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Nocturnal Growth Hormone Release in Children with Short Stature and Atopic Dermatitis

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This study was designed to test the hypothesis that children with atopic dermatitis and short stature fail to release growth hormone after falling asleep. Peak serum growth hormone response to arginine was compared with peak growth hormone concentration during sleep in 6 children with atopic dermatitis and short stature (> 3 SD below the mean) aged 7 to 12 years, and 5 control children aged 9 to 12 years without atopic dermatitis or asthma but with unexplained short stature (> 3 SD below the mean). All 5 control children achieved normal levels of growth hormone after falling asleep, whereas 3 of the 6 children with dermatitis did not. All patients with dermatitis were capable of releasing growth hormone after arginine stimulation. The results suggest that in some prepubertal children with atopic dermatitis and short stature there may be an impairment of growth hormone release during stage 4 sleep.

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Growth impairment is an important association of atopic dermatitis (AD) in childhood. Short stature, defined as a standing height below the third centile when corrected for mid-parental height, was found in 22% of 89 children with atopic dermatitis troublesome enough to cause regular attendance at hospital (1). Impaired growth was particularly associated with the surface area of skin affected by dermatitis, with the potency of topical steroid used and with the presence of co-existing asthma (1). Possible causes of poor growth in AD include percutaneous absorpation of topical steroids, co-existing asthma or systemic absorption of inhaled steroids, an inadequate intake or absorption of nutrients, or a non-specific effect of a chronic disease (2).

Severe night-time pruritus (3) is a common feature of AD, with increased scratching particularly in stage 1 and 2 sleep (4,5), accompanied by a reduction in stage 4 sleep (6). The highest peak of plasma growth hormone (GH) concentration in a 24-h period occurs during stage 4 sleep (7,8), and accordingly a further possible cause of short stature might be (*a*) a reduction in the amount of stage 4 sleep, or (*b*) failure to release GH during stage 4 sleep, in either case leading to a reduced nocturnal release of GH. The present study was designed to test the hypothesis that children with AD and short stature fail to release GH after falling asleep.

MATERIALS AND METHODS

Patients

Six Caucasian children with severe atopic dermatitis (AD), who fulfilled the diagnostic criteria of Hanifin & Rajka (9), aged 7 to 12 years (mean 10.3 ± 1.9 years), and 5 control Caucasian children aged 9 to 12 years (mean 9.6 ± 1.3 years) were studied (see Table I). The control children did not have AD, but had been referred for investigation of short stature which was unexplained at the time and which was not associated with any other chronic disease state. After investigation, all these controls were regarded as having constitutional growth delay (10). Informed consent was obtained in all cases, and the study was approved by the Medical Ethics Committee of the North Manchester Health District.

All the children were prepubertal and had marked short stature, with a standing height more than three standard deviations below the mean for British children. The skin surface area affected by AD ranged from 25% to 95% (mean 68% ± 32%) (see Table I). Three patients (cases 2, 3 and 4) had received topical 1% hydrocortisone ointment in the previous year, but the others were not receiving topical steroids. Three patients (cases 1, 2 and 4) were avoiding certain food triggers, but five day diet surveys (11) had demonstrated an intake of nutrients greater than the recommended daily amounts (12) in all 6 patients, and all patients had a serum zinc concentration which was within normal limits.

Methods

The patients were studied with a standard protocol for sleeping GH release (13) and GH release after stimulation with arginine (14). The children were admitted to hospital, connected to a four-channel ambulatory electroencephalogram (EEG) monitoring system and an intravenous cannula inserted. One ml of blood was taken at cannulation, and then every 15 min for 2 h after the patient had fallen asleep. The samples were numbered and analysed blind, to determine the time and extent of GH release. The EEG

