

Nocturnal growth hormone and gonadotrophin secretion in growth retarded children with Crohn's disease

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SUMMARY Although impaired growth hormone secretion in response to pharmacological stimuli occurs in some growth retarded children with Crohn's disease, its relationship to past and future growth is uncertain. We have therefore determined the growth hormone and gonadotrophin response to the physiological stimulus of sleep by continuous venous sampling in five severely growth retarded children. Growth hormone and gonadotrophin profiles, the mean plasma hormone concentrations during the first five hours of sleep were determined. In three of the five patients, five hour mean growth hormone levels were reduced (3.8, 5.0, and 8.5 mU/l) compared with levels reported previously in normal short children (10-43 mU/l), although the pulsatile pattern of growth hormone secretion was preserved in all. Nocturnal growth hormone secretion was unrelated to the growth velocities of these children during both pre- and post-treatment assessment periods but a significant correlation was found between growth hormone concentration and a disease activity score ($r = 0.79$, $P < 0.05$), suggesting that growth hormone release by the pituitary was influenced by the severity of the disease. Nocturnal growth hormone secretion was also correlated with gonadotrophin secretion (luteinising hormone, $r = 0.99$, and follicle stimulating hormone, $r = 0.96$; $P < 0.01$) indicating more extensive hypothalamic-pituitary disturbance. These findings suggest that hypothalamic-pituitary function is depressed in growth retarded children with Crohn's disease, but that abnormalities of growth hormone secretion are unlikely to be directly involved in the growth retardation seen in this condition.

Severe retardation of linear growth and delayed sexual development occur in children with Crohn's disease.¹⁻¹¹ Growth retardation may precede the development of gastrointestinal symptoms and be unrelated to the severity of the disease.^{12 13}

Although endocrine dysfunction^{6 9} and nutritional deficiency¹⁴ have been implicated as possible factors in the pathogenesis of growth retardation in Crohn's disease, the precise pathophysiological mechanisms have not been established. Impairment of growth hormone secretion in response to pharmacological stimuli occurs in some children with Crohn's disease^{6 9} but equivocal or normal growth hormone secretion has

been reported by others.^{14 15 17} The physiological rise in growth hormone during sleep¹⁸ is recognised to provide a more reliable assessment of growth hormone secretion than the conventional provocation tests^{19 20} with which results of the former may conflict.²⁰ Limited studies of growth hormone secretion during sleep in children with Crohn's disease determined by intermittent venous sampling have produced discordant results.^{14 15 17}

To clarify these issues nocturnal growth hormone secretion in growth retarded children with Crohn's disease was assessed by continuous venous sampling and compared with the growth hormone response to insulin-induced hypoglycaemia. In addition, nocturnal growth hormone secretion was related to disease activity, pre- and post-treatment growth velocity, and

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to nocturnal gonadotrophin secretion, another index of hypothalamic-pituitary function.

Methods

PATIENTS

Five consecutive children with growth retardation due to Crohn's disease were investigated. The diagnosis was based on clinical, radiological, and histological criteria.²¹ Clinical details with respect to sex, age, duration of symptoms, extent of disease, sexual development,²² and anthropometric data are shown in Table 1. All patients had marked reduction in linear growth during the year preceding the study (all were below the 3rd centile for height and weight except patient 5 who was below the 10th centile for both) and bone-age²³ was delayed by at least two years. None of the patients was receiving corticosteroid therapy or had had surgery before this study. Disease activity was rated using an activity score²⁴ which took into account both clinical and laboratory data. The maximum theoretical score using this method is 38, although in clinical practice scores rarely exceed 20.

Continuous venous sampling was achieved through a teflon or silicone elastomer²⁵ cannula in an antecubital vein, connected by polyvinyl chloride tubing and a Watson Marlowe flow inducer to an automatic sample collector. Thrombogenesis was prevented by a simultaneous, constant heparin infusion (10000 IU/ml) into the collecting system. A small dilution factor (approximately 5%) was determined from the total volume of heparin infused and the volume of the plasma samples was corrected accordingly. Blood was collected in 20 minute aliquots between approximately 22.00 and 10.00 hours. The plasma was separated immediately and stored at -20°C before analysis. Sampling was performed in a single room so that sleep was undisturbed and the periods when the child was asleep or awake were determined by continuous direct observation.

Standard insulin hypoglycaemia²⁶ (dose 0.15 u/kg) was obtained on a different day during the same

admission under identical conditions of bed rest and fasting from 20.00 hours on the evening before the study.

