TESTICULAR FAILURE IN DYSTROPHIA MYOTONICA

By

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The occurrence of testicular atrophy in the course of dystrophia myotonica has frequently been attributed to changes in the anterior lobe of the pituitary gland. Recently, (Caughey & Brown, 1950) evidence has been obtained suggesting that testicular atrophy in this condition may be due to primary failure of the gland. An increase in the understanding of the pituitary-gonadal relationship has opened the way to a more direct approach to the problem. In this study of four patients suffering from dystrophia myotonica, the testes were subjected to intense stimulation by chorionic gonadotrophin, whilst the response was judged by changes in urinary steroid output.

METHOD AND MATERIAL

The subjects for this study were four patients with dystrophia myotonica admitted to the wards of the University Department of Neurology, Manchester Royal Infirmary. All the patients were ambulant and were allowed to participate in the usual ward activities. In order to avoid any possible effect they may have had on 17-ketosteroid (17-KS) output, all other investigations and forms of treatment were suspended during the period of observation. Chorionic gonadotrophin was administered intramuscularly in a single daily dose of 3,000 I.U. for seven days. This scheme of dosage is similar to that used by Landau et al. (1951) and in our hands has previously proved to be an effective dose. Urine was collected, without preservative, in 24 hour aliquots. Analyses were usually performed immediately but on the rare occasions when a 24 hour delay was unavoidable, the specimen was kept in a refrigerator.

17-KS were determined by the method recommended in the report of the Medical Research Council committee on Clinical Endocrinology (1951). 17-ketogenic steroids by the method of Norymberski, Stubbs & West (1953). Urinary oestrogens were estimated by the biological method of Maddock & Nelson (1952).
CASE REPORTS

Case 1. R. C. Male aged 19:
Difficulty in relaxing his grip after voluntary grasping was the first manifestation of the disease at the age of sixteen. He was accepted for service in the Armed Forces at the age of 17 but was discharged nine months later from the Army with the diagnosis of dystrophia myotonica. His maternal grandmother suffered from bilateral cataracts and his mother suffered from typical dystrophia myotonica.
Examination revealed normal hair distribution, although the secondary sexual hair growth was thinner than normal. The body and limb musculature was only moderately well developed but wasting was obvious in the sternomastoid muscles. The facial muscles were weak giving the typical myopathic facies. Myotonia after voluntary movement was widespread and easily demonstrable after percussion in the thenar muscles, the proximal muscles of the limbs, and the tongue. The testes were of average size but soft to palpation. Slit lamp examination of the lens revealed a few atypical capsular lens opacities.

Investigations: The x-ray of the skull was normal.
Urinary gonadotrophins: 5 M. U./24 hours. Basal metabolic rate: + 5 %.
Kepler Test: negative.
Creatinine excretion: 899 mg./24 hours.
Creatine excretion: 27 mg./24 hours.

Case 2. M. S. Male aged 21:
The initial symptom of difficulty in relaxing the grip appeared at the age of 17. The disability had persisted up to the time of admission to hospital, four years later. The immediate cause of his admission was the occurrence of three attacks of unconsciousness which were considered to be epileptic in origin and investigations directed towards this aspect did not reveal any evidence of an underlying intracranial lesion. He claimed to be potent. There was no family history suggestive of either dystrophia myotonica or cataracts.
Examination revealed frontal baldness but the secondary sexual hair growth was normal in distribution. The facial muscles were weak and the sternomastoids were wasted. Myotonia after voluntary action was easily demonstrable in the hands. The testes were thought to be softer than normal but were of normal size.

Investigations: The x-ray of the skull showed some calcification of the petroclinoid ligaments. Urinary gonadotrophins – less than 7 M. U./24 hours. Basal metabolic rate + 10 %.

Case 3. J. B. Male aged 35:
At the age of 22 he was discharged from the Army because of a developing weakness in the right arm and both legs. After the initial onset of weakness there has been no noticeable change in muscle power over the next 11 years, although a steadily increasing baldness was noted. A year prior to admission to hospital he was unconscious for 14 days following a head injury and immediately afterwards he observed a marked deterioration of power in all four limbs. Although married for ten years there was no offspring and he had rarely had sexual intercourse. His elder brother was severely disabled by dystrophia myotonica and his mother suffered from cataracts.
Examination revealed almost complete baldness. Muscle wasting was generalized over the trunk and limbs and in the latter more marked in the proximal than the peripheral
groups. Myotonia was also generalized in the trunk and limb muscles. The testes were very soft in consistency and abnormally small.

**Investigations:** The x-ray of the skull was normal.
Urinary gonadotrophins 30 M. U./24 hours. Basal metabolic rate + 25%.
Creatinine excretion – 1160 mg./24 hours. Creatine excretion – 168 mg./24 hours.
Glucose Tolerance Curve – within normal limits.

