

# Monitoring treatment in congenital adrenal hyperplasia

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**SUMMARY** We report results of monitoring treatment in 41 patients with congenital adrenal hyperplasia controlled over 0.3–13.1 years using standard auxological techniques alone. Doses of glucocorticoid (15–25 mg/m<sup>2</sup>/day) and mineralocorticoid (0.15 mg/m<sup>2</sup>/day) replacement were determined initially using biochemical indices and thereafter adjusted according to surface area. Monitoring was solely directed at maintaining a 50th centile height velocity for chronological age. Of 41 patients, 32 were referred after the newborn period. Nearly half of these patients were either overtreated or undertreated before their referral. Of the nine treated from birth, all but one were in good control and only two have had a second hospital admission. Present height standard deviation scores (SDS) for chronological age range from –1.60 to –0.26. Height SDS for bone age were compared with midparental heights in 33 patients: 15 treated with early emphasis on growth had a height prognosis exceeding midparental values; patients who had experienced appreciable prior overtreatment or undertreatment fared less well. In the long term management of congenital adrenal hyperplasia correction of salt loss is of prime importance. Doses of glucocorticoid required in addition to mineralocorticoid replacement should be continuously assessed and adjusted to maintain a normal growth velocity. This is most conveniently achieved by standardising replacement doses on surface area.

The object of treatment in congenital adrenal hyperplasia is to maintain normal health and growth by glucocorticoid and mineralocorticoid replacement, which has the effect of suppressing adrenal production of androgens and their precursors. Overtreatment or undertreatment with cortisol or fludrocortisone is detrimental in all respects but especially to growth, and strict monitoring of steroid profiles in conjunction with clinical indices has been recommended.<sup>1</sup> The pursuit of normal biochemical indices of control has been disappointing in terms of outcome.<sup>2</sup> This is probably attributable to episodic fluctuations in the secretion of steroids. We propose that the use of standard auxological techniques alone is a simple, effective, and painless method of monitoring control, and we have studied the growth of 41 patients with congenital adrenal hyperplasia who were monitored in this manner over 13 years.

## Patients and methods

Forty one patients (22 boys, 19 girls) with congenital adrenal hyperplasia (21-hydroxylase deficiency)

who had been followed up in the endocrine clinic were studied. Diagnosis was based on detailed endocrine investigations. All patients initially had raised serum 17-OH progesterone, androgen, and adrenocorticotrophic hormone concentrations and abnormal 24 hour urinary steroid excretion. A salt losing state was confirmed by the presence of hyponatraemia, hyperkalaemia, and raised plasma renin activity with low serum aldosterone concentration. Doses of replacement steroids were initially individually established while the diagnosis was being made or confirmed after referral using biochemical indices and thenceforward adjusted according to surface area to ensure the maintenance of normal growth velocity, which was taken as evidence of good control.

The patients were followed up every three months for the first one to two years of life and every six months thereafter. At all visits standard auxological assessment was performed.<sup>3</sup> Blood pressure was monitored in all salt losing patients on fludrocortisone replacement. Bone age assessment was performed at yearly or two yearly intervals after the

age of 2 years by the Tanner-Whitehouse method.<sup>4</sup> No biochemical monitoring was done after the initial investigations.

All growth measurements in this study have been expressed as a standard deviation score (SDS) for chronological age and bone age. A score was calculated from the formula<sup>5</sup>  $SDS = \frac{(X - \bar{X})}{S}$  where X is the measurement in the individual and  $\bar{X}$  and S are the mean and standard deviation respectively for the general population.<sup>6</sup> The midparental height adjusted for sex was taken as the target height and this was also expressed as a SDS.

Patients received treatment with oral hydrocortisone 15–25 mg/m<sup>2</sup>/day in two or three divided doses; prednisolone 4 mg/m<sup>2</sup>/day was used in some patients with problems of hypoglycaemia. Fludrocortisone (0.15 mg/m<sup>2</sup>/day) was given to salt losing patients in addition. In infancy, a higher dose of fludrocortisone (up to 0.25 mg/m<sup>2</sup>/day) was used on occasion in addition to salt supplementation.

