree of myopathy |              |              | Total patients with affected of different muscles |               |
|--------------------------------|--------------------|--------------|--------------|---|---------------|
|                                | Mild               | Moderate     | Severe       | Weakness  | Atrophy       |
| 1                              | 2                  | 3            | 4            | 5   | 6             |
| Orbicularis oculi, frontalis   | 26<br>(28.5)       | 22<br>(51.1) | 11<br>(64.7) | 59<br>(39.7)                                      | -             |
| Neck flexors                   | 49<br>(53.8)       | 33<br>(76.7) | 17<br>(100)  | 99<br>(65.5)                                      | -             |
| Sternocleido-mastoideus        | 6<br>(6.6)         | 10<br>(23.2) | 2<br>(11.7)  | 18<br>(11.9)                                      | 7<br>(4.6)    |
| Trapezius, serratus anterior   | 16<br>(17.5)       | 19<br>(44.1) | 12<br>(70.5) | 47<br>(31.1)                                      | 94<br>(62.2)  |
| Rhomboid                       | -                  | 9<br>(20.9)  | 9<br>(52.9)  | 18<br>(11.9)                                      | 94<br>(62.2)  |
| Pectorales major               | 2<br>(2.1)         | 1<br>(2.3)   | 3<br>(17.6)  | 6<br>(3.9)  | -             |
| Supraspinatus, infraspinatus   | -                  | 7<br>(16.2)  | 6<br>(35.2)  | 13<br>(8.6)                                       | 94<br>(62.2)  |
| Deltoid                        | 28<br>(30.7)       | 25<br>(58.1) | 11<br>(64.7) | 64<br>(42.3)                                      | 79<br>(52.3)  |
| Biceps brachii                 | 34<br>(37.3)       | 43<br>(100)  | 17<br>(100)  | 94<br>(62.2)                                      | 110<br>(72.8) |
| Triceps brachii                | 4<br>(4.3)         | 5<br>(11.6)  | 5<br>(29.4)  | 14<br>(9.3)                                       | 102<br>(67.5) |
| Wrist flexors                  | 2<br>(2.2)         | 2<br>(4.6)   | 1<br>(5.8)   | 5<br>(3.3)  | 5<br>(3.3)    |
| Wrist extensors                | 5<br>(5.5)         | 4<br>(9.3)   | 2<br>(11.7)  | 11<br>(7.3)                                       | 11<br>(7.3)   |
| Thenar, hypothenar             | -                  | 3<br>(6.9)   | -            | 3<br>(1.9)  | 10<br>(6.6)   |
| Palmar interossei, lumbricales | 63<br>(69.2)       | 32<br>(74.4) | 17<br>(100)  | 112<br>(74.2)                                     | 31<br>(20.5)  |
| Rectus and obliques abdominis  | 3<br>(3.3)         | 13<br>(30.2) | 16<br>(94.1) | 32<br>(21.1)                                      | -             |
| Iliopsoas                      | 85<br>(93.4)       | 43<br>(100)  | 17<br>(100)  | 145<br>(96)                                       | -             |
| Gluteus maximus                | 64<br>(70.3)       | 38<br>(88.3) | 17<br>(100)  | 119<br>(78.8)                                     | 3<br>(1.9)    |
| Gluteus medius                 | 1<br>(1.1)         | 6<br>(13.9)  | 4<br>(23.5)  | 11<br>(7.3)                                       | -             |
| Quadriceps                     | -                  | 2<br>(4.6)   | 4<br>(23.5)  | 6<br>(3.9)  | 83<br>(54.9)  |
| Hip posterior groups           | 2<br>(2.2)         | 12<br>(27.9) | 3<br>(17.6)  | 17<br>(11.2)                                      | 79<br>(52.3)  |
| Hip adductor group             | 6<br>(6.6)         | 14<br>(32.5) | 6<br>(35.3)  | 26<br>(17.2)                                      | 86<br>(59.9)  |
| Tibialis anterior              | 1<br>(1.09)        | 2<br>(4.6)   | 1<br>(5.8)   | 4<br>(2.6)  | 23<br>(15.2)  |
| Gastrocnemius                  | 2<br>(2.2)         | 4<br>(9.3)   | -            | 6<br>(3.6)  | 23<br>(15.2)  |

of 91). Among the cases taken from literature such pattern of muscle affection occurred in 46,7% patients with mild myopathy.

