

Diagnosis of Hypopituitarism in Childhood

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The diagnosis of hypopituitarism in childhood, particularly in the idiopathic type, has been a matter of great difficulty. Growth retardation is the constant presenting sign, and since this is a common occurrence in childhood, differential diagnosis has required an assessment of the clinical story and the results of investigations which too often have not yielded a precise answer. Most of the children with idiopathic hypopituitarism will, at the appropriate ages, show evidence of failure of the sex hormones in some degree, but paediatricians have naturally been concerned to make a correct diagnosis before the age of puberty. Some of these children will show evidence of deficiency of the trophic hormones by a functional defect in the other target glands—thyroid and adrenal cortex, though the clinical pictures and the results of investigations usually indicate the hypopituitarism by this standard to be incomplete.

Where the hypopituitarism is secondary to demonstrable lesions of the central nervous system, the onset of retarded growth is sufficient to establish an acceptable diagnosis, but even in these children the evidence of panhypopituitarism is often either incomplete or non-existent.

The advances in diagnostic techniques of hypopituitarism have allowed the more detailed examination of these children, and in the two papers that follow are recorded our experience with a radio-immunoassay of growth hormone in insulin-induced hypoglycaemia (Stimmler and Brown, 1967) and the response in urinary nitrogen excretion before, during, and after the administration of human growth hormone (HGH) (Brown, Stimmler, and Lines, 1967). The results of our experience with the metyrapone test and of the levels of plasma cortisol in insulin-induced hypoglycaemia are to be reported elsewhere (Rudd and Stimmler).

Of the 10 patients diagnosed as suffering from hypopituitarism and described in this paper, all had

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TABLE
Clinical, Biochemical, and Radiological

| Case No. | Sex | Age and (Height Age) (yr.) | Height (cm.) | Sexual Development Girls over 13 Boys over 15 | Evidence of Hypoglycaemia |
|----------|-----|----------------------------|--------------|---|---|
| 1 | F | 8 (3½) | 98 | | None |
| 2 | F | 13½ (7½) | 122 | None | None |
| 3 | F | 19 (10½) | 140 | None | None |
| 4 | M | 13½ (8½) | 129 | | None |
| 5 | M | 12½ (7½) | 125 | | Convulsions; CSF sugar 20 mg.; blood sugar 42 mg./100 ml. (Folin Wu) |
| 6 | M | 15½ (9½) | 135 | Some pubertal development | None |
| 7 | M | 11½ (7½) | 123 | | None |
| 8 | F | 15½ (5½) | 113 | None | Fasting blood glucose 20 mg./100 ml.; glucose tolerance test followed by prolonged hypoglycaemia 27-42 mg./100 ml. (glucose oxidase method) |
| 9 | M | 17½ (13½) | 152 | None | None |
| 10 | F | 13½ (8) | 125 | None | Increased sensitivity to subcutaneous insulin |

* The cholesterol concentrations in hypothyroid patients were determined during adequate thyroid replacement therapy.

† Estimated as Silber-Porter chromogens. Normal range derived from 31 children, age range 2½-18½ years, who showed no evidence of endocrine

‡ Method of Riach (1966).

a nitrogen retention test, 7 had a growth hormone assay, 7 had plasma cortisol levels made, and 6 were given a metyrapone test.

the naso-orbital bridge is less well defined than it should be.

Diagnosis of Idiopathic Hypopituitarism

This diagnosis depends on the summation of a number of features which are summarized below.

Retardation of growth. The age at which growth failure has been observed has been much debated. For many years it was accepted that growth was not retarded until between the ages of 2 and 4 years. Brasel, Wright, Wilkins, and Blizzard (1965) in their recent review of Lawson Wilkins' patients recorded that in nearly half the children with idiopathic hypopituitarism growth was retarded at 2 years of age and in about one-third of them at 12 months of age. This is now generally accepted by those who have made a special study of the subject. Growth retardation is not easy to detect in the first year of rapid growth in children who are not yet standing, but doctors and parents are now showing much greater interest in the linear growth of children. As the child gets older growth failure becomes more apparent, and the gap between the child's growth curve and the 3rd centile steadily widens. The body proportions remain normal, or nearly normal, for the chronological age.