Plasma growth hormone concentration was determined by double antibody radioimmunoassay. Growth hormone values were expressed in mU/litre against the First International Reference Preparation (MRC 66/217). Luteinising hormone and follicle stimulating hormone were also determined by double antibody radioimmunoassay and expressed as U/litre of MRC Standards 68/40 and 78/549 respectively. All assays were subject to quality control on the Supraregional Assay Service QC Schemes.

After the growth hormone studies, patients 1, 2, and 4 were treated surgically, and patients 3 and 5 received corticosteroids. Post-treatment growth velocity was determined during the first six months follow-up. Nocturnal growth hormone secretion in these children with Crohn's disease was compared with control data obtained in normal short children reported by Howse *et al.*²⁷ who used a virtually identical continuous sampling technique and the same International Reference Standard in the growth hormone assay. Informed consent was obtained from the children and their parents before entry into the study.

Results

Growth hormone

Individual nocturnal growth hormone profiles of the five patients with Crohn's disease are shown in Fig. 1. Growth hormone is secreted in a pulsatile manner, the major peaks usually occurring during the first five hours of sleep. Although peak frequency is similar in all patients, the magnitude of the peaks varies in different patients, most markedly between patients 1 and 5. A convenient method of comparing the growth hormone response to sleep in different subjects is by determining the nocturnal mean growth hormone concentrations during the first five hours of sleep (Table 2). From the control data of Howse *et al.*,²⁷ children with chrono-

Table 1 Anthropometric and clinical details

Patient no.	Sex	Age (yr)	Bone age (yr)	Height (cm)	Weight (kg)	Puberty stage ²²	Growth velocity (cm/yr)	Growth velocity expected for bone age ²⁸ (cm/yr)	Growth rate as % of predicted	Clinical presentation	Duration of symptoms (yr)	Site of involvement		Medication at time of study
												Ileum	Colon	
1	F	15.1	10.0	129	26.1	I	0.5	5.4	9.3	Short stature	3	+	-	Nil
2	M	14.8	12.5	140	33.4	II	2.0	5.2	38.5	Short stature	2	+	+	Nil
3	M	13.1	11.0	136	30.0	I	1.6	5.0	32.0	Diarrhoea	3	+	+	Nil
4	M	20.2	15.5	155	44.3	III	2.0	4.7	42.6	Short stature	1.5	+	+	Nil
5	F	13.3	9.0	143	33.5	I	1.6	5.5	29.0	Perianal disease Diarrhoea	1.3	-	+	SZP* 3 g/day

*SZP: sulphasalazine.

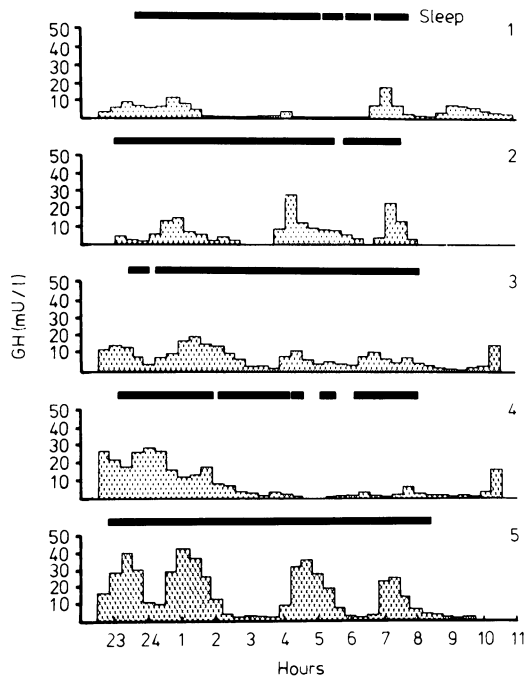


Fig. 1 Nocturnal growth hormone profiles in growth retarded children (patients 1-5) with Crohn's disease.

Table 2 Growth hormone secretion during sleep and insulin hypoglycaemia

Patient no.	Nocturnal growth hormone (mU/l)		Insulin hypoglycaemia growth hormone (mU/l)	
	Sleep 5 hour mean	Sleep peak	Basal	Peak
1	3.8	18.1	< 1.0	6.4
2	5.0	28.6	3.4	22.0
3	8.5	19.0	2.8	31.0
4	14.0	29.7	< 1.0	40.0
5	18.0	41.7	15.0	15.0
Normal values ²⁷	> 10	> 29		> 20

logical and bone ages similar to those in the present study had five hour mean growth hormone levels above 10 mU/l. According to this criterion, patients 1, 2, and 3 have inadequate sleep growth hormone responses. Similarly, peak sleep growth hormone concentrations (Table 2) in these three patients were below those of normal short children of similar age.²⁷

However, of these three patients, only patient 1 failed to demonstrate an adequate growth hormone response to insulin hypoglycaemia. Patient 5 also had an inadequate growth hormone response to insulin hypoglycaemia (Table 2), although sleep growth hormone response appeared to be normal.