**Case 4. I. M. N. Male, aged 45:**
Drooping of the eyelids was the first symptom to appear at the age of 38. Three years later difficulty in relaxing the grip was noted and a year later he complained of weakness of the upper arms, forearms and hand. This weakness was steadily progressive. He was separated from his wife and there had been no children by the marriage. There was no family history of significance.
Examination revealed frontal baldness and the classical myopathic facies. There was well-marked wasting of both the trapezi, the sternomastoid muscles, and the proximal muscles of the shoulder girdles. Myotonia was widespread both after voluntary movement and mechanical stimulation. The testes were of normal size but very soft to palpation.

**Investigation:**
The x-ray of the skull was normal.
Basal metabolic rate — 10%.
Creatinine excretion 730 mg./24 hours.
Creatine excretion 85 mg./24 hours.
Glucose tolerance test – within normal limits.

**RESULTS**

**17-ketosteroid excretion.** The mean control excretion rate of 17-KS was low or low normal in three subjects, i.e. 5.6 mg./24 hours in R. C. 4.3 mg./24 hours in subject M. S. and 3.6 mg./24 hours in J. B. In the case of I. M. N. the mean value of 9.2 mg./24 hours was within normal limits. During the administration of chorionic gonadotrophin there was a marked rise in excretion values in two subjects. In M. S. (Fig. 2) the value rose from 4.4 mg./24 hours to a maximum of 14.6 mg./24 hours. In subject I. M. N. (Fig. 4) there was an equally substantial rise from 9.0 mg./24 hours to a maximum of 17.4 mg./24 on the seventh day. In

![Graph](image)

*Fig. 1.* Subject R. C. Arrows indicate the administration of 3,000 I. U. chorionic gonadotrophin intramuscularly.
subject J. B. (Fig. 3) there was a very small increase which was not sustained throughout the injection period. There was no significant change in values in subject R. C. (Fig. 1).

**Oestrogen excretion.** The bio-assay of urinary extracts for oestrogens produced very small amounts in all cases. We have obtained yields four to five times greater in normal males. I. M. N. (Fig. 4) was the only subject in whom there occurred an unequivocal increase in oestrogenic activity with values rising from 1.0 to 2.3 mg./24 hours in terms of oestradiol benzoate. In case M. S. (Fig. 2) the peak value of 2.6 mg./24 hours is not appreciably different from the value of 2.2 mg. observed in the pre-injection period.

**17-ketogenic steroid excretion.** The estimation of urinary 17-ketogenic steroids was performed only in subject I. M. N. (Fig. 4). There was no increase in output during the administration of chorionic gonadotrophin.

**Eosinophils.** Daily eosinophil counts were performed in cases J. B. and I. M. N. (Figs. 3 and 5). No significant change was observed during the experimental periods.
DISCUSSION

Urinary 17-KS are metabolites of adrenal and testicular secretions. The low values observed in three out of four cases of dystrophia myotonica are in agreement with the findings of previous authors (Benda & Bixby, 1947; Caughey & Brown, 1950), but do not shed any light on the cause of the disorder.

Testosterone, a precursor of urinary 17-KS, is produced by the Leydig cells of the testes in response to the stimulus provided by the luteinizing hormone of the anterior lobe of the pituitary gland. Chorionic gonadotrophin has a similar effect on the testes (Maddok & Nelson, 1952; Landau et al., 1951), and its administration results, in normal males, in the outpouring of increased amounts of 17-KS in the urine. On clinical grounds it has been suggested (Albright et al., 1942), that luteinizing hormone has a stimulating action on the androgen producing mechanism of the adrenal cortex. In such circumstances, any increment in 17-KS output during the administration of chorionic gonadotrophin to a normal male, would represent the summation of the testicular and adrenal
responses. On the basis of total 17-KS estimation, it would then be impossible to differentiate between a dual response and a single response of either gland. The evidence on this point is highly circumstantial though Plate (1952) has demonstrated an increase in 17-KS excretion during the administration of chorionic gonadotrophin in a eunuch and an ovarietomized female. The dose given in these two cases was, however, far larger than is necessary for testicular stimulation and contamination with corticotrophins was not adequately excluded. In studies on castrated males (four cases), we have not so far observed an increase in 17-KS excretion after the administration of chorionic gonadotrophin in the present dosage.

Any increase in urinary 17-KS excretion after the administration of chorionic gonadotrophin in the present dosage can probably be justifiably attributed to a testicular response. An absence of change in excretion rates signifies refractoriness of the testes to hormonal stimulation since Maddock & Nelson (1952) have demonstrated a response in cases of testicular atrophy secondary to anterior pituitary failure.

