The Role of Releasing Hormones in the Diagnosis of Hypopituitarism

AN ANALYSIS OF 9 PATIENTS

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SUMMARY

Luteinising hormone-releasing factor and thyrotrophin-releasing factor were used in conjunction with the insulin tolerance test in 9 patients with known or suspected panhypopituitarism. It appears that growth hormone and luteinising hormone fail early in panhypopituitarism. Cortisol and thyroid-stimulating hormone production fail later. On the basis of this study, it is suggested that luteinising hormone-releasing factor, alone or combined with thyrotrophin-releasing factor, may prove a suitable sensitive screening test of pituitary function in patients with panhypopituitarism due to pituitary tumour or occurring after radiation therapy. The hypothalamic type of response seen after administration of the two releasing factors in many of the patients in this series who had had radiation therapy to the pituitary gland, suggests that hypothalamic damage may follow this form of therapy.

S. Afr. Med. J., **48**, 1612 (1974).

During the past decade the recognition, isolation and synthesis of hypothalamic releasing factors has opened new horizons in the understanding of hypothalamic-pituitary interactions. More particularly, the availability of luteinising hormone-releasing factor (LHRF) and thyrotrophin-releasing factor (TRF) has widened the diagnostic approach to the investigation of hypopituitarism.

It is widely quoted in standard texts[1] and reviews[2] of the pituitary gland that there is a progressive selective loss of anterior pituitary function in lesions of the pituitary gland in the following order: (*i*) gonadotrophins, (*ii*) growth hormone, (*iii*) ACTH or TSH. This observation is based on extensive clinical experience. Combined testing of reserves of human growth hormone (HGH), cortisol, luteinising hormone (LH) and thyroid-stimulating hormone (TSH) in various degrees of hypopituitarism should confirm this concept.

Until recently the primary diagnostic procedure utilised in the assessment of panhypopituitarism was the HGH and cortisol response to insulin-induced hypoglycaemia.[3] An alternative, less stressful means of screening patients with pituitary disease may prove useful. Both LHRF and TRF administration are harmless and virtually free of all side-effects.[4,5]

In order to investigate these possibilities we have analysed 'total' pituitary function in 9 patients presenting with hypopituitarism.

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Date received: 17 April 1974.

PATIENTS AND METHODS

Nine patients with known or suspected panhypopituitarism were admitted to the study. The clinical features are listed in Table I. Seven of the 9 patients had proven pituitary tumours treated by radiation therapy with or without surgery, and these 7 patients were already on long-term thyroid and corticosteroid replacement. In these instances

TABLE I. CLINICAL DETAILS OF PATIENTS STUDIED

Patient	Age	Sex	Presenting feature	Diagnosis	Treatment
1	67	F	Headache	Pituitary tumour	Radiation therapy
2	47	M	Visual disturbance	Pituitary tumour	Surgery and radiation therapy
3	33	M	Headache and weakness	Pituitary tumour	Surgery and radiation therapy
4	47	F	Headache	Pituitary tumour	Radiation therapy
5	50	F	Visual disturbance	Pituitary tumour	Surgery and radiation therapy
6	23	F	Amenorrhoea	Idiopathic hypopituitarism	Nil
7	34	M	Headache and visual disturbance	Pituitary tumour	Surgery and radiation therapy
8	38	M	Weakness	Sarcoidosis of pituitary	Nil
9	26	F	Headache	Malignant chordoma of pituitary	Surgery and radiation therapy

thyroid replacement was withheld for six weeks and the corticosteroid replacement was withheld for one week, under observation, prior to testing. In patient 9 it was considered inadvisable to withhold corticosteroids and therefore cortisol measurements could not be performed.

The following tests were performed:

Standard insulin tolerance test,[3] using 0,1 - 0,15 units/kg body weight soluble insulin, with measurement of serum HGH and cortisol response basally and at 30, 60 and 120 minutes. Blood was withdrawn via an indwelling venous catheter. In all cases adequate hypoglycaemia was attained, i.e. the blood sugar decreased to below 40 mg/100 ml.