GROWTH HORMONE AND GROWTH VELOCITY
The relationship between growth velocity and five hour mean growth hormone concentrations for each of the five patients is shown in Fig. 2. Five hour mean growth hormone response to sleep is not closely related

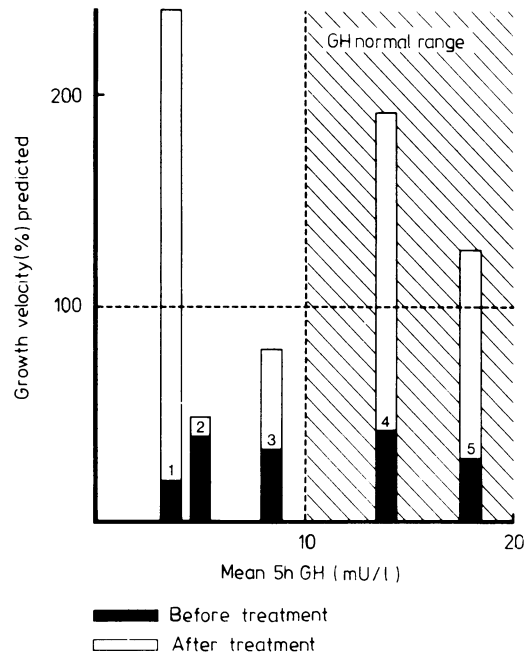


Fig. 2 Pre-treatment five hour mean growth hormone secretion during sleep and its relationship to growth velocity²⁸ before and after treatment. Growth velocities of the individual patients (numbers 1-5, Table 1) are plotted according to the five hour mean growth hormone concentration shown on the horizontal axis. The hatched area represents the normal range for five hour mean growth hormone secretion in children and adolescents of similar ages.²⁷

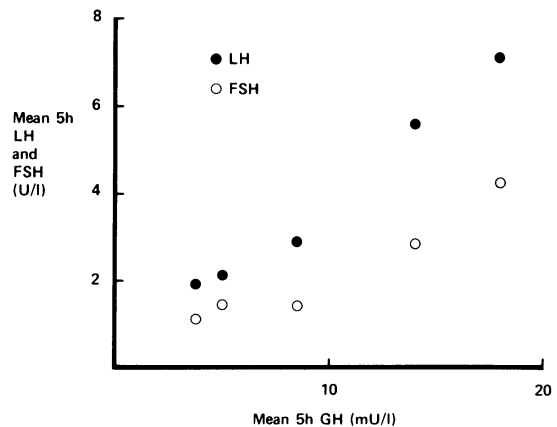


Fig. 3 The relationship between five hour mean growth hormone and gonadotrophin secretion during sleep.

to growth velocity (plotted as a percentage of the expected growth velocity for bone age²⁸) during the year before this study, nor to subsequent growth after treatment. The failure of the growth hormone response to sleep to predict future growth is particularly evident in patient 1 who had the lowest five hour mean growth hormone concentration but who had the most marked improvement in linear growth after treatment.

GROWTH HORMONE AND GONADOTROPHINS

Episodic secretion of luteinising hormone and follicle stimulating hormone was detectable only in patients 4 and 5 who had the highest five hour mean gonadotrophin levels. Figure 3 shows the highly significant linear relationship between five hour mean and growth hormone and five hour mean gonadotrophin levels in these patients with Crohn's disease (luteinising hormone, $r = 0.99$; follicle stimulating hormone, $r = 0.96$, $P < 0.01$).

GROWTH HORMONE AND DISEASE ACTIVITY

There was a significant correlation between five hour mean growth hormone secretion and the Crohn's disease activity score determined at the time of the study ($r = 0.79$, $P < 0.05$).

Discussion

This study demonstrates that the growth hormone response to sleep and insulin hypoglycaemia is reduced in some growth retarded children with Crohn's disease. Although control data for plasma nocturnal growth hormone profiles and five hour mean growth hormone concentrations were derived from published work from another centre,²⁷ this was considered reasonable in view of the difficulties of performing such studies in healthy children, and as the continuous sampling technique and growth hormone assay standards were identical.