Table I. *Description of patients and results*

Case	Sex	Age (years)	Bone age (years)	Birth weight (kg)	Height velocity (cm/year)	Skin surface area affected (%)	Peak serum growth hormone (mU/l)	
							During sleep	After arginine
Patients								
1	F	12.1	9.2	2.98	1.4	95	11.4	26
2	M	10.0	7.6	3.57	1.0	25	16	23
3	M	10.2	8.0	2.21	5.5	80	4.4	24
4	M	7.3	4.1	3.63	1.2	90	31	36
5	M	12.0	10.9	2.72	5.9	30	24	43
6	M	11.4	9.1	3.66	3.1	90	5	20
Controls								
1	M	9.8	6.9	2.95	2.1	–	16.2	6.4
2	M	9.0	6.2	3.32	3.4	–	36	35
3	F	9.6	6.2	2.69	6.7	–	68	30
4	M	9.4	6.0	2.58	1.6	–	27	25
5	M	12.0	9.3	2.75	3.4	–	17.4	79.5

recordings were analysed blind (RWN) to ensure that stage 4 sleep as defined by standard criteria (15) had occurred during blood sampling.

The following morning, after an overnight fast, an arginine stimulation test was performed. After collection of a basal sample of blood, 0.5 g arginine per kg in a 20% solution was administered intravenously over one hour. Samples of blood were collected at 15, 30, 45, 60, 90 and 120 min after the infusion was complete. Blood samples were spun, separated, and stored at −20°C until assay, and subsequently analysed for GH using a modification of Pennisi's double antibody radio-immunoassay, with the first international reference GH standard 66/217 (16).

The standard criterion that the peak serum GH level should exceed 15 mU/l was stipulated for both sleep testing (13) and arginine testing (17).

RESULTS

All patients reached stage 4 sleep during sleep sampling. The results are shown in Table I. All patients had a normal GH response to arginine, but 3 of the 6 patients had a peak sleep GH concentration below 15 mU/I. All but one of the control children with short stature had a normal GH response to arginine, and in all, the peak sleep GH concentration exceeded 15 mU/I.

DISCUSSION

The results are based on a small, selected sample of exceptionally short children with AD. In addition, interpretation of the results of the 12-year-old patient is hampered by the fact that there may be a physiological retarding of GH secretion shortly before the onset of puberty (18). Furthermore, tests of GH production are notoriously difficult to interpret, and discrepancies in results of tests using physiological and pharmacological stimuli are well known, though poorly understood (19). Finally, the setting of a normal peak GH concentration at $\geq$ 15 mU/L is entirely arbitrary, and others have used other cut-off points such as 20 mU/I (20). Nevertheless, the results showed that all 5 control children with short stature achieved normal levels of GH release after falling asleep, whereas 3 of the 6 children with AD and short stature did not. The results of arginine stimulation testing demonstrated that all patients with AD were capable of releasing GH normally in response to a pharmacological stimulus. It is important to point out that these are screening tests for GH deficiency, and that the aim of the test is simply to establish whether an individual subject releases GH above a pre-defined peak value, so that comparison of the actual values of peak GH in the two groups is inappropriate.

It is established that children with AD may have reduced amount of stage 4 sleep (6). The results suggest that there may also be an impairment of GH release during stage 4 sleep. To test this hypothesis one would need to (*a*) assess the quantity of stage 4 sleep and (*b*) quantify the release of GH throughout the periods of stage 4 sleep. It is not known whether there is a causal connection between either reduced stage 4 sleep or nocturnal GH release and short stature in children with AD. The normal levels of nocturnal GH release in three patients imply that

impaired GH release during sleep cannot be the sole mechanism causing short stature.

Parental fear of even greater growth impairment was the reason why 3 patients were not receiving topical steroids (21). The use of more potent topical steroids was avoided by us for the same reason, partly because of an increased risk of percutaneous absorption with the very widespread skin lesions, and also because the patients were approaching the pubertal growth spurt. It is possible that more vigorous steroid therapy could have resulted in clinical benefit, but this might have been at the risk of permanent growth stunting.

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