Sleep-induced growth hormone release—evaluation of a simple test for clinical use

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SUMMARY Plasma growth hormone (GH) levels were measured during the first 2 hours of sleep without electroencephalogram monitoring and then after arginine infusion in 28 children investigated for short stature. Ten children considered GH deficient on clinical and biochemical grounds had concordantly low GH levels during sleep and after arginine stimulation. Of the 18 children without GH deficiency, 17 had GH levels ≥ 15 mU/l during the sleep test (mean peak 39 mU/l) and 13 had GH levels ≥ 15 mU/l after arginine infusion (mean peak 25 mU/l). A sleep test is safe, reliable, and practicable for routine clinical use.

The use of insulin-provoked hypoglycaemia to induce growth hormone (GH) release is known to be dangerous, has caused death in the past, and, it may be argued, is too readily used in children of short stature unlikely on clinical grounds to be GH deficient. Although the insulin test is widely regarded as the definitive diagnostic test for GH deficiency in children false-negative results occur.^{1 2}

Deep sleep is a major physiological stimulus for GH release in adults and children,^{3–6} and tests with electroencephalogram (EEG) recording of the depth of sleep in children have been found clinically useful.^{4–6}

This study reports the results of a simple test during sleep, structured without the use of EEG monitoring, carried out routinely in a paediatric ward in children needing evaluation of GH status on clinical grounds. Plasma GH levels during sleep were compared with levels achieved after standard arginine provocation.

Patients and methods

Twenty-eight (13 girls and 15 boys) children aged 2–16 years undergoing investigation of short stature were tested for GH status after clinical assessment and measurement of growth velocity. Two children with craniopharyngioma were investigated twice, once after surgery and again after radiotherapy. In those children diagnosed GH deficient (Table 1) confirmation by auxological response to GH therapy was available in 7 children. A low GH response to insulin-induced hypoglycaemia was present in 8 children, excluding the 2 with craniopharyngioma.

Two children with diabetes insipidus and biochemical GH deficiency have had persistently low GH responses to tests but have a normal growth velocity.

The children were admitted during the morning or afternoon to this hospital. Before sleep, between 1900 and 2100 hours, a 21 gauge scalp vein butterfly needle filled with heparinised 0.9 isotonic saline was inserted into the antecubital vein of the forearm. The timing of onset of sleep was simply observed and occurred in all children between 2100 and 2400 hours.

Blood samples (2 ml volume) were taken at insertion of the needle and at 15-minute intervals between 30 and 120 minutes after sleep onset. Sampling was omitted at +15 minutes to avoid waking the child before deep sleep was insured. Samples were placed in lithium heparin tubes, stored at 4°C, and the plasma separated the next morning.

An arginine stimulation test¹ using 0.5 g/kg or arginine hydrochloride infused over 30 minutes was carried out the next day. Plasma samples for GH were taken at –30 minutes and at 15-minute intervals from the end of the infusion for 2 hours. Other general and endocrinological tests were performed as indicated.

Plasma GH levels were measured by radioimmunoassay using reference standard IRP 66/217. A peak level of at least GH 15 mU/l was taken to indicate a normal response and between 10 and 14.9 mU/l to indicate partial GH deficiency.

Children over age 12 years and prepubertal were primed with androgens or oestrogens; boys were given 100 mg testosterone intramuscularly 3 days before the test and again on the day of the test,

Table 1 Age, diagnosis, and peak GH level after sleep and after arginine and insulin provocation

Case	Age (years)	Sex	Peak sleep GH (mU/l)	Time of peak sleep GH (min)	Peak GH (mU/l)		Diagnosis
					After arginine	After insulin	
1	7	F	4.9	30	8.5	5.6	Isolated GH deficiency
2	8	F	1.4	30	1.6	1.2	Isolated GH deficiency
3a	8	F	2.1	105	3.9		Craniopharyngioma after surgery
b	9	F	1.6	60	2.0		Craniopharyngioma after surgery and radiotherapy
4	12	F	3.0	30	3.6	<1	Isolated GH deficiency
5	5	M	2.2	Pre	2.6	2.2	Hypopituitarism
6	8	M	6.1	30	3.6	5.6	GH deficiency and diabetes insipidus
7	9	M	8.9	60	8.2	3.2	Isolated GH deficiency
8	10	M	1.7	105	6.0	2.1	GH deficiency and diabetes insipidus
9a	14	M	<1	—	<1		Craniopharyngioma after surgery
b	14	M	1.7	Pre	2.3		Craniopharyngioma after surgery and radiotherapy
10*	16	M	6.8	30	14	5.0	Isolated partial GH deficiency
11	2	F	105	30	100		Laron dwarf
12	6	F	80	60	19		Constitutional short stature
13	8	F	7	45	25		Constitutional short stature
14	10	F	28	Pre	14		Turner's syndrome
15	10	F	28	Pre	17		Turner's syndrome
16	10	F	32	30	6		Thalassaemia major
17	11	F	23	45	31		Turner's syndrome
18	14	F	35	45	100		Celiac disease
19*	14	F	20	105	11		Constitutional delayed puberty
20	5	M	24	45	16		Constitutional short stature
21	7	M	50	75	33		Short stature, low birthweight associated
22	9	M	35	30	1.9		Constitutional short stature
23	12	M	24	60	19		Constitutional short stature
24*	12	M	45	45	24		Constitutional short stature
25	13	M	18	30	11		Constitutional short stature
26*	14	M	41	90	35		Constitutional delayed puberty
27*	15	M	100	30	30		Constitutional delayed puberty
28*	15	M	71	60	28		Constitutional delayed puberty