LHRF was given as a 200-μg intravenous bolus, and blood was withdrawn for serum LH estimations basally and at 30, 60 and 120 minutes.

TRF was given as a 200-μg intravenous bolus, and blood was withdrawn for serum TSH estimations basally and at 20, 40 and 60 minutes.[5]

Serum HGH, LH and TSH were measured by a double-antibody radio-immunoassay technique using kits supplied by CEA-Sorin. Serum cortisol was measured by a competitive protein-binding assay.[6]

In the first 5 patients, the three tests were performed on three consecutive days, but following the demonstration that these tests may be combined without interference with the various responses,[7,8] the remaining 4 patients were investigated by combining the three tests over a single two-hour period.

RESULTS

The results obtained are graphically illustrated in Fig. 1. A wide variation in response was obtained. With the exception of patient 5, who had no biochemical evidence of hypopituitarism despite pituitary surgery and radiation therapy 12 years previously, the patients showed various degrees of pituitary hypofunction. In all but 1 patient, HGH and LH function were similarly impaired, but in patient 8 there was HGH loss with some LH reserve still present. In all 8 patients with pituitary dysfunction, HGH and LH failed before cortisol and TSH.

In 4 of the patients who had had radiation therapy to the pituitary gland, the pattern of the TSH response was abnormal in that there was a delay in the peak response and a delayed return to basal levels. This type of response is highly suggestive of hypothalamic dysfunction.[9]

