Hypothalamic-pituitary-testicular function in 70 patients with myotonic dystrophy


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ABSTRACT. Hypothalamic-pituitary-testicular function was studied in 70 patients with myotonic dystrophy (MD). The diagnosis was confirmed by electromyography. The mean age of the patients was 36.2 ± 13.2 yr and the duration of the disease was 11.17 ± 8.01 yr. Testicular atrophy (testes ≤ 12 ml on a Prader orchidometer) was present in 65.5% of patients. Fertility among married patients was 66.6%. Mean testosterone plasma levels were 438 ± 298 ng/dl vs 520 ± 185 ng/dl in the control group (P = NS). Basal plasma FSH and LH levels, and their response after the administration of 100 mcg of LH-RH were significantly increased although a wide dispersion was observed. Sperm count was carried out in 27 cases, showing a normal count in 7, oligospermia in 12, and azoospermia in 8 patients. Testicular biopsy was performed in 45 patients being normal in 2, showing mild testicular damage in 8, moderate in 14, and severe in 18; it was nule in 3 of them. A significant relationship between testicular atrophy and the sperm count (p < 0.01), testicular damage and testicular atrophy (p < 0.025), and sperm count and testicular damage (p = 0.017) was found. Basal plasma FSH and LH level were significantly related to the degree of damage in the testicular biopsy. All these findings indicate a primary testicular pathology, prevailing tubular over interstitial damage. We have not found any association between the duration of the disease and gonadal dysfunction.

INTRODUCTION

Myotonic dystrophy (MD) is a multisystemic disease characterized by myopathy and myotony, inherited as an autosomic dominant trait. Steinert in 1909 (1) pointed out the high frequency of testicular atrophy, subsequently reported by Druker (2), and Caughey and Saucier (3) in 80% of their patients, in association with sterility and few and mild clinical features of hypoandrogenism. In 1972 Harper et al. (4) reported high levels of basal serum LH and FSH and low levels of testosterone. These data were consistent with primary testicular failure. Several reports (5-7) have shown an increased FSH and LH response to LH RH stimulus.

Since 1975, when Febres et al. (8) presented 4 patients with hypogonadotropic hypogonadism, hypothalamic dysfunction has been suggested as the cause of hypogonadism. Barreca et al. (9) have proposed such a dysfunction as the cause of the abnormal circadian rhythm of gonadotropin secretion observed in some of their patients. Maher and Paridel (10) postulated that hyperprolactinemia could be the cause of hypogonadism.

The present study was designed to evaluate the hypothalamic-pituitary-testicular function in the MD in order to establish its possible association with the clinical, physical examination, spermographic and testicular biopsy data. It has also been studied the association between the duration of the disease and testicular damage.

MATERIALS AND METHODS

The study group included 70 male patients affected by MD a mean (± 50) age 36.2 ± 13.2 yr, range 13-60 yr. The diagnosis was confirmed by clinical physical examination, electromiographic, ophthalmoscopic, biochemical and hormonal data, as it was reported previously (11). The duration of the disease was 11.2 ± 8 yr (range 1-28 yr).

The patients were grouped arbitrarily attending the duration of the disease: 39 patients (55.7%) from 1
to 10 yr, 15 (21.4%) from 11 to 20 yr, and 11 (50.7%) with more than 20 yr. In 5 patients (7.1%) the precise duration was unknown.

The study protocol included a clinical and laboratory evaluation of hypogonadism. Thirty-five patients were single and 30 married, all of them were asked for fertility.

Testicular size was measured by Prader's orchiometer: testes \( \leq 12 \) ml being considered atrophic. Basal levels of testosterone, LH, FSH, and PRL, and LH and FSH after 100 \( \mu g \) of LH-RH at 0-20-40-60-90 and 120 min were determined between 08:00 and 09:00 h. Serum was separated and stored at -20 C until used.

The testicular biopsy was performed under local anesthesia in 45 unselected patients in accordance with the procedures established by the local Ethical Committee for Human Investigation Studies. The spermogram was proposed to all the patients but only 27 of them gave their permission, and 19 of these underwent to the testicular biopsy.

Testosterone, FSH, LH, and PRL were measured by radioimmunoassay (RIA) by double antibody techniques following the CEA IRE SORIN commercial kit with reference to FSH 68/39 MRC Mill-Hill, LH 60/40 MRC Mill-Hill, PRL 75/504 MRC IRP. The inter and intra assay coefficients were: testosterone 10% and 7.3%, LH 6.4% and 5.6%, FSH 4.5% and 4.1%, and PRL 9.3% and 7.5%, respectively. Twenty male subjects aged 23-45 yr were taken as normal control.

The spermogram was analyzed following the method described by Paulsen (12), considering normal when the motility and normal forms were more than 60%, and the spermatozoa number between 20 and 100,000,000/ml., oligosperma when the density dropped to less than 20,000,000/ml, and azoosperma when there were not observed any spermatozoa.

Testicular biopsy specimens were processed and stained with hematoxin-eosin, and then analyzed by the same pathologist and classified according to the degree of tubular damage. Thus, the tubular damage was arbitrarily arranged in 3 groups: a) mild: small patches of damage with thickening of the basal membrane and poor germinal tissue beside indemnes tubules with mature spermatozoa; b) moderate: areas of significative damage with almost total hyalinosis together with other areas of less damaged tissue, with germinal cells in different states of maturity; c) severe: almost total hyalinization with absence or great reduction of germinal tissue.

Student's \( t \) test was used for the statistical comparison of two samples. Association between qualitative variables was done by \( X^2 \) and relation between qualitative and quantitative variables was carried out by analysis of variance (ANOVA) followed by Scheffé's test. An IBM personal XT computer with a Sigma computer program based in Carrasco's statistical method was used (13).

**RESULTS**

Only 3 of the patients (4.2%) showed clinical data of hypoandrogenism. Twenty out of 30 of those married were fertile (66.6%), 9 sterile (30%), and in one case fertility was not ascertain. No study of paternity was made, and among the 35 single patients, nothing is known about their possible fertility. Testicular atrophy was present in 65.5% of the patients. Consistency was variable, most patients having soft and badly defined testicles.

Mean testosterone plasma levels were reduced in MD patients (438.4 ± 298.8 vs 520 ± 185 ng/dl in controls) although this difference was not statistically significant unless 3 patients with levels above 1,000 ng/dl were excluded. A great dispersion of data was observed (range 34-1,324 ng/dl) (Fig. 1). Mean basal FSH and LH plasma values were 23.3 ± 21.8 mU/ml and 10.8 ± 5.3 mU/ml in MD patients vs 7.2 ± 2.4 mU/ml and 4.6 ± 1.3 mU/ml in the control group \( (p < 0.001 \) in both). A great dispersion was observed (range 1.7-96 mU/ml for FSH and 2-34.5 mU/ml for LH) (Fig. 1). FSH plasma levels after LH RH was significantly greater than in the

![Fig. 1 - Values of serum testosterone, FSH and LH in patients with myotonie dystrophy (the framed area represents the mean ± SD for normal adult male subjects).](image-url)