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Personal practice

Investigation of suspected growth hormone deficiency

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On behalf of the Health Services Human Growth Hormone Committee

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SUMMARY This paper describes views of the Health Services Human Growth Hormone Committee on how a child suspected of growth hormone deficiency should be investigated in a district general hospital or in a regional growth centre.

Growth hormone (GH) deficiency is rare whereas short children are common. The successful management of children who are short or failing to grow normally will depend on an effective partnership between the paediatrician working in a district general hospital and those in charge of the 20 regional growth centres in the UK. The former sees the majority of short children whereas the latter have special expertise in growth problems and the facilities necessary for the full investigation of patients who may need GH therapy.

The evaluation of a short child or one whose growth has slowed encompasses all aspects of paediatrics and the initial expert assessment by a paediatric consultant who knows the child in his environment is complementary, not supplementary, to the expertise of the paediatric endocrinologist working in a growth centre. Two lines of investigation are essential in making the diagnosis of GH deficiency: auxology and endocrinology. Just as there are many causes of short stature other than GH deficiency, a low peak plasma GH level is not sufficient to make the diagnosis in a child who is growing at a normal rate, be he short or not. The measurement of height is painless but unfortunately some of the GH stimulation tests are unpleasant and in unskilled hands may be dangerous. It is therefore vital that a national scheme for the clinical evaluation and investigation of these patients uses the skills of the district general hospital and the regional growth centre rationally so that a specific diagnosis can be made with the minimum discomfort and inconvenience to the child. This paper describes the recommendations of the Health Services Human Growth Hormone Committee for the assessment of GH status of children in the UK.

Clinical members of the Committee: Dr J M H Buckler, Dr I A Hughes, Dr D C L Savage, Dr C C Forsyth, Dr C S Smith, Professor J M Tanner

The district general hospital

The accurate measurement of height is essential for the diagnosis of GH deficiency. Every paediatric department should have a reliable stadiometer in regular use and if there is concern about poor growth the paediatrician should measure the child personally.

Measurements are made at 3-monthly intervals and the results plotted on height centile charts. The majority of short children or those growing abnormally slowly are not GH deficient and it is important to take note of the parents' height and to interpret the patient's height in the context of the bone age as well as the chronological age. If successive height measurements over at least 6 months are crossing centile lines downwards or deviating from the 3rd centile, the height velocity should be calculated and plotted on a centile chart.[1] (Charts for both height and weight velocity are available from Creaseys of Hertford Ltd, Castlemead, Hertford SG14 1LH.) Subnormal growth can be indicated by the height of the patient but height velocity is a more powerful diagnostic tool. If the height velocity over a full year is normal (above the 25th centile) the child is unlikely to be suffering from GH deficiency. Conversely a child with a height velocity below the 25th centile measured over a full year should be reviewed carefully even if he is of normal height and even if the initial assessment and investigations have proved negative.

The assessment of a short child will pay particular attention to the heights of the parents and siblings.

Table *Useful laboratory screening tests for short children*

Full blood count, serum iron	Coeliac disease
Blood chemistry	
Potassium	Bartter's syndrome
Bicarbonate	Renal tubular acidosis
Creatinine	Renal parenchymal disease
T4/TSH	Hypothyroidism
Chromosomes in girls	Turner's syndrome
Skull *x*-ray film	Craniopharyngioma

Evidence of intrauterine growth retardation will be sought. A search for dysmorphic build will be made on physical examination. Investigations will be dictated by clinical presentation but a useful set of laboratory screening tests is given in the Table. In all cases a radiograph of the left hand and wrist should be examined carefully for determination of accurate bone age,[2] since analysis of height by bone age as well as by chronological age may be a most reassuring index of normality.

