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Tests for growth hormone secretion

The pattern of growth in childhood is well known to paediatricians: the rapid and rapidly decelerating growth from the third trimester to the second year of life gives way to the steady and slowly decelerating growth of middle childhood (with the mid childhood growth spurt between ages 6 and 8), and the adolescent growth spurt. Possibly less well known is the mathematical division of these phases of growth into infancy, childhood, and puberty components,[1] which correspond to three major control mechanisms.

Growth during fetal life and the first postnatal year is dependent on nutrition. Children born of low birth weight or starved in the first year of life fail to grow at an adequate rate and, if this continues for any length of time, incur a growth deficit which is irrecoverable. Children overfed in utero (infants of diabetic mothers) or shortly after birth become not only fat but also large.

The height which an individual achieves is determined largely by the rate of growth. A child destined to become a tall adult grows at a rate consistently rather greater than his third centile peer. It is now well recognised that growth rate is determined by the amplitude of pulsatile growth hormone secretion.[2] What this means is that just as height velocity is a continuous variable, so also is growth hormone secretion. Thus the idea that there is a cut off value for either of these parameters which strictly defines normality is as illusory as seeking to define obesity or hypertension in terms of cut off values.

Who needs tests?

Thriving is an active process and no child should be investigated for having previously failed to thrive, except insofar as an explanation may be available from what has gone before to explain short stature: investigations are not likely to prove helpful in any child currently growing at a normal rate. The answer, therefore, to who needs investigating is any child, regardless of the stature he or she has attained, who is not growing at a normal rate.

The definition of what constitutes a normal rate of growth has always caused paediatricians anxiety and it was for this reason that we promulgated some years ago the Middlesex height velocity chart,[3] which is now available as a Perspex sheet designed to lie on the desk of physicians who look after children. The only children who should be candidates for tests of growth hormone secretion are those growing at a slow rate in middle childhood in whom other causes of failure to thrive have been excluded by clinical examination and/or screening investigations.

A pragmatic solution is to investigate immediately all children growing at a less than third centile velocity (with thereby a 97% chance of detecting an abnormality) and closely to follow up those growing at rates between the third and 25th centiles with a view to investigating them if such a growth rate persists into a second year[4]; in this case the chance of normality is not 25% but 25% of 25% or 6·25%. Recent data fit these concepts well.[5]

What tests are available?

Table 1 shows some of the tests that are regularly employed.

Table 1 Tests of growth hormone secretion

Screening tests:	
Serum insulin like growth factor-1 concentration	
Exercise	
Physiological tests:	
24 hour profile	
Sleep study	
Urinary growth hormone excretion	
Pharmacological tests:	
Insulin induced hypoglycaemia	L-dopa
Arginine	Clonidine
Glucose	Glucagon
Growth hormone releasing hormone	

One of the major problems is that the growth hormone axis is very sensitive and the reproducibility of results in individual children is only ±35%, as opposed to group data which are much more reliable. Further, children growing slowly as a result of gastrointestinal disease, respiratory disease, or renal disease often have depressed concentrations of growth hormone to any stimulus. Our view, therefore, is that the physician seeing a child growing slowly should decide whether or not an endocrine cause is likely and if there is a serious worry about an insufficiency of growth hormone secretion he or she should not be worrying about the screening tests.

The tests of physiological secretion of growth hormone are expensive and time consuming. The analysis of pulsatile growth hormone secretion has become an extremely complex mathematical task and is not suitable for everyday purposes and reproducibility is a real problem. Only a department which has sufficient facilities ought to be going to the length of taking blood samples from children for the assessment of spontaneous growth hormone secretion. It is possible that the measurement of urinary growth hormone could be used as an assessment of integrated hormone secretion but at present the problem with this test, as with all other tests, is that it will detect successfully children in whom it is perfectly obvious that there is a problem with growth hormone secretion and it will detect excessively high concentrations of growth hormone secretion. Over the range of height velocity where there is a serious dilemma, the test does not provide much help and the reproducibility is obviously just as variable as for profiles of serum concentration.[6]

This leaves the pharmacological tests of growth hormone secretion and the same applies to them as it does to measurements of urinary growth hormone. Figure 1 shows the association between growth hormone secretion and growth rate in 50 short prepubertal children demonstrating the continuous nature of the two variables. Figure 2 shows the results of insulin tolerance tests performed on these children and superimposed on the asymptotic relation. The overlapping nature of the results shown in fig 2 could be reproduced equally well for measurements of insulin like growth factor-1, urinary growth hormone, responses to clonidine or arginine, etc. Different stimuli also act in different ways and it is not known which neuroendocrine pathways are most relevant to physiological growth hormone secretion.

