Myotonic Dystrophy: Lack of Correlation Between CTG Expansion and Thyroid and Carbohydrate Status

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Abstract
Two groups of patients affected by Myotonic Dystrophy (MD) were studied. The first group (33 subjects) performed a morpho-functional evaluation of the thyroid by assessment of thyroid hormones and echotomography, in the second group (38 subjects) glucose metabolism (by OGTT) was evaluated.

All patients showed a normal hormonal thyroid pattern. The incidence of thyroid nodules, single or multiple, resulted 54.5%, significantly higher than in control group (16.1%) (p < 0.003) and their incidence was similar in both sexes contrarily to what occurs in normal population. We did not find any correlation between CTG expansion and nodule incidence or their volume.

The mean glycemic values after glucose administration resulted similar to those observed in controls; both basal and stimulated insulineamic values resulted higher than controls (p < 0.001); these findings demonstrate the occurrence of a reduced peripheral insulineamic tolerance. We found a direct correlation between insulineamic values (at 90 and 120 minutes) and entity of muscular involvement (score) with a p < 0.018. No correlation exists between these values and entity of genetic damage. We retain therefore that the glucidic alteration represents a complication likely due to reduction of muscle mass and in particular of the type I muscle fibers.

Key words: myotonic dystrophy, CTG expansion, thyroid nodule, glucose metabolism.

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In myotonic dystrophy (MD), the great variability of the CTG triplet expansion (always higher than in normal population) at the 3’ untranslated region of a protein-kinase (myotonin, MT-PK) gene, mapping to chromosome 19, is responsible of the more or less severity of muscle impairment [26] and correlates with onset of symptomatology [19]. Furthermore both cardiac disturbances [24] and cerebral symptoms [7] are more evident in the subjects showing a higher expansion. We have already demonstrated a significant relationship between several hormonal and clinical parameters [22, 27], related to male hypogonadism, and the CTG triplet number. These findings suggest that these aspects (psychological, testicular and cardiac) are an integrant part of the disease and correlate to the size of expansion.

This does not mean, obviously, that all the observed and described symptoms in myotonic dystrophy have the same value. To define the exact limits of this poliedric disease, it is therefore necessary that the comparison between the alterations of the different districts and the genetic abnormality is studied.

Among endocrinological disturbances, thyroid function and glucose metabolism have been studied and in particular nodular goitre [10], hyperinsulinism and diabetes mellitus have been reported [3, 17].

We have re-evaluated these aspects to establish if the eventual abnormalities are linked to entity of the expansion and/or to severity of muscular involvement.

Materials and Methods
82 (48 male and 34 female) MD patients were studied. In most patients the diagnosis was made by electromyography, muscle biopsy and in all cases DNA expansion by Southern blot and PCR methods was assessed in the Genetic Centre of the University of Rome “La Sapienza”.

In all subjects age of onset of the disease was determined and the entity of the muscular impairment has been evalu-
Thyroid and carbohydrate status in MD

ated according to the Matheus criteria (MDRS) and in each patients a score (from 1 to 5) has been determined [23].

In all cases we found one hyperthyroid subject treated by metimazole, 3 patients (2 male and 1 female) have been submitted to sub-total thyroideectomy for colloid goitre and another female patient underwent total thyroideectomy for a papilliferous thyroid carcinoma when she was 35 years old. A female patient, during the pregnancy, suffered from diabetes mellitus. These subjects and another patient who was takingestro-progestin drug have been excluded from the specific group study. No one patient suffered from diabetes mellitus. 20 subjects were not submitted to either thyroid echography or to OGTT. The choice of the subjects submitted to our study has been casual. The analysis in the two different endocrinological aspects were made in a short time and they were not contemporary.

- Morpho-functional thyroideal study: 33 subjects (21 male and 12 female) mean age 37.6 ± 11.9 years, CTG expansion of 712 ± 408 and a score of 2.5 ± 0.9 were studied (Group A).

- Glucose metabolism study: 38 subjects (24 male and 14 female), mean age 38 ± 11 years, CTG expansion 650 ± 375 and a score of 2.5 ± 0.9 (Group B).