In most cases the initial assessment of the patient, including measurement of height velocity over 6 to 12 months will be carried out at the district general hospital. If the balance of evidence favours GH deficiency the paediatrician will wish to test for it biochemically. Since a plasma GH level of >15 mU/l excludes GH deficiency biochemically, formal tests of GH secretion are commonly preceded by screening tests which are completed quickly, often on an outpatient basis at the price of only one venepuncture. All plasma GH determinations should be performed by laboratories that participate in the supraregional assay service and this can be arranged by consultation with the hospital chemical pathologist.

One of three screening tests is recommended in each of which one blood sample is collected for plasma GH. They are: (1) Post-prandial. (2) Post-exercise. (3) Sleep.

A serum GH result of >15 mU/l from a screening test absolves the paediatrician from further biochemical investigation for GH deficiency. A result of <15 mU/l means that the child should have a formal test of GH secretion. The type of formal test and the place where it is performed depends on the bone age of the child. Children with a bone age of at least 10 years should be referred to the regional growth centre for a sex steroid-primed test. If the bone age is below 10 years a formal GH secretion test can be performed at the district general hospital or at the regional growth centre.

Many tests of GH stimulation have been described and all have strengths and weaknesses, devotees and critics. The insulin tolerance test has been favoured in the past by the Health Services Human Growth Hormone Committee because the committee had more experience of it than any other test, but it is acknowledged to be unpleasant for the patient and potentially dangerous. For these reasons it is recommended that the formal GH stimulation tests undertaken at district general hospitals should be: (1) Oral clonidine test. (2) Intravenous arginine test. (3) Intramuscular glucagon test.

It is now recognised that these tests have a false-positive and false-negative response rate similar to the insulin tolerance test.

If the plasma GH rises above 15 mU/l in the test GH deficiency is excluded biochemically. If the peak result is <7 mU/l the child has biochemical evidence of GH deficiency. If the peak result is between 7 and 15 mU/l the child may have partial deficiency. All children with biochemical evidence of partial or complete GH deficiency should be referred to the regional growth centre for further assessment.

The regional growth centre

The child who presents at the regional growth centre may be a primary referral from the local community in which case the initial assessment is similar to that at the district general hospital described above. There are also some children referred by colleagues for detailed evaluation before a possible application for therapeutic human GH to the Health Services Human Growth Hormone Committee. The committee normally accepts only anthropometric measurements that have been made at a growth centre but will also consider earlier measurements if these are concordant with those made at the centre.

The paediatrician in charge of the growth centre has the responsibility to provide a professional auxology service, to be able to assess bone age accurately by the TW2 method, and to carry out the more complicated biochemical tests of GH secretion. Which test is most appropriate depends partly on the patient and partly on the experience of the paediatrician, but the most important factor is the age of the patient. If a child below a bone age of 10 years has a peak serum GH of <7 mU/l on formal testing and has the typical clinical stigmata of GH deficiency or evidence of idiopathic or secondary hypopituitarism, no further biochemical test is required and the case should be submitted for GH treatment when the appropriate auxological measurements are available.

If a patient below a bone age of 10 years is referred to the growth centre with a peak serum GH of less than 15 mU/l in a screening test or a value of 7 to 15 mU/l in a formal test, a further formal test is performed. The test performed at the growth centre may be one of the three tests recommended for use

in the district general hospital but it will not normally be the same as the one initially performed. Other tests that may be used are: (1) Insulin tolerance test. (2) Insulin tolerance test followed by intravenous arginine.

At the time the formal test of GH secretion is performed at the regional growth centre it may be convenient to carry out simultaneously a thyroid-releasing hormone (TRH) or a luteinising hormone–releasing hormone (LH–RH) test.[3]

Patients who achieve a peak serum GH of more than 15 mU/l are considered not to be biochemically GH deficient and other causes of growth delay should be pursued as indicated. For example, some children present with impaired growth as the sole clinical evidence of coeliac disease and there is a rare group of patients who have immunoreactive but biologically ineffective GH. The further investigation of such difficult problems lies within the remit of the director of the growth centre and is one of the reasons for the establishment of the centres.