The second group included 48 personal patients in whom the proximal parts of arms (and more rarely of legs) were involved simultaneously with the weakness

of the muscles mentioned above. This group was formed mainly of patients with moderate myopathy (21 men i.e. 48.8% out of 43).

In the third group (38 personal patients) besides the weakness of muscles revealed in the first two groups, the muscles of shoulder girdle suffered also.

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**Table 2.** Frequency and degree of weakness of the some muscles and muscles groups depending from the severity of Thyrotoxic Myopathy in 151 patients ( 91-with mild Myopathy, 43-with moderate and 17- with severe Myopathy)

| Name of muscle and muscle groups | Degree of myopathy and the degree of muscle weakness |    |   |          |    |    |        |    |    | Total patients |
|----------------------------------|--|----|---|----------|----|----|--------|----|----|----------------|
|                                  | Mild   |    |   | Moderate |    |    | Severe |    |    |                |
|                                  | S  | M  | H | S        | M  | H  | S      | M  | H  |                |
| Orbicularis oculi, frontalis     | 24   | 1  | 1 | 18       | 2  | 2  | 9      | -  | 2  | 59             |
| Neck flexors                     | 24   | 25 | - | 3        | 30 | -  | 2      | 15 | -  | 99             |
| Sternocleidomastoid              | 3  | 3  | - | 7        | 3  | -  | 2      | -  | -  | 18             |
| Trapezius, serratus anterior     | 16   | -  | - | 15       | 4  | -  | 6      | 6  | -  | 47             |
| Rhomboids                        | -  | -  | - | 6        | 3  | -  | 5      | 4  | -  | 18             |
| Pectoralis major                 | 2  | -  | - | 1        | -  | -  | 3      | -  | -  | 6              |
| Supraspinatus, infraspinatus     | 2  | -  | - | 5        | 2  | -  | 4      | 2  | -  | 13             |
| Deltoides                        | 27   | 1  | - | 17       | 8  | -  | 4      | 7  | -  | 64             |
| Biceps brachii                   | 32   | 2  | - | 35       | 8  | -  | 8      | 9  | -  | 94             |
| Triceps brachii                  | 3  | 1  | - | 5        | -  | -  | 2      | 3  | -  | 14             |
| Thenar, hypothenar               | -  | -  | - | 1        | 1  | 1  | -      | -  | -  | 3              |
| Palmar interossei, lumbricales   | 19   | 44 | - | 1        | 31 | -  | -      | 12 | 5  | 112            |
| Rectus and obliques abdominis    | 2  | -  | 1 | 5        | -  | 8  | -      | -  | 16 | 32             |
| Iliopsoas                        | 46   | 39 | - | 3        | 40 | -  | -      | 17 | -  | 145            |
| Gluteus maximus                  | 40   | 24 | - | 2        | 24 | 12 | -      | 3  | 14 | 119            |
| Gluteus medius                   | 1  | -  | - | 3        | 3  | -  | 3      | 1  | -  | 11             |
| Quadriceps                       | -  | -  | - | 2        | -  | -  | 4      | -  | -  | 6              |
| Hip adductor group               | 3  | 3  | - | 8        | 6  | -  | -      | -  | 6  | 26             |
| Hip posterior group              | 2  | -  | - | 4        | 8  | -  | 3      | -  | -  | 17             |
| Tibialis anterior                | 1  | -  | - | 2        | -  | -  | -      | 1  | -  | 4              |
| Gastrocnemius                    | -  | -  | - | 2        | -  | -  | 4      | -  | -  | 6              |

Note: S - slight weakness of muscle, M - Moderate, H - Heavy

This group was formed mostly of patients with severe myopathy (12 men i.e. 70.6% out of 17).

Mostly the cases taken from the literature (86.6%) with moderate and severe myopathy by the topography of muscular affections corresponded to our 2 and 3 groups for the exception that in 17 subjects the shin muscles and in 14 - bulbar muscles were simultaneously weak.