In contrast, rises in plasma growth hormone concentration during sleep in a total of 15 growth retarded children with Crohn's disease assessed by intermittent venous sampling were considered adequate.^{14 15 17} However, the lowest acceptable sleep-related growth hormone concentration varied and decisions regarding normality in one study¹⁴ would have been reversed in another,¹⁷ depending on which control data from the literature were used. In addition, Gotlin and Dubois¹⁷ failed to find a difference between diurnal and nocturnal plasma growth hormone concentration, an observation which would now be regarded as abnormal.

Although investigators using the growth hormone response to insulin hypoglycaemia have uniformly acknowledged the occurrence of inadequate growth hormone responses in growth retarded children with Crohn's disease,^{6 9 16} there is no obvious explanation

for the discordance between the findings of the present study and earlier reports regarding sleep-related growth hormone secretion. However, the continuous sampling technique used in the present study is probably the most reliable method, as it produces a complete nocturnal growth hormone profile which permits detection of all sleep-related growth hormone peaks and therefore excludes false assignments of growth hormone insufficiency, an inherent disadvantage of the intermittent sampling methods. Previous reports,^{14 15 17} unlike the present study, did not take into account the age-related changes that occur in nocturnal growth hormone secretion,^{27 29} a factor which may account for some of the discrepancies in the literature. Disagreement between the numerous pharmacological and physiological tests of growth hormone secretion is well recognised³⁰ and was confirmed by the present study when concordance between growth hormone responses to sleep and hypoglycaemia was reached in only two of the five subjects.

The relevance of diminished growth secretion to the impairment of linear growth in children and adolescents with Crohn's disease has not been answered by previous studies, although McCaffery *et al.*⁶ did not find abnormal growth hormone responses to hypoglycaemia in any of the control subjects with Crohn's disease who had grown normally. The present study failed to detect any obvious relationship between sleep-related growth hormone secretion and growth velocity, indicating that impaired growth hormone secretion cannot be implicated directly in the growth retardation of children with Crohn's disease. There was, however, a striking relationship between five hour mean growth hormone levels and the Crohn's disease activity score in these growth retarded children with Crohn's disease, a finding which ideally should be confirmed in children with Crohn's disease who have developed normally. The severity of the disease has not been adequately stated in earlier assessments of growth hormone secretion in Crohn's disease and may have been an important factor contributing to the disparity between published findings. The importance of disease activity was emphasised by Green *et al.*⁹ who demonstrated the reversibility of abnormal growth hormone response to hypoglycaemia when the disease was in remission.

The close correlation between five hour mean growth hormone and five hour mean gonadotrophin concentrations suggest that, whatever inhibitory factors are operating, other aspects of hypothalamic-pituitary function are also involved. This finding is consistent with previous reports of reduced 24 hour urinary gonadotrophins in growth retarded children with Crohn's disease and restoration of normal plasma gonadotrophins when the disease was in remission.⁹

The mechanisms involved in the disturbance of growth hormone secretion in some growth retarded

children with Crohn's disease remain a matter for speculation. The observation that impaired growth hormone secretion in response to hypoglycaemia also occurs in children with coeliac disease^{31 32} suggests that it is probably not disease specific. Although a strong case has been made to implicate calorie deprivation as an important cause of growth retardation in children with Crohn's disease,^{14 33} basal growth hormone concentrations are usually raised during starvation and protein-calorie malnutrition.^{34 35} For this reason, it was concluded that impairment of growth secretion in coeliac disease was unlikely to be due simply to malnutrition.³¹

However, raised basal growth hormone concentration has been reported in some children with Crohn's disease^{9 15 17} and was observed in one subject in the present study (patient 5, Table 2). In addition, anterior pituitary function and growth hormone production in particular is impaired in malnourished experimental animals.^{36 37} Finally, there is now considerable evidence of reduced catecholaminergic drive during semi-starvation or fasting associated with reduction in tissue noradrenaline turnover.^{38 39} Catecholamines are important facilitatory influences on the hypothalamic-pituitary secretion of both growth hormone and the gonadotrophins⁴⁰ and it is possible that a reduced catecholaminergic drive due to calorie deprivation may partly explain the endocrine disturbance of childhood Crohn's disease and possibly coeliac disease. Although the present study has demonstrated an association between sleep-related growth hormone secretion and the severity of the Crohn's disease, disease activity and calorie deprivation are likely to be dependent variables.

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