In the present study chorionic gonadotrophin was administered intramuscularly to four cases of dystrophia myotonica. Two patients, M. S. and I. M. N. (Figs. 2 and 4) responded by a sharp rise in 17-KS output on the 2nd and 3rd day respectively. The increase is of the same order as that observed by Landau et al. (1951) in normal males. The testes in both cases were judged, on clinical examination, to be softer than normal but of average size. The size and consistency of the testes depend primarily on the state of the seminiferous tubules which occupy a very much greater volume than the combined Leydig cells and intertubular connective tissues. It seems, therefore, that in these two cases some degree of tubular degeneration had taken place at a time when the Leydig cells were still responsive to stimulation and, in case I. M. N. who excreted normal amounts of 17-KS in control periods, were still producing a normal amount of hormone in the absence of exogenous stimulation. A clinical study led Heller & Nelson (1945) to believe that a similar sequence of events occurs in puberal seminiferous tubule failure (Klinefelter's syndrome). There is little information concerning the histology of the testes in dystrophia myotonica but Nadler et al. (1950), considered the appearances to be similar to those seen in puberal seminiferous tubule failure.

No significant change in the rate of excretion of 17-KS was observed in cases R. C. and J. B. (Figs. 1 and 3). In one case (J. B.) the testes were very small and soft, but in the other (R. C.) they were soft without any clinical change in size. The Leydig cells in these two cases were completely unresponsive to stimulation by exogenous gonadotrophins. It is probable, therefore, that a similar state of refractoriness existed in relation to the patient's own pituitary gonadotrophin. A comparable failure of the ovary occurs at the menopause and is associated with an increased excretion of gonadotrophins in the urine.
Caughey & Brown (1950) found such increased excretion in dystrophia myotonica but in one of the patients reported by Benda & Bixby (1947) the values were normal despite the presence of testicular atrophy which was confirmed at autopsy. Normal values were found in the patients we are reporting here and others unpublished. In these patients there was no obvious relationship between the age of the patient or the duration of the disease and the existence of testicular failure. It seems that at some stage during the evolution of dystrophia myotonica, the androgen producing cells of the testes fail to respond to the normal stimulus from the anterior lobe of the pituitary gland. The atrophy of the seminiferous tubules may precede the Leydig cell failure by an unknown interval and is, therefore, not the result of a deficiency of androgens. Both phenomena arise from an intrinsic defect of the testes and are presumably genetically determined.

The data on urinary oestrogen excretion are included because of the claim of Maddock & Nelson (1952) that the urinary oestrogen response to chorionic gonadotrophin administration is a more sensitive index of testicular function than 17-KS excretion. All the control values were low but absolute values are probably of little significance when obtained by this biological method. Sustained alterations in output are probably more informative. During the administration of chorionic gonadotrophin no changes in output were observed in cases R. C., M. S., and J. B. In case I. M. N., however, there was a definite increase in oestrogen output and it is interesting to observe that, in addition to a 17-KS response during the experimental period, this patient also had a 17-KS output within normal limits during control periods. It seems probable that the findings in this patient represent a very early phase in the development of gonadal atrophy.

The site of origin of oestrogens within the testes, has not been determined with any certainty but since there is evidence that they may be produced by the Sertoli cells of the tubules, the urinary oestrogen response to our experimental procedure may correlate with the state of the seminiferous tubules rather than with Leydig cell function.

The absence of eosinophil depression on cases M. S. and I. M. N. and the absence of increase in 17-ketogenic steroid output in case I. M. N. confirm, to some extent, that there was no increase in adrenocortical secretion during the injection periods and are added confirmation that the increases in 17-KS output, observed in two cases, were entirely of testicular origin.

The occasional simultaneous occurrence of diabetes mellitus, goitre and gonadal atrophy in dystrophia myotonica led earlier observers to seek an explanation for these phenomena in the pars anterior of the pituitary gland. Apparent support for this view was obtained when histological changes were observed in this gland. Adie & Greenfield (1925) found an increase in colloid material in the pars intermedia and pars anterior, whilst others (Benda & Bix-
by, 1947; Jager, 1951) described «pituitary basophilism» and cyst formation. Although the existence of changes in the anterior lobe are well authenticated there is no a priori reason to attribute to them a leading role in the endocrine dysfunction seen in this disease. Adrenocortical carcinoma producing Cushing’s syndrome is frequently associated with Crooke’s changes in the anterior lobe of the pituitary gland, but it is generally conceded that they are the result and not the cause of the increase in adrenocortical hormone production. Similarly, castration results in the appearance of castration cells in the anterior lobe. Recent detailed studies (Farquhar & Rinehart, 1954) of anterior pituitary cytology in rats, have demonstrated morphological changes in certain basophils cells after castration. These changes include enlargement, vesiculation and alterations in granular content. From an endocrinological point of view, primary atrophy of the testes is equivalent to surgical castration and might, therefore, be expected to lead to secondary pituitary changes. In any case, the existence of these changes does not necessarily conflict with the view that the testicular failure is a primary atrophy.

SUMMARY

The endocrine function of the testes has been investigated in four patients with dystrophia myotonica. The urinary excretion of 17-ketosteroids and oestrogens was used as a guide to testicular hormone production during stimulation with chorionic gonadotrophin. The testes in two patients failed to respond to hormonal stimulation. A partial and a normal response was obtained in the other two patients. These results suggest that testicular failure occurring in the course of dystrophia myotonica is not necessarily dependent on changes in the pituitary gland.

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