In the fourth and fifth groups were included 10 personal patients having mild myopathy. Among them 4 cases the weakness of shoulder and pelvic girdles

muscles and in 6- weakness of shoulder girdle and upper arm muscles was found simultaneously with the weakness of hands/ or neck muscles.

To clarify the sequence in the involvement of individual muscles and muscular groups into myopathic process we compared how the localization of muscle weakness changes depending on the severity of myopathy. It was found out that patients with mild myopathy reveal first the weakness of the muscles of iliopsoas (93.4%), gluteus maximus (70.3%), interosseous palmaris and lumbricales (69.2%) and/or neck flexors

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(53.8%) (table 1, 2). With progressing of myopathy muscles of the upper arms (biceps and deltoideus), thighs (adductors and posterior group muscles) and shoulder girdle (trapezius, serratus anterior, supra- and infraspinatus) are involved sequentially.

Thus, we established the frequency of weakness in some muscles with different severity forms of TM. The sequence in the involvement of different muscular groups into myopathic process was also determined. Basing on this, the patterns of muscular weakness were developed for patients with mild, moderate and severe forms of TM. These data along with clinical specific features described above permitted to diagnose TM at different stages of development.

At the earliest stage TM could be recognized by the next criteria: 1. The pattern of muscular weakness with involvement of the muscles of iliopsoas, gluteus maximus, interossei palmaris and lumbricales of the hands and/ or neck flexors and 2. The "atrophy" of triceps brachii and quadriceps femoris muscles without reduction in their strength with the excessive folded the skin over these muscles due to subcutaneous fat atrophy. The diagnosis is confirmed by the studies gland function, electromyography and muscle biopsy.

In the majority patients (77.5 and 87.7% personal and from literature observations, respectively) the myopathic symptoms developed during the first months (6 – 7 months in average) from onset of thyrotoxicosis. Only in 11-16% of patients the myopathy occurred later, in average 2 and 3, 6 years, respectively

## Morphological and Electrophysiological Studies

The muscle fiber diameter was significantly decreased in TM patients as well as thyrotoxic patients without muscular weakness as compared to the control (fig. 1). The biopsies of TM patients contained muscle fibers with decrease in longitudinal and transverse striation (in 100% patients), hyaline, granular and vascular degeneration (97, 79 and 19%, respectively), necrosis (86%), fragmentation (21%), increase in number of sarcolemmal, vesicular and internal nuclei (74, 65 and 54%, respectively), gathering of nuclei in small groups and in chains (46%).

In more than half of biopsies these changes in 4.6-7.6% of muscle fibers was found. In only 21-35% patients the some morphological changes in 25-40% of muscle fibers was found. As a rule, degenerative changes were focal or segmental nature. The percentage of altered fibers no dependence of the degree of muscular weakness and of the severity and duration of thyrotoxicosis.

The many preterminal axons had multiple swelling and winding. The single of distal axons had spheric form local expansion, resembling "vacuole". Excessive branching of terminal and preterminal axons was found. These collateral branches finished with multiple nerve endings on the same muscle fiber.

In our experimental model TM in mice (fig. 2) were found the similar abnormalities in skeletal muscle and in terminal motor innervation with TM patients (fig.3 a-d) [80,81].

**Table 3.** Changes of mean values on the EMG in biceps brachii muscles of Thyrotoxic Myopathy patients

| Groups            | Biceps brachii muscle |                  |                                |                 |                                |                      |                                |
|-------------------|-----------------------|------------------|--------------------------------|-----------------|--------------------------------|----------------------|--------------------------------|
|                   | Number of MUP (n)     | Amplitude of MUP |                                | Duration of MUP |                                | Polyphasic potential |                                |
|                   |                       | M ± m (μV)       | L <sub>1</sub> -L <sub>2</sub> | M ± m (msec)    | L <sub>1</sub> -L <sub>2</sub> | M ± m (%)            | L <sub>1</sub> -L <sub>2</sub> |
| Patients (26 men) | 616                   | 210 ± 7          | 194.4-224.1                    | 5.1 ± 0.3       | 4.9 - 5.3                      | 7.7 ± 0.6            | 6.5-8.8                        |
| Control (15 men)  | 429                   | 248 ± 4          | 240.5-255.9                    | 5.6 ± 0.07      | 5.4 - 5.8                      | 4.3 ± 0.4            | 3.4-5.1                        |
| P                 |                       | <0.001           |                                | <0.05           |                                | <0.01                |                                |

