GROWTH HORMONE RESPONSES TO HYPOGLYCAEMIA IN WOMEN WITH SECONDARY AMENORRHOEA

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Summary. Growth hormone (HGH) responses to insulin-induced hypoglycaemia were examined in sixteen normal women and twenty-eight women with secondary amenorrhoea. A normal response (blood levels rising above 10 ng/ml) was found in fifteen of sixteen (94%) of the controls but in only nineteen of twenty-eight (68%) of the patients with amenorrhoea. Oestrogen administration induced a normal response in only two out of six patients with a previously abnormal result. The patients with subnormal HGH responses all had a low gonadotrophin excretion, but tests of thyroid and adrenocortical function were normal and pituitary fossa X-rays were normal. This tendency to a poor HGH response must be taken into account when screening amenorrhoeic patients for pituitary tumours.

INTRODUCTION

Women who present with local signs of a tumour in the pituitary region frequently give a long history of amenorrhoea. It would seem desirable, therefore, to examine pituitary function in cases of secondary amenorrhoea for which no cause has been found. Since deficient production of growth hormone (HGH) and gonadotrophins often precedes diminishes secretion of ACTH and TSH in compression lesions of the pituitary (Rabkin & Frantz, 1966), tests should include an HGH response to hypoglycaemia and a gonadotrophin assay. In the course of this study, however, it was found that patients with secondary amenorrhoea and a low gonadotrophin excretion frequently show an absent or sub-normal response of HGH to hypoglycaemia but no other clinical, biochemical or X-ray evidence of a pituitary tumour.

MATERIALS AND METHODS

The twenty-eight women with amenorrhoea had absence of periods for more than 6 months (age range, 18 to 34 years). Six of these had 'post-pill' amenorrhoea: no cause was discovered in the others. Hypoglycaemia was induced by
the intravenous injection of 0.1 U soluble insulin/kg body weight: HGH was estimated by a solid phase radioimmunoassay system (Abbott Laboratories). Results are reported in terms of the Abbott standard for HGH, 1.0 ng of this being equivalent of 1.25 ng of the WHO standard 66/217. Glucose was estimated by a glucose oxidase method, serum thyroxine by the method of Murphy & Jachan (1965), and serum cortisol (09.30 to 10.00 hours) by the method of Rudd, Sampson & Brooke (1963). The ACTH reserve was measured by the excretion of 17-hydroxycorticosteroids (17-OHCS) and 17-oxosteroids before and after the administration of metyrapone (500 mg 4-hourly for six doses), and urinary total gonadotrophins by the bioassay procedure of Johnsen (1958). Total oestrogens in the urine were estimated by the method of Ittrich (1960). All the patients had a lateral X-ray of the pituitary fossa. In thirteen cases, the volume of the fossa was measured by the technique of Di Chiro & Nelson (1962).

The controls were sixteen women, informed volunteers from the hospital staff, with no history of menstrual irregularity; the age range was 20 to 32 years.

The hypoglycaemic response was considered satisfactory if the blood glucose fell to 50% of the initial level or to below 50 mg/100 ml. A positive HGH response was one in which the level rose above 10 ng/ml. In five of the amenorrhoeic women, the HGH response was positive although the criteria for hypoglycaemia were not fulfilled; these cases were included. In six of the patients with a poor HGH response, the test was repeated after treatment with stilboestrol, 10 mg twice daily for 4 days.