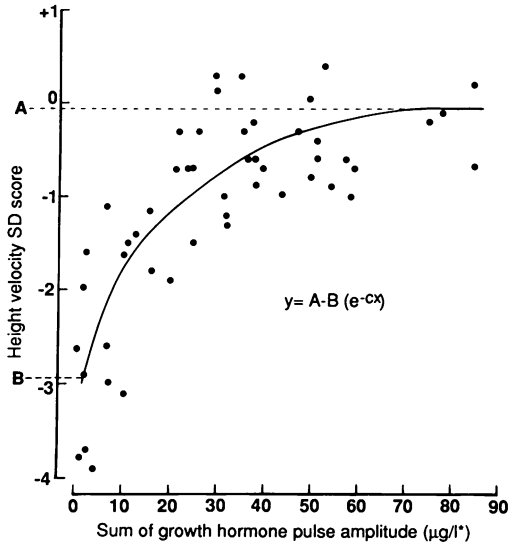

*Figure 1 Association between growth hormone secretion and height velocity in 50 short prepubertal children.[9] *Growth hormone conversion factor 1 μg/l=2 mU/l.*

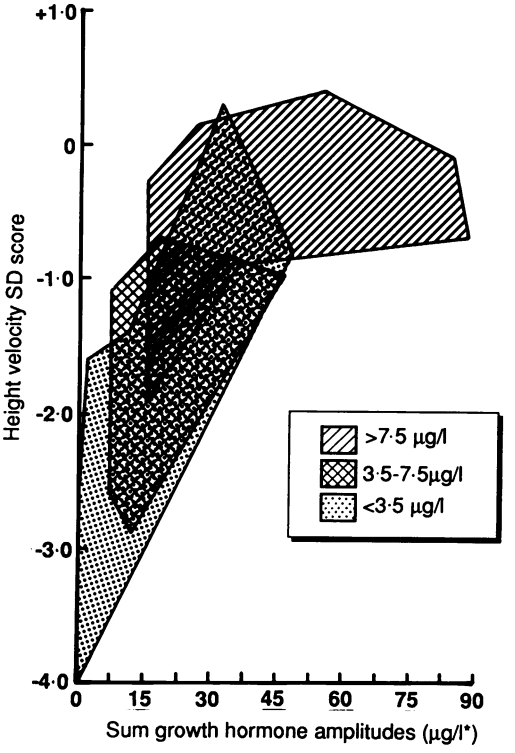

*Figure 2 Results of tests of peak response of growth hormone to insulin induced hypoglycaemia in the same 50 children. *Growth hormone conversion factor 1μg/l=2 mU/l.*

Interpreting the results

We have already made clear that growth velocity is the most sensitive indicator of an abnormality of growth hormone secretion. In order to grow along the third or 97th centile on a height distance centile chart, a patient needs to have a growth velocity between −0·8 and +0·8 standard deviations year on year, which is the mathematical basis for the Middlesex height velocity chart. When one compares the results of growth hormone tests against such a gold standard criterion, one can come up with estimates of sensitivity and specificity that vary according to the cut off point which is chosen to represent normality (table 2).

Further difficulties are imposed by the demonstration that the state of the hypothalamo-pituitary axis before the peformance of a test has an important influence on its result. Every test is designed to test the readily releasable pool of growth hormone that happens to be in the pituitary at the time the test is performed. If there has recently been a pulse of growth hormone secretion and the gland is empty, nothing will make it produce a further response. A high baseline value in a provocative test may presage a misleading result. In a patient in whom there is an abnormality of the control of growth hormone secretion (neurosecretory dysfunction), a pharmacological test may falsely suggest that growth hormone secretion is normal when in fact the pattern is grossly disorganised. Nutritional state is also important: in states of starvation (intrauterine growth retardation) growth hormone concentrations are high and responses to stimuli are blunted in obese children growing quite normally.

Table 2 The effect of employing cut off values to test results in 64 children

	Height velocity SD score		Sensitivity in detecting true positive	Specificity in excluding true negative
	<−0·8	>−0·8		
Peak growth hormone responses to insulin induced hypoglycaemia (μg/l*):				
<7·5	35	5	87·5%	83·3%
> 4	4	20		
<5·0	27	1	96·4%	66·6%
>5·0	12	24		

*Growth hormone conversion factor 1μg/l=2mU/l.

The second common situation in which tests may be misleading is in late prepuberty. The pubertal increase in growth hormone secretion requires an increase in sex steroid concentration and tests of growth hormone secretion done in patients over 11 years of age need very special consideration.

Finally, as indicated, many conditions that interfere with growth have secondary effects on growth hormone secretion. The correction of the basic abnormality (gluten free diet or removal of a child from an inclement emotional environment) will restore growth hormone secretion.

Who needs tests of growth hormone secretion?

All this brings us back to what the point of such tests were in the first place. It is now abundantly clear both from the implication in figs 1 and 2 and from clinical practice[7] that any child given growth hormone will grow more quickly. The amount of growth hormone that has to be given is determined by the pretreatment rate at which the children are growing (the most slowly growing, the most severely insufficient of growth hormone secretion will respond best), the dose of growth hormone used, and the condition being treated.[8] The only reason for a test of growth hormone secretion is therefore to confirm that the problem lies in this area and not elsewhere; we have already seen that the tests do not achieve this result.

A plan for action

It will be clear that tests of growth hormone secretion are currently in a mess and we purpose the following scheme for the management of the short child seen in general paediatric practice:

(1) Measure the child and the heights of his parents. In the absence of other indications:
(2) Measure the child again after four months and calculate an annual growth velocity.
(3) Plot the velocity on the Middlesex height velocity chart.

(4) If the velocity is way below the lower limit of normal (third centile), take immediate action.
(5) If the velocity is close to the lower limit of normality (third to 25th centile), follow up the child for a longer period of time.
(6) In cases of doubt, the paediatrician has the option of either giving the child growth hormone or seeking advice from a specialist centre.

In these days of cost consciousness, the latter is likely to be a cheaper option for the referring health district than the former.

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