MUP: motor unit potential; L1- L2= 95% confederal limits of mean values

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Table 4. Changes of mean indices of terminal and residual latency, duration of M-wave MCVe in stimulation of ulnar nerve in Thyrotoxic Myopathy patients

| Groups               | TL              |                                | RL              |                                | M wave          |                                | MCV <sub>e</sub> |                                |
|----------------------|-----------------|--------------------------------|-----------------|--------------------------------|-----------------|--------------------------------|------------------|--------------------------------|
|                      | M ± m<br>(msec) | L <sub>1</sub> -L <sub>2</sub> | M ± m<br>(msec) | L <sub>1</sub> -L <sub>2</sub> | M ± m<br>(msec) | L <sub>1</sub> -L <sub>2</sub> | M ± m<br>(m/sec) | L <sub>1</sub> -L <sub>2</sub> |
| Patients<br>(26 men) | 2.7 ±<br>0.1    | 2.5 -<br>2.9                   | 1.63 ±<br>0.1   | 1.4 -<br>1.9                   | 11.0 ±<br>0.2   | 10.5 -<br>11.4                 | 69.1 ±<br>1.2    | 66.7 ±<br>71.6                 |
| Control<br>(15 men)  | 2.9 ±<br>0.2    | 2.5 -<br>3.3                   | 1.4 ±<br>0.1    | 1.2 -<br>1.65                  | 11.3 ±<br>0.2   | 10.8 -<br>11.8                 | 63.8 ±<br>1.9    | 59.5 -<br>68.2                 |
| P                    | >0.05           |                                | >0.05           |                                | >0.05           |                                | <0.05            |                                |

TL= terminal latency, RL = residual latency, MCVe = Maximal Conductance velocity in efferent fibres of ulnar nerve: L1-L2 = 95% confidential limits of mean values

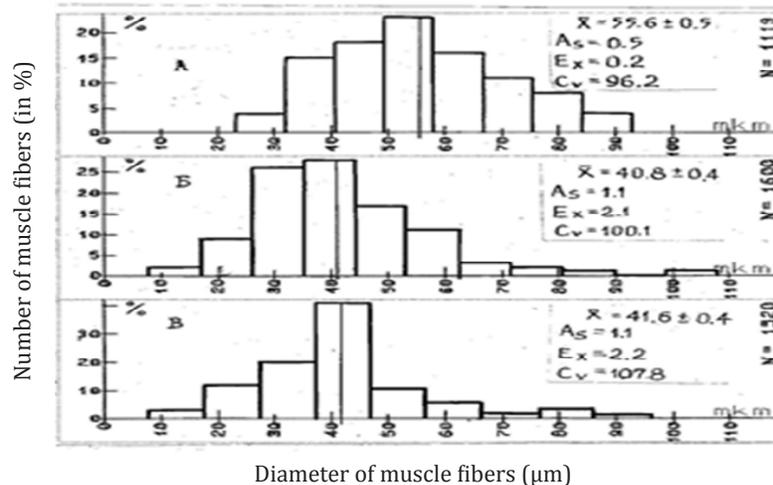
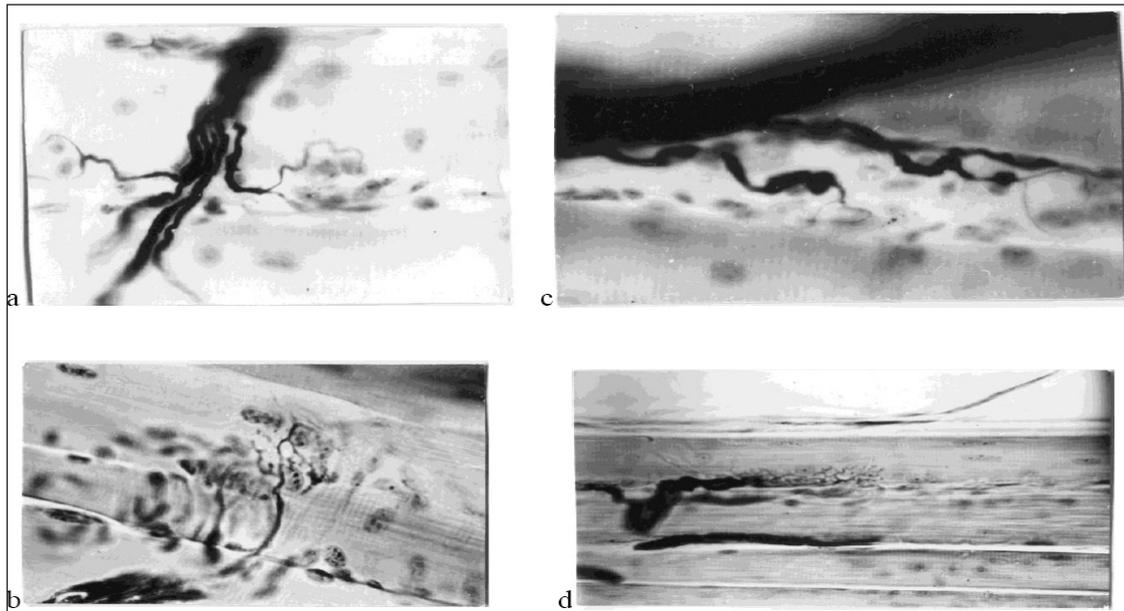