Group A

In all subjects a thyroid echotomography by a linear 7.5 MHz probe (Esaote Biomedica “Idea”) was performed. Serum T3 and T4 by RIA kits and serum fT4 and TSH (by MEIA) were assessed. Thyroid antibodies to thyresglobulin (TG) and microsomes were measured by indirect immuno-fluorescence method. As control group we used 31 healthy subjects matched for age (20 male and 11 female) who were living in Padua.

In 6 patients a cytological examination collected by FNAB was performed.

Group B

An oral glucose tolerance test (OGTT) was performed in all patients according to the WHO criteria: blood was drawn before and 30, 60, 90 and 120 minutes after 75 g of glucose administration (per os) for the measurement of glycemia and serum insulin.

In all subjects antibodies to pancreatic isle cells were measured. As control group we used 31 healthy subjects matched for age (20 male and 11 female) who were living in Padua.

In 6 patients a cytological examination collected by FNAB was performed.

Group A

TSH and thyroid hormone levels assessed in 33 patients were in normal range.

In two subjects antibodies to TG and microsomes were detectable (1:400 in the first and 1:100 in the second patient).

Thyroid echotomography revealed the presence of single or multiple nodules in 54.5% of patients (18 out of 33) for a total of complessive 33 nodules. 9 subjects showed a single nodule while the other 9 patients presented two or more nodules. 24 nodules had a diameter < 10 mm, 7 showed a diameter between 10 and 20 mm and one nodule had a diameter > 20 mm. 67% of the nodules had a hypo or isoechogenic structure while the 17% resulted anechoogenic (fig. 1). Among the control group 5 subjects (16.1%) presented an echotomography positive for nodules (7 nodules in all), no one nodule showed a diameter greater than 10 mm.

The MD patients showed either a greater incidence of nodules or of multinodular goiter or nodules having a diameter more than 1 cm than in control group (respectively $x^2 = 8.6, p < 0.003$, $x^2 = 4.5, p < 0.03$ and $x^2 = 7.7, p < 0.005$).

Noteworthy we did not find any difference in the incidence of nodules in MD patients related to sex unlike in controls and general population which show a higher incidence among women, also in endemic areas, than in men.

The distribution is shown in detail in fig. 1.

6 patients (2 male and 4 female subjects) showing hypoechogenic nodules with a diameter greater than 1 cm, were submitted to FNAB: in five of them a diagnosis of colloid goitre was made. In one male subject the cytologic finding was consistent for follicular neoplasm and he was
Thyroid and carbohydrate status in MD

 submitted to thyroid lobectomy and the histological examination confirmed the presence of a follicular thyroid adenoma (fig. 2).

Group B

In our cases we did not find any patient suffering from diabetes mellitus. Our data are shown in fig. 3. The OGTT showed a mean value of glycemia at 120 minutes following the glucose administration higher compared to controls (p < 0.01); the other values did not show any difference compared to control group. The mean insulinemic values, both basal or after stimulus, were significantly higher than in controls (p < 0.001). No one showed antibodies to pancreatic isle cells.

Comparison with molecular expansion and muscle score

The CTG triplet number among the MD patients showing thyroid nodules was 709 ± 511 without any statistical difference with subjects without nodules (715 ± 314). The mean score was 2.7 ± 0.9 in the first patients and 2.3 ± 0.9 in the second. As far as the subjects with greater or more nodules are concerned, we did not find any correlations with the parameters related to the severity of the disease.

None point of the insulinemic slope correlated significantly with the CTG expansion, while serum insulinemic values at 90 and 120 min after the stimulus showed a significant relationship with the score (r = 0.4, p < 0.018).

Discussion

MD patients rarely show hyperthyroidism [28, 34] which may worsen the muscular impairment, on the contrary a decrease in basal metabolic rate has been often found [6, 20] and some authors hypothesized the presence of a hypothyroidism [20]. The neuromuscular clinical syndromes associated to hypothyroidism are numerous; the most frequent is a diffuse hypertrophic myopathy predominantly to the limbs (Hoffman’s syndrome) [12] which in 5% of the cases is associated to pseudo-myotonia [16]. Venable and coll. [35] observed that in a MD patient affected by hypothyroidism, substitutive treatment induced a regression of the muscular deficit even if the electromiographic alterations were still present. In reality the finding of an evident hypothyroidism is also seen [5, 29] and the thyroid hormone parameters are in the normal range and most of the Authors are in agreement to consider the reduced basal metabolism as expression of the muscular hypotrophy rather than due to a decreased thyroid function [12]. Some Authors found also a hyporesponsiveness of TSH to TRH stimulation [15, 33, 30] and alterations not univocal in I uptake [9, 14].