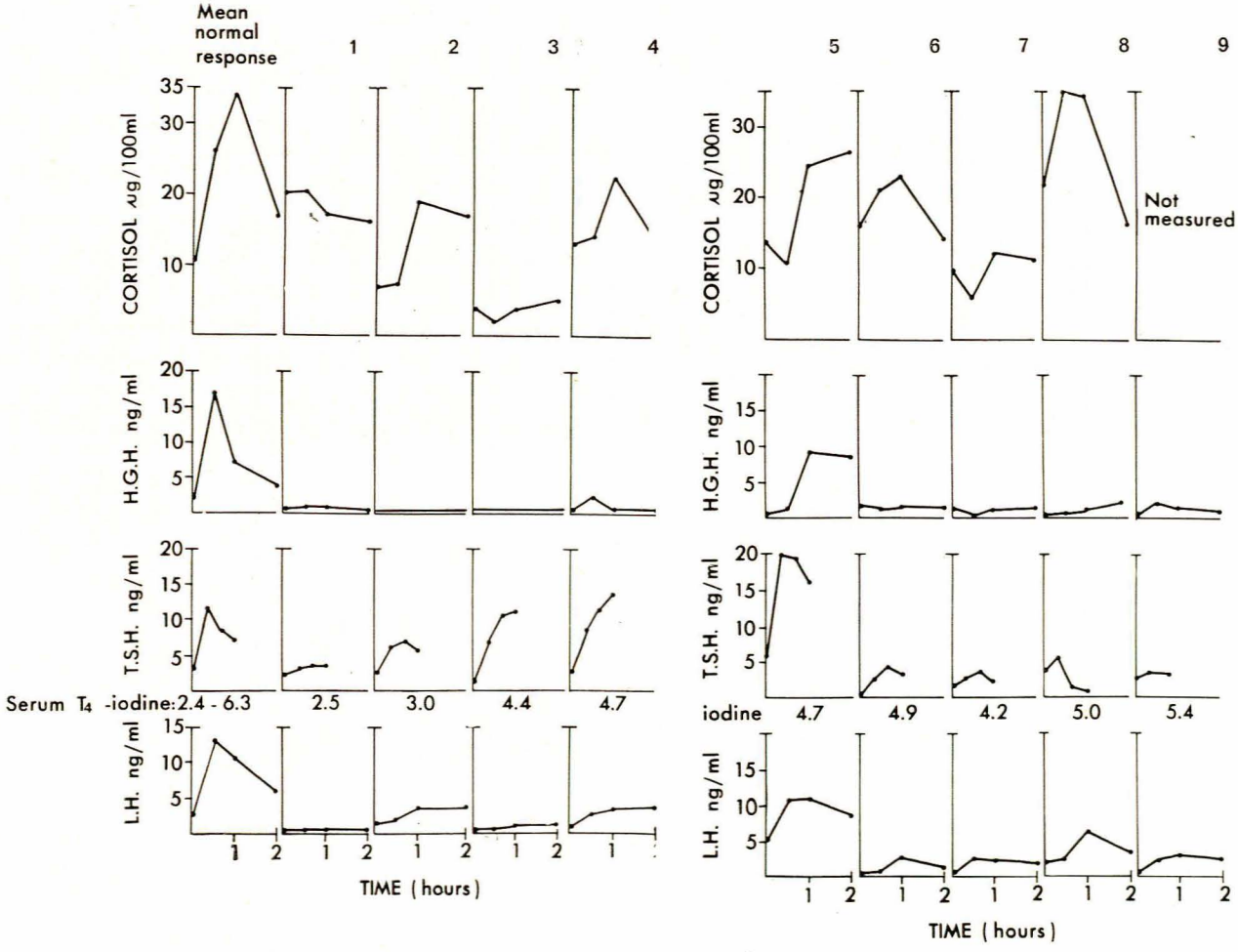

Fig. 1. Pituitary responses to stimulation tests (T_4-iodine measured in μg/100 ml).

DISCUSSION

This series demonstrates that HGH is probably the first hormone to fail in hypopituitarism. It appears to be closely related to failure of LH secretion, but preceded it in 1 of our patients. As anticipated on clinical grounds, TSH and ACTH loss occurred later.

The TSH response to TRF has been shown to be an extremely sensitive test of thyroid function,[10] but nevertheless it is interesting to note that the serum T_4-iodine may remain well within normal limits, in spite of obviously failing TSH secretion. This would suggest that routine serum biochemistry is a very poor measure of thyroid reserve in patients with hypopituitarism, a finding which has also been documented by Hajjer *et al.*[10]

The insulin tolerance test is contra-indicated in patients with ischaemic heart disease. It is difficult to perform in the presence of diabetes mellitus and the HGH response may be impaired in patients with obesity,[11] psychological growth retardation,[12] and delayed puberty.[13] The test is unpleasant and not without hazard. Furthermore, in patients who have been on prolonged corticosteroid replacement, the duration and degree of pituitary corticotrophin suppression is unpredictable, and this may make interpretation of a poor cortisol response to the insulin tolerance test difficult.

For all these reasons an alternative, harmless and easily administered sensitive screening test of pituitary function would be useful in cases of suspected panhypopituitarism. On the basis of the results presented it is suggested that measurement of the LH response to LHRF may fulfil many of the necessary requirements. Should the pituitary respond adequately to the intravenous administration of LHRF, this would virtually exclude early hypopituitarism due to pituitary tumour or after radiation therapy. However, a flat LH response to LHRF would require further extensive investigation to determine the extent of pituitary disease and to exclude hypothalamic disease, since it has been well demonstrated that prolonged hypothalamic malfunction may produce a pituitary gland non-responsive to LHRF.[14]

At the other end of the spectrum, a TRF stimulation test may be useful as a marker of the degree of panhypopituitarism. An absent TSH response to TRF would be suggestive of total panhypopituitarism.

It may therefore be recommended that in cases where the insulin tolerance test is contra-indicated or difficult to interpret, a combined LHRF/TRF test could suffice as an alternative means of assessing the two extremes of the pituitary hormonal production spectrum.

The hypothalamic type of hormonal response seen in many patients who underwent radiation therapy to the pituitary fossa may imply hypothalamic radiation damage and tends to confirm previous reports that external radiation therapy of the pituitary fossa may result in hypothalamic destruction.[14] This highlights the importance of lumbar air encephalography in all cases of pituitary tumour, in order to localise more accurately the extent of the neoplasm and thereby make radiation therapy more accurate in an attempt to avoid damage to surrounding tissues.

We wish to thank Ayerst International (SA) for supplying LHRF and Roche Products (Pty) Ltd for the TRF used in this study.

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