Figure 1. Gistogramma distribution diameter of muscle fibers in sternohyoideus muscle in control (A) and patients with TM (B) and thyrotoxic patients without TM (C)



Figure 2. Mouse with thyrotoxic myopathy, Wasting and weakness of pelvic girdle and hind limb muscles. Fatty overgrowth on the posterior surface of the neck.

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**Figure 3.** Longitudinal sections of rectus femoris muscle from control (a) and thyrotoxic myopathy mice (b-d). a) Preterminal axons dichotomic division into two terminals forming motor endings. No collateral and terminal branching of nerve fibers. X 450. b) Terminal branching and formation of small new motor endings on the same muscle fiber in the zone of degenerative changes. X 450. c) Winding preterminal axons with swellings in the necrotic zone on the same muscle fiber. X 700. d) Terminal branching and formation of new motor endings (en grappe endings) on the same muscle fiber. X 700.

The mean amplitude and mean duration of MUP were significantly decreased and percentage of polyphasic potentials was increased (table 3). On maximum voluntary contraction interference pattern was evident. No spontaneous activity in rest. The conduction velocity of the ulnar nerve was some increased, the mean indices of terminal and residual latency, and duration of M-reply were normal limits as compared to the control (table 4). The neuromuscular transmission was normal.

### DISCUSSION AND CONCLUSION

The clinical peculiarity of TM should be considered the frequent weakness of iliopsoas and gluteus maximus muscles. Similar data was received also by other authors [2,20–22]. However, by data of Ramsay [6, 23] the iliopsoas and glutei muscles are involved (weakness and/or atrophy) were rarely than supraspinatus and triceps brachii muscles, namely in 26 (48%) and 9 (16.6%) against 33 (61.1%) from 54 patients respectively. In Nosedá's opinion [30] the pelvic (iliopsoas) and shoulder girdle muscles are weakened with equal frequency, namely in 13 (76.4%) and 14 (82.3%) from 17 patients, respectively.

Some investigators assumed that muscles of thenar and hypothenar were often involved [24-29]. We have studied separately the frequency of muscle weakness thenar and hypothenar as compared to interosseous palmaris and lumbricales of the hand muscles. Muscles of the first group are involved rarely (in 1.9%), the weakness of muscles in the second group occurs quite often (74.1%).

The 4-th place in frequency of weakness is occupied by neck flexors muscles (65/5%) after interosseous of hand muscles. Some investigators also noted that these muscles are often involved [4, 30]. However, the other authors [6, 23, 31] believe that the weakness of neck flexors muscles occurs rarely. In cases taken from literature these muscles were also rarely affected (in 23.2%). It seems to be caused by the fact that the many of authors [6, 37, 57] investigated the strength of sternomastoid muscles instead of neck flexors. The frequency of affection of these particular muscles considerably less (18%) in personal observations also.