Our hormonal study confirms the normal thyroid function in most MD patients. Hyperthyroidism was found in only one case and we consider that this finding (only a subject in the whole series) may be casual.

The most frequent thyroid disease described in literature is represented by colloid goiter [2, 21] but it is possible also to observe either unill nodular goitre and rarely differentiated thyroid neoplasms have been described [30]. Also in our series we found only a subject affected by thyroid neoplasm.

Nodular goitre incidence is present in 54.5% of our MD patients and results notably higher than that described in literature (18.5%) [17].

We also performed, for the first time, a systematic study by echotomography which obviously increases the possibility to discover nodules especially those showing little size [11]. It is noteworthy that we found an incidence of nodular goitre of 16% in the control group.

Our study over all demonstrated that large nodules are more frequent and it is confirmed by the finding that other three subjects out of 49 (in addition to the 33 patients submitted to our protocol) underwent thyroidectomy due to nodular goitre. These data support the high incidence of thyroid nodules in the MD patients.

The lack of correlation between CTG expansion or muscular score and nodule incidence or their volume seems to demonstrate the absence of any relationships both with the severity of the disease or with genetic defect.

It is surprising the occurrence of thyroid nodules, even voluminous, in male patients with an incidence similar to female sex. This is absolutely different to what occurs in control group. It is well known that, likely under favorable estrogenic action, women present a thyroid morbility remarkable higher than men. The same behaviour between the sexes that we observed, suggests the existence of a more important factor than the hormonal difference in determining the onset of thyroid disease.

It is known that in MD disease, CTG triplet expansion can show differences in various tissues and in fact a mosaicism characterized by a greater amplification in some tissues, namely muscles, and a reduced expansion in spermatozoa [22], has been demonstrated [4, 1].

The only study evaluating CTG triplet expansion in thyroid tissue in a patient submitted to surgery for diffuse nodule goitre demonstrated values 7 times higher than those found in lymphocytes [8].
If this finding could be confirmed, an increased incidence of thyroid nodules in MD patients without antibodies to TG or microsomes could be the expression of a higher severity of the genetic defect in thyroid tissue. This hypothesis needs further investigation.

Huff and coll. [18] were the first Authors who described in MD basal and stimulated hyperinsulinemia with glycemia in normal range; several Authors confirmed these data and they found hyperinsulinemic percentual values ranging between 40 and 80% [3] while in 16% of the patients it is possible to observe a reduced glucose tolerance [17]. These findings suggest the occurrence of peripheral insulin-resistance [13, 25, 31].

It has been demonstrated that there is not primary defect of the insulinemic receptor [32] and thus it has been hypothesized the existence of a reduced affinity due to membrane alteration around the receptor. It has been attributed to a diffuse plasmatic membrane defect considered as an important phenomenon in the pathogenesis of MD and of the diabetes mellitus in this disease.

We confirm the changes found by other Authors, but in our cases they are less evident: in our 82 studied patients we did not find any patient suffering from diabetes mellitus and we had a normal glucidic response to OGTT. However we found hyperinsulinemic values, either basal and after glucose load, and it can mean an insulin resistance.

It is surprisingly that hyperinsulinemic serum values do not correlate with entity of CTG triplet number while they show a significant relationship with muscular impairment (score) since muscular damage and genetic one correlate each other. Lack of correlation with expansion suggests that the eventual tendency to diabetes is not a typical expression of the disease but it is linked to the reduced muscular mass particularly of the type I fibers, which have a high oxidative capability and are insulin-sensitive. These fibers play the more important role in glucose uptake induced by insulin and they are more affected in MD.

In conclusion we confirm a frequent incidence of nodular goitre, especially in male subjects if compared to a normal population which does not seem related to muscle score or CTG expansion assessed in lymphocytes. We have now to verify if a change of expression of the gene responsible of the MD in thyroid tissue can be considered responsible for the endocrinological abnormalities.

Our data confirm also a hyperinsulinemic state which we do not consider as an integral part of the disease but due to a secondary abnormality such as the reduction of muscle mass.

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References

Thyroid and carbohydrate status in MD