Facies. The child's features are immature for its age (a sign much subject to observer error) and

Sexual infantilism. This is common at the age when puberty should develop, and even the younger boys may show ill-developed external genitalia which add to the suspicion of hypopituitarism. However, the range of development of the male external genitalia at different ages in normal children is remarkably wide. No secondary sexual development had occurred in the 5 girls reported below who had reached the age of 13 years or older. One boy aged 15 had some sexual development and one boy aged 17½ had none (see Table).

Skeletal maturation. Skeletal maturation in many children with idiopathic hypopituitarism is retarded but it is less retarded than is growth; that is, the bone age, though retarded, is less retarded than the height age. This dissociation between height age and bone age is greater as the child grows older. Of the 45 children reported by Brasel *et al.* (1965), 15 showed this dissociation.

Size of sella turcica. Riach (1966) has developed a new method for measuring the size of the sella turcica. In 4 of our 7 patients with idiopathic hypopituitarism the area of the sella turcica was on the 5th centile or below (whether corrected for height or for height age). Three cases with intrasellar craniopharyngiomata were on or above the 95th centile. Measuring the relation

Findings in 10 cases of Hypopituitarism

| Serum PBI (µg./100 ml.) (normal 4-8) | Serum Cholesterol (mg./100 ml.)* (normal 120-250) | Urine 17 OHCS (mg./kg. 24 hr.)† (normal 0.02-0.16) | Lateral Area of Sella Turcica‡ (sq. mm.) | Diagnosis |
|--|---|--|---|--|
| 1.7 | 171 | 0.17 | 12 (< 5th centile) | Idiopathic hypopituitarism |
| 1.8 | 216-288 | 0.13 | 110 (< 95th centile) | Intrasellar tumour |
| 4.1 | 370-420 | — | 89 (> 95th centile) intrasellar calcification | Calcified craniopharyngioma |
| 4.6, 6.5 | 334-340 | 0.06 | 70 (normal) | Idiopathic hypopituitarism |
| 3.5, 3.7 | 193-222 | 0.10 | 39 (< 5th centile) | Idiopathic hypopituitarism |
| 3.3, 3.5 | 142-155 | 0.05 | 56 (normal) | Idiopathic hypopituitarism |
| 2.9 | 182 | 0.20 | 70 (normal) | Idiopathic hypopituitarism |
| 3.9, 6.5 | 249-309 | 0.02 | 35.5 (< 5th centile) | Idiopathic hypopituitarism |
| 3.9, 5.3 | 314 | 0.05 | 71 (normal) suprasellar calcification | Tuberculous meningitis at 6 yr.; acquired hypopituitarism |
| 3.7, 4.3 | 167-236 | 0.04 | 31.25 (< 5th centile) | Hypopituitarism, idiopathic or ? due to perinatal brain damage |

abnormality

between the area of the sella turcica and the lateral area of the skull, I. C. F. Riach (personal communication, 1966) has devised a sellar index (normal range between 1·4 and 2·8). By this index 3 of the 7 children with idiopathic hypopituitarism fell within the normal range and 4 below it.

Riach's methods are a useful addition to the diagnostic inquiries when hypopituitarism in childhood is suspected and as the child's age increases. Some doubt has recently arisen on the degree of reproducibility of Riach's method. He is conducting an 'observer-error' experiment to define this further.

Carbohydrate metabolism. Disorders of carbohydrate metabolism have been frequently demonstrated in patients with hypopituitarism. Of the 41 patients described by Brasel *et al.* (1965), 8 showed symptomatic hypoglycaemia, and of the 10 patients described below, 4 had shown symptomatic hypoglycaemia at some time during their lives. Symptomatic hypoglycaemia from any cause appears to be self-corrected as children grow older.

Hypoglycaemic unresponsiveness was reported by Brasel *et al.* (1965) in 22 of their 41 patients.

Increased insulin sensitivity has been regarded as one of the cardinal signs of hypopituitarism since it was first described by Fraser, Albright, and Smith (1941). This has been confirmed in idiopathic hypopituitarism by Prader, Illig, Széky, and Wagner (1964) and by Trygstad (1965). Intravenous insulin tolerance tests were performed by Brasel *et al.* (1965) in 12 patients: 8 were insulin sensitive and 4 gave an entirely normal response. Of the five of our patients suffering from idiopathic hypopituitarism who were given an intravenous insulin tolerance test, only one showed blood glucose below the lowest level found in non-hypopituitary dwarfed children by Stimmler and Brown (1967). In the other 4, and in the 2 children with organic hypopituitarism, who also had the test, the blood glucose response was indistinguishable from normal.