Patients who are growing subnormally and have a peak plasma GH of between 7 and 15 mU/l in two formal tests should be considered as suffering from partial GH deficiency and are eligible for GH therapy. Patients who have a peak serum GH of less than 7 mU/l in a formal test and have compatible clinical and auxological findings are diagnosed as GH deficient and submitted for GH therapy. This leaves a subgroup who are growing poorly, who have a peak serum GH of less than 7 mU/l on formal testing but no other clinical signs suggestive of GH deficiency. In these cases the paediatrician in charge of the growth centre may decide to perform a second formal stimulation test.

When the bone age is at least 10 years and the initial screening test produces a plasma GH of less than 15 mU/l the child should proceed to a sex hormone-primed insulin tolerance formal test at the growth centre. For boys various androgen regimens have been suggested; a typical one is to give 100 mg of mixed testosterone esters intramuscularly (Sustanon, Organon Laboratories Limited). The formal test in boys is performed 3 to 5 days later. Girls are given 100 μg ethinyl oestradiol orally on each of 3 days before the test.[3]

If the result of the sex hormone-primed test is a peak plasma GH of <7 mU/l and the patient has other clinical or laboratory evidence of hypopituitarism the diagnosis of GH deficiency is established and application for GH therapy should be made. If the result is a peak GH of <7 and there are no other stigmata of GH deficiency the director of the centre may at his discretion perform a second sex hormone-primed formal stimulation test. If the result of the first sex hormone-primed insulin tolerance test gives a peak serum GH of 7 to 15 mU/l a second sex hormone-primed formal test is mandatory before the case can be considered one of partial GH deficiency.

Appendix

Tests for GH, TSH, and gonadotrophin secretion. Brief details of screening and formal tests for GH thyroid-stimulating hormone (TSH), and gonadotrophin secretion are given below. It is advisable to check locally with the laboratory the volume of blood and preservative required for the hormone determinations.

Post-prandial test. Blood sample for GH to be taken 3 and 4 hours after the ingestion of glucose (1·4 g/kg) or a high carbohydrate-containing meal. In many normal children, glucose intake is followed initially by low GH levels and then a secondary rise to normal values.[4 5]

Post-exercise test. Blood sample for GH to be taken 25–30 minutes after strenuous exercise—for example cycling on a static bicycle or running up and down stairs for 10 minutes. Eighty per cent of healthy children have normal GH levels after strenuous exercise. Unfortunately some younger children will not co-operate for this test.[6]

Sleep test. Blood sample for GH to be taken 45–90 minutes after the onset of sleep, before the first cycle of rapid eye movement sleep. About 70% of children have normal GH levels on the sleep tests if electroencephalogram control is used.[7 8]

Oral clonidine test. Blood samples for GH to be taken at 0, 30, 60, 90, 120, and 150 minutes after oral intake of clonidine (0·15 mg/m^2). Clonidine may cause hypotensive side effects in some patients.[9]

Intravenous arginine test. Blood samples for GH to be taken at 0, 30, 60, 90, 120, and 150 minutes after the administration of intravenous arginine (0·5 g/kg; maximum dose 40 g), which should be infused during the first 30 minutes of the test.[10]

Intramuscular glucagon test. Blood samples for GH to be taken at 0, 30, 60, 90, 120, and 150 minutes after the administration of intramuscular glucagon (30–100 μg/kg; maximum dose 1 mg). The pituitary-adrenal axis may be assessed during the test by estimating the plasma cortisol from the 0, 120, and 150 minute samples. Glucagon causes side effects of nausea and vomiting in some patients.[11]

Insulin tolerance test. Blood samples for GH to be taken at 0, 20, 30, 45, 60, 90, 120, and 150 minutes after the administration of intravenous insulin (0·1 U/kg; in patients with suspected or established

panhypopituitarism 0·05 U/kg is recommended). The test is considered valid only if the blood sugar falls to less than half the fasting value or to 2·2 mmol/l or less. The pituitary-adrenal axis may be assessed during the test by estimating the plasma cortisol on the 0, 45, and 60 minute samples. The main danger of the test is severe hypoglycaemia; it should not therefore be performed in patients if a good intravenous line cannot be secured. Glucose and hydrocortisone for intravenous injection should be readily available throughout the investigation.[12]