A biceps brachii muscle occupies the 5-th place in frequency of weakness. Some investigators believe

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that biceps and triceps brachii muscles are involved with equal frequency [30], but Ramsay's data (6) the triceps brachii were involved more frequently than biceps brachii, namely in 33 (61.1%) and 2 (3.7%) from 54 patients, respectively.

However, we established that weakness of biceps brachii muscles is revealed more often (62.2%), is accompanied by their atrophy (72.8%) and depends on the degree of myopathy: with mild form- in 37.3% patients, with moderate and severe forms – in 100% ( personal observations). On the other hand, the weakness of triceps brachii muscles was found only in 9.3% patients while the atrophy of these muscles without weakness was in 67.5% (table 1).

In literature the opinion are spread that weakness of quadriceps muscles often occurs and is the cardinal sign of TM (3, 5, 6, 32, 33). Ramsay (6) and Nosedá (30) described affection of quadriceps muscles in 11 (20%) from 54 and in 6 (15, 2%) from 17 patients respectively. In cases taken from the literature weakness of these muscles often occurred also (in 71.4%).

However, the analysis of personal observations given all grounds to express another opinion: weakness in quadriceps muscles is extremely rarely revealed in TM patients (in 3.9%), while their wasting without reduction in their strength more often (in 54.9%). Similar opinions have been expressed by other authors also (4, 20, 21, 34, 35, 36).

The confused description of more often weakness of quadriceps muscle in cases taken from the literature seems to be caused by two factors: firstly, many authors investigated the strength of this muscle by using special Lahey test (37) which determined to a greater extent the level of fatigue of muscle quadriceps than its weakness; secondly, some investigators [6, 23] did not take into consideration the frequency of weakness and atrophied muscle separately and included its "weakness and/or atrophy" into the notion "affected of the muscle". In TM patients, as our data show, there is no direct connection between weakness, atrophy and fatigue of the muscles.

Meanwhile, in literature there are controversial opinions about the relationships between the frequency of weakness and atrophy of muscles in TM

patients. Some authors consider that the weakness of the muscles is usually conducted with their atrophy (2, 5, 6, 23, 34), but other [27, 30] believe that the atrophy of muscles occurred more often than their weakness. However, others [20, 21, 38] express the contrary opinions. Satoyoshi et al. (38) observed local muscular atrophy only in 7% from 146 TM patients.

We studied this problem taking into consideration the anatomical regions and individual muscles and muscle groups (see above) and represented our data in table 2. It was found out also that heavy atrophy of isolated muscles may not be conducted by their significant weakness and vice versa, the other isolated muscles with normal volume often have strong weakness.

Thus, in literature there are many controversial opinions about the frequency (and degree) of the muscle weakness and atrophy, and the topography of muscle affection on TM. Analysis of isolated observations described by different authors does not allow to solve this problem.

The study of 263 case histories permitted us to find out more accurate sequence of extension of the muscle affection in TM. At the early stage TM may be supposed if in patient there is the weakness of iliopsoas muscles (often in combination with weakness of gluteus maximus), small hand muscles (namely interossei palmaris and lumbricales) and/or neck flexors muscles. Simultaneous the discovery of atrophy of triceps brachii and quadriceps muscles without reduction of their strength and with the excessive folded the skin over these muscles due to subcutaneous fat atrophy made the supposition about TM probably.

Consequently, the data obtained by us, especially the pattern of muscular weakness and atrophy give the possibility to suppose the presence of thyrotoxicosis before its evident clinical manifestations since TM in many cases could be the earliest sign of the developing thyrotoxicosis.

In literature there are sharply controversial opinions on relationships of TM with duration and severity of thyrotoxicosis. Some authors suppose that severity of thyrotoxicosis does not correlate with degree of myopathy (34, 28, 36) but it is tightly connected with duration of thyrotoxicosis [20, 38]. Some other ones

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have different point of view: heavy myopathy is being develop only for short duration but under severe thyrotoxicosis (2, 4). The third group of authors does not agree with the opinions of the first and second groups of authors: by their opinion the development of TM as well as its degree does not correlate with severity and duration of thyrotoxicosis (1, 6, 21, 23, 30, 33). Our data confirmed this last point of view.