Serum cholesterol. The serum cholesterol may be raised above 250 mg./100 ml. in hypopituitary children, even when there is no evidence of hypothyroidism, or when there is hypothyroidism which has been adequately treated by thyroxine (Hubble, 1966). Of the 7 children with idiopathic hypopituitarism reported here, 2 had hypercholesterolaemia without evidence of hypothyroidism. Of the 3 patients with organic hypopituitarism, all had evidence of hypercholesterolaemia; 2 of these patients were receiving thyroxine for treatment of hypothyroidism.

Anterior pituitary hormones

TSH deficiency. In the 41 patients reported by Brasel *et al.* (1965), 5 had TSH deficiency and 15 partial evidence of TSH deficiency. In the patients recorded here, 2 had evidence of TSH deficiency and 2 some evidence of TSH deficiency as judged by the serum PBI (normal range 4-8 μ g./100 ml.).

ACTH deficiency. The baseline urinary 17-OHCS levels were within the normal range for our laboratory (0·02-0·16 mg./kg. 24 hr.) in all but 1 of the 10 hypopituitary children. The 7 children who were tested showed normal fasting levels of plasma cortisol and a normal response to hypoglycaemia (B. T. Rudd and L. Stimmler, personal communication).

Pituitary-adrenal axis. Of the 6 patients tested, 4 showed an abnormal response to the metyrapone test as it has been developed in our laboratory (B. T. Rudd and L. Stimmler, personal communication).

Growth hormone assay; and nitrogen retention test. The results of these two investigations, which are reported in the two articles that follow, show that they add considerably to the accuracy of the diagnosis of hypopituitarism in childhood.

The radio-immunoassay of growth hormone in response to insulin-induced hypoglycaemia gave levels of less than 10 μ mg./ml. in those children already diagnosed as suffering from hypopituitarism. There were, however, 4 children of short stature not suspected of hypopituitarism who gave similar low levels. These children may have a selective deficiency of growth hormone, or it is possible that low levels of growth hormone may occur for undefined reasons in a few children of short stature. Whether levels below 10 μ mg./ml. may occur in some normal children we have not determined. 2 of these 4 children had a nitrogen retention test. One of the tests was unsatisfactory and the other gave a normal response. Clinical and biochemical summaries for the 4 cases (Cases 11-14) appear in the appendix of case histories, in the following paper by Stimmler and Brown.

Although the intravenous insulin test produced no anxiety in this series of children, yet the test requires extreme care and watchfulness. Moreover, these hypopituitary children suffered from *partial* hypopituitarism, and the 7 who were tested showed normal plasma cortisol response to hypoglycaemia.

In the nitrogen retention test we have not encountered any patients of short stature, not suspected of hypopituitarism, who give the hypo-

pituitary pattern of response. Our results, limited to 22 patients, appear to give a more complete separation between hypopituitary and non-hypopituitary children than does the growth hormone response to hypoglycaemia. Yet this test is tedious for these young patients, and a shortening of the test period diminishes to a small extent the accuracy of these results.

However, these two investigations have added considerably to our diagnostic capacity, and there are now few patients in whom the diagnosis of hypopituitarism cannot be made with confidence. This is important as we are now moving into the time when human growth hormone should be available for all children who can be diagnosed with certainty as suffering from hypopituitarism.

Ten Hypopituitary Patients

Of the 10 hypopituitary patients reported here (Table), 5 were girls and 5 were boys. All were over the age of 11 years at the time of their final investigations, except for one girl aged 8 years. Several of the tests to be described are too demanding for younger patients. The long period of basal diet required in the nitrogen retention test, and the use of insulin-induced hypoglycaemia, can only be employed in co-operative children. We are current-

ly experimenting with other methods of performing these investigations.

Seven of these patients were diagnosed as having idiopathic hypopituitarism, and 3 had organic hypopituitarism.

Summary

The diagnostic findings in 10 cases of hypopituitarism, aged 8 to 19, have been summarized.

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