Combined intravenous insulin and arginine test. Blood samples for GH to be taken at 0, 20, 30, 45, 60, and 90 minutes after the administration of intravenous insulin (0·1 or 0·05 U/kg see above). Immediately on collection of the 90 minute sample, intravenous arginine should be given (0·5 g/kg) over 30 minutes and samples collected at 30, 45, 60, 90, and 120 minutes after this injection.

TRH test. A blood sample for TSH and thyroxine is taken at 0 minutes, after which 200 μg TRH (Roche) is injected intravenously and further samples are taken at 20 and 60 minutes for the measurement of TSH concentration.

LH–RH test. A blood sample for luteinising hormone (LH) and follicle-stimulating hormone (FSH) determination is taken at 0 minutes, after which 100 μg LH–RH (Relefact LH–RH, Hoechst) is injected intravenously and further samples are taken at 20 and 60 minutes for the measurement of LH and FSH. The TRH and LH–RH tests may be conveniently combined (Relefact LH–RH/TRH, Hoechest).

References

1 Tanner J M. Physical growth and development. In: Forfar J O, Arneil G C, eds. *Textbook of paediatrics*, second edition. Edinburgh: Churchill Livingstone, 1978: 276–90.

2 Tanner J M, Whitehouse R H, Marshall W A, Healy M J R, Goldstein H. *Assessment of skeletal maturity and prediction of adult height (TW2 method)*. London: Academic Press, 1975.

3 Preece M A. Growth hormone deficiency. In: Brook C G D, ed. *Clinical paediatric endocrinology*. Oxford: Blackwell, 1981: 285–304.

4 Hunter W M, Wolfsdorf J, Farquhar J W, Rigal W M. Screening tests for growth hormone deficiency in dwarfism. *Lancet* 1967; **ii**: 1271–3.

5 Hofeldt F D, Reed J W, Forsham P H. Growth hormone responses following double pulse oral glucose administration in various clinical states. *J Clin Endocrinol Metab* 1975; **40**: 387–92.

6 Lacey K E, Hewison A, Parkin J M. Exercise as a screening test for growth hormone deficiency in children. *Arch Dis Child* 1973; **48**: 508–12.

7 Fass B, Lippe B M, Kaplan S A. Relative usefulness of three growth hormone stimulation screening tests. *Am J Dis Child* 1979; **133**: 931–3.

8 Howse P M, Rayner P H W, Williams J W. Nyctohemeral secretion of growth hormone in normal children of short stature and in children with hypopituitarism and growth retardation. *Clin Endocrinol* 1977; **6**: 347–59.

9 Health Services Human Growth Hormone Committee. Comparison of the intravenous insulin and oral clonidine tolerance tests for growth hormone secretion. *Arch Dis Child* 1981; **56**: 852–4.

10 Raiti S, Davis W T, Blizzard R M. A comparison of the effects of insulin hypoglycaemia and arginine infusion on the release of human growth hormone. *Lancet* 1967; **ii**: 1182–3.

11 Vanderschueren-Lodeweyckx M, Wolter R, Malvaux P, Eggermont E, Eeckels R. The glucagon stimulation test: effect on plasma growth hormone and on immunoreactive insulin, cortisol, and glucose in children. *J Pediatr* 1974; **85**: 182–7.

12 Tanner J M, Whitehouse R H, Hughes P C R, Vince F P. Effect of human growth hormone treatment for one to seven years on the growth of 100 children with growth hormone deficiency, low birthweight, inherited smallness, Turner's syndrome, and other complaints. *Arch Dis Child* 1971; **46**: 745–82.

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