**Text-fig. 1.** Peak growth hormone responses to insulin-induced hypoglycaemia in twenty-eight patients with secondary amenorrhoea and sixteen controls.
RESULTS

Of the twenty-eight women with amenorrhoea, nine (32%) failed to show a positive HGH response: this group included two of the six 'post-pill' patients. All nine patients with a poor HGH response had a gonadotrophin excretion of less than 12 M.U.U./24 hr (4 M.U.U. are equivalent to 1/40 of an ampoule of the 2nd IRP-HMG); eight of the amenorrhoeic patients with a positive HGH response had levels above 12 M.U.U./24 hr, while the remaining eleven patients had a positive HGH response but gonadotrophin excretion was below 12 M.U.U./24 hr. Serum cortisol, serum thyroxine, urinary 17-OHCS and 17-oxosteroids and metyrapone responses were normal, and the skull X-rays were normal in every case. Urinary excretion of total oestrogens in the amenorrhoeic group ranged from 3·3 to 65·4 µg/24 hr (mean 24·2 µg).

The degree of response of HGH in the control and amenorrhoeic women is shown in Text-fig. 1. As a group, the patients with amenorrhoea did not respond as well as the controls (P<0·01). Oestrogen treatment only produced a normal response of HGH to hypoglycaemia in two of the six patients who agreed to the repeat test.

DISCUSSION

Several factors may be involved in the poor response of HGH to insulin hypoglycaemia in our patients with amenorrhoea. The mean degree of hypoglycaemia was greater (P<0·001) in the control group than in the amenorrhoeic patients, the percentage falls in the blood glucose being 66·4±7·0 and 50·1±12·4, respectively. The mean body weight of the amenorrhoeic patients (50·5±12·6 kg) was less than that of the controls (61·3±10 kg) and, consequently, they were given less insulin. On the other hand, the poorer hypoglycaemic response to insulin might be due to a specific hormonal factor. It has been shown that oestrogen therapy in acromegalic women increases the hypoglycaemic response to insulin (Mintz, Finster & Josimovich, 1967). In the present series, the total oestrogen excretion in the amenorrhoeic patients was low or in the low part of the normal range and possibly this may have been a factor in causing the smaller falls in blood glucose. In four of the patients re-tested after oestrogen administration, there was a greater hypoglycaemic response to insulin. In the other two patients, there was no change in the decline in blood glucose.

Another factor in the poor HGH response might be the direct effect of the lower level of oestrogens in the amenorrhoeic women. Oestrogens are known to increase the response of HGH to exercise in men (Frantz & Rabkin, 1965), and to insulin hypoglycaemia in children (Lippe, Wong & Kaplan, 1971). The variation in the response to arginine infusion in normal women during the menstrual cycle (Merimee, Fineberg & Tyson, 1969) is compatible with this explanation, but although patients with Turner's syndrome would certainly have a low oestrogen secretion, normal responses to hypoglycaemia have been recorded in the majority of cases (Lindsten, Cerasi, Luft & Hultquist, 1967; Donaldson, Wegienka, Miller & Forsham, 1968). In the present investigation, there was no correlation between the oestrogen excretion and HGH responses or the degree of hypoglycaemia in the amenorrhoeic women. Furthermore,
administration of oestrogen only converted the HGH response to normal in two of the six re-tested patients.

A further possibility is that some of the patients with amenorrhoea have a basic defect in the hypothalamus which is responsible both for the amenorrhoea and for the tendency to poor HGH response (Spellacy & Carlson, 1968). In the present series, the fact that the nine patients who failed to respond to hypoglycaemia all had low gonadotrophin excretion is consistent with this hypothesis, but there was no correlation between HGH responses and gonadotrophin excretion in individual cases. Spellacy & Carlson (1968) favoured a hypothalamic cause for the blunted HGH response in cases of secondary amenorrhoea because they found a correlation with subsequent ovulatory response to clomiphene. In our small series of ten patients treated with clomiphene, HGH responses were of no value in predicting the response to clomiphene. One of the patients with a poor response menstruated spontaneously 6 months after investigation.

In the screening of patients for organic pituitary disease, it is clearly important not to base a diagnosis only on the absence of gonadotrophins and poor HGH response to hypoglycaemia. Administration of oestrogen before the HGH test as suggested by Lippe et al. (1971) for children does not seem to be a practical advantage in adults.

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REFERENCES