We never discovered the strict relationships between the degree of myopathy, on the one hand, and the severity and duration of thyrotoxicosis, on the other hand. No dependence of the severity of myopathy on the level of thyroid gland enlargement and pronouncement of ocular signs of thyrotoxicosis was established also.

Nosedá [50] supposed that the period of development of myopathy in thyrotoxic patients was very difficult and may be impossible to be determined.

However we could establish that in the majority of our patients the myopathic symptoms developed during 6 – 7 months from the onset of thyrotoxicosis. This corresponds to Ramsay's data [23] obtained.

In histological study of skeletal muscle were found myopathic changes. Similar data for human TM have been obtained by other authors (38-40). The percentage of affected fibers was a very small, the degenerative changes were of focal nature and the fiber mean diameter was decreased only by 26.6% as compared to the control. These morphological changes were not so extensive as to be the reason of muscle weakness and motor disorders. Same histological changes were found in muscle of thyrotoxic patients without clinical muscular weakness.

Changes in terminal motor innervation were found to be similar abnormalities in patients with thyrotoxic myopathy and muscular dystrophies (21, 41-44). No damage of intramuscular axons without signs of true reinnervation was found. Those changes of terminal motor innervation as well as swelling and spherical expansion ("vacuole") are secondary to morphological changes in muscle fibers and could be caused by the disturbed function and degeneration of the muscle fibers (44, 45). These changes are not specific for TM.

Our EMG data are similar with results for human TM obtained by other investigators (46-51) and

correspond to EMG "myopathic" criteria (52). The disturbance of muscle electrogenesis was weak. Mean amplitude and mean duration of MUP was decreased only by 15.4 and 12.4% in biceps brachii muscle, and by 8.9 and 7.4% in vastus lateralis, respectively as compared to the control. The conduction velocity of the ulnar nerve was not decreased. No abnormalities of nerve conduction in TM patients also were found by other authors (53-55). The neuromuscular transmission was normal. These data agree with results obtained by other investigators (56, 57).

Thus, we cannot establish the signs of affection of lower motor neurons, which can be the organic reason for appearance of transient muscular weakness in TM patients. The EMG study indicates slightly primary muscular disorder.

The level of ATP and creatin phosphate in skeletal muscle of TM patients appears to be normal (7, 8). Data about uncoupling of oxidative phosphorylation in mitochondria from muscle of thyrotoxic patients could not be substantiated (58-60, 61-62). Therefore, the disorders of energetic metabolism in skeletal muscle are not chief in development of muscular weakness.

However in our experimental model TM in mice was found disorders of cyclic nucleotide system in skeletal muscle: a decrease in protein kinase affinity to cAMP with simultaneous decrease in cAMP (64-66).

Obtained data allowed to advance the hypothesis of the mechanism of muscular weakness in experimental TM (64-67, 72): the reduction in efficiency of cAMP-dependent regulation of  $Ca^{2+}$ -active transport through the SR membranes, the decrease in the rate of  $Ca^{2+}$  uptake by SR vesicles, that result in the impairment of contracting-relaxing mechanisms of muscle fiber; it is the disturbance of Ca metabolism that can lead to the "transient block of muscle fibers" (52) and to the "reduction in the number of functioning muscle fibers" (68, 69).

However, it is well known, that a many data received in experimental animals perfectly may be used in studies of pathogenesis of human neuromuscular diseases (70). All the more these does to concern model of thyrotoxicosis. Created model of TM fully approaches similar pathology in man: in thyrotoxic

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patients as well as thyrotoxic mice there is a common (unity) cause for developing of myopathy- excess of thyroid hormones. Changes in muscle fibers and in terminal motor innervation in skeletal muscle of TM patients were found to be similar abnormalities in TM mice (65, 66, 71, 72). Human and animal TM also revealed identical distribution in membranes of the T-system, mitochondria and sarcoplasm (40, 62). Apparently, thyroid hormones have some "targets" and affect similar ways in TM skeletal muscle in man and animal.

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This investigation had not the financial (or sponsor) supports.

### Conflicts of Interests

All authors are not conflicts of interests between them.

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