*Test in children primed with sex steroids. Insulin tolerance tests carried out only in those submitted to Health Service Human Growth Hormone Committee for GH treatment, with exception of the 2 children with craniopharyngioma.

girls were given 100 µg ethinyloestradiol twice a day orally for 3 days before the test.

Results

Peak GH levels achieved in the sleep test and after arginine are shown in Table 1 with the eventual diagnosis and are positively correlated ($r = 0.68$, $P < 0.001$) (Figure). On 5 occasions, normal levels were achieved during sleep but arginine infusion failed to provoke a GH level of 15 mU/l. Sleep failed to provoke a GH level of 15 mU/l on one occasion when arginine infusion was successful.

In 12 GH-deficient children mean peak values of plasma GH during sleep and arginine tests, 3.4 and 4.7 mU/l respectively, were not significantly different ($P > 0.1$), paired t test. In 17 children considered to have normal GH levels (excluding the child with Laron dwarfism) the mean peak level in sleep exceeded that in the arginine test, 38.9 and 24.8 mU/l respectively, but not significantly so ($P > 0.05$, paired t test).

In 5 children GH levels exceeded 15 mU/l before the onset of sleep after insertion of the butterfly needle. Peak values in children with an overall positive sleep test tended to occur at between 30 and

60 minutes. All children who achieved a GH level ≥ 15 mU/l had done so by 90 minutes after the onset of sleep (Table 2).

No serious practical difficulty was encountered during testing. Two children woke briefly during sampling but subsequent normal GH peaks were recorded.

Discussion

Investigations performed in the assessment of GH secretion in short children should be safe, reliable, and easy to carry out. An exercise test⁷ is an acceptable though fallible screening procedure in the

Table 2 Comparison of sampling times producing peak GH levels in 18 children without GH deficiency

	Sampling times (minutes)							
	Before	+30	+45	+60	+75	+90	+105	+120
Total number of children who reached peak level of GH before or at each sampling time	2	7	12	15	16	17	18*	18

*One child with GH > 15 mU/l at 60 min, but peak level at 105 min.

Figure Comparison of peak sleep GH and peak GH after arginine stimulation.

older child, but a low response requires confirmation from other tests. The insulin tolerance test is widely considered an essential investigation for patients who are considered candidates for GH deficiency.² However an insulin tolerance test may occasionally provoke a grand mal convulsion and rarely may prove a fatal stimulus. A recent investigation² reported a 25% incidence of false-negative results after an insulin tolerance test and great vigilance is necessary with continuous medical supervision.

Previously, clinical tests with sleep have concerned either single sampling after the onset of sleep⁸ as a screening procedure or greater sophistication than is practicable in routine work—such as EEG monitoring,^{5,6} use of sleep laboratories,⁵ or continuous sampling.⁹ This study was designed to compare the usefulness of a standardised sleep test in normal clinical work with a safe and acceptable pharmacological stimulus such as arginine infusion.

The results indicate a low false-negative rate for the sleep test (5%) compared with arginine (29%) and show that a plasma GH level of at least 15 mU/l is achieved by 90 minutes after the onset of sleep.

Disadvantages of the sleep test include the necessity of overnight admission and the inconvenience of sampling times. Advantages include

complete safety, apparently greater reliability, and the use of a physiological stimulus more appropriate on theoretical and practical grounds. Wise *et al.*¹⁰ described 2 children with normal responses to pharmacological stimuli (insulin and arginine) and low responses to physiological stimuli (exercise and sleep) who responded to GH therapy.

The assessment of GH secretion in the short child should always be prefaced by a sound clinical analysis, measurement of growth, and if appropriate, a screening test. Confirmation of the diagnosis should be made using two independent, safe investigations. This study suggests that a sleep test is appropriate and practicable.

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