The height SDS for chronological age and bone age at the time of presentation to the clinic were compared with present values. Wilcoxon matched pairs signed rank test was used to compare these

Table Clinical profile and growth data on patients with congenital adrenal hyperplasia

Patient No	Sex	Salt loser	Age at diagnosis	Age at referral to clinic	Follow up (years)	Height SDS for chronological age		Height SDS for bone age		Midparental height SDS	Comments
						At referral	At present	At referral	At present		
1	M	+	0.05	0.98	13.12	-3.08	-0.07	-3.88	-0.86	-1.26	Overtreated*
2	F	+	0.03	0.30	3.60	-2.50	-0.58	—	+0.91	+0.63	Overtreated*
3	F	+	0.03	0.30	2.09	-1.27	-1.60	—	+1.54	+1.39	Overtreated*
4	F	+	0.02	3.21	7.60	-2.00	-2.10	—	+1.34	-0.20	Overtreated*
5	M	+	0.03	2.24	3.06	-2.18	-0.75	-1.63	+0.66	-0.82	Overtreated*
6	M	+	0.03	8.35	7.65	-1.06	-1.97	+0.88	-2.36	-1.63	Overtreated*
7	M	+	0.03	10.90	6.90	-2.32	-3.34	-2.00	-3.34	-1.63	Overtreated*
8	M	+	0.04	1.50	0.30	-2.49	-2.10	—	—	-1.83	Overtreated*
9	F	+	0.03	16.23	1.60	-2.73	-2.58	-2.23	-2.58	-1.00	Undertreated*
10	F	+	0.02	5.40	5.60	+0.69	-0.60	-1.54	-1.10	+0.40	Undertreated*
11	M	+	0.05	7.73	2.83	+1.76	+0.60	-0.56	-0.63	+0.63	Undertreated*
12	M	+	0.10	9.30	4.90	+0.48	+0.42	-0.86	-0.22	+1.36	Undertreated*
13	M	+	0.04	5.50	6.20	+1.01	-0.30	-2.52	-2.14	-0.85	Undertreated*
14	F	+	0.03	12.00	6.26	+0.88	-0.70	-0.93	-0.70	+0.46	Undertreated*
15	M	+	0.03	14.60	8.20	-1.00	-2.00	-2.37	-2.00	+0.04	Undertreated*
16	M	+	0.04	6.63	4.91	-2.84	-1.79	+0.37	+0.32	-0.51	Associated partial growth hormone insufficiency
17	F	+	0.04	0.20	6.10	-1.07	-1.70	—	+1.00	+0.65	Associated partial growth hormone insufficiency
18	F	-	8.00	8.00	0.60	+1.96	+2.00	-1.60	—	+1.05	Virilisation
19	M	-	9.00	9.00	6.30	+2.39	-0.97	-2.45	-2.20	-1.15	Precocious puberty
20	M	-	7.15	12.60	2.40	+2.60	+0.63	-0.50	-0.34	+1.53	Precocious puberty
21	M	+	0.04	4.00	2.00	-0.48	-1.28	—	-1.90	-0.85	Poor compliance
22	M	+	0.04	0.44	6.67	-0.43	-0.27	-1.50	-2.30	-0.40	Poor compliance
23	M	+	0.08	2.14	1.80	-1.75	-1.30	—	-2.50	-0.40	Poor compliance
24	F	+	0.02	1.73	4.70	-0.12	0.00	-0.09	+2.80	—	Adopted child
25	M	+	0.02	3.50	5.60	-0.54	+0.25	+0.41	+0.50	+0.40	
26	F	+	0.05	0.60	4.23	-1.70	-1.13	—	+1.30	+0.63	
27	M	+	0.10	0.40	0.63	-1.10	-1.48	—	—	-0.93	
28	F	+	0.02	0.20	1.75	-0.20	-0.33	—	+1.49	+0.53	
29	F	+	0.04	1.00	3.38	-0.60	-0.66	-0.90	-0.18	-1.26	
30	F	+	0.05	7.50	9.30	-0.57	-0.30	-0.79	-0.30	-0.20	
31	F	+	0.03	0.82	2.60	-0.57	+0.96	—	+3.08	+0.97	
32	F	+	0.02	0.24	4.26	-0.32	+1.46	+0.28	-0.40	-0.20	
33	F	-	0.12	0.12	5.91	+0.88	+1.28	+1.80	-0.60	+0.35	Poor compliance
34	F	+	0.03	0.03	6.31	-2.08	-1.33	-1.59	+0.95	-0.24	Low birth weight
35	M	+	0.02	0.02	3.81	-2.00	-0.16	—	+0.34	+0.39	Low birth weight
36	F	+	0.02	0.10	3.20	-3.26	-1.60	—	+0.20	-1.00	Low birth weight
37	M	+	0.15	0.15	10.35	-2.03	-1.47	+1.76	+1.15	—	Adopted child
38	F	+	0.03	0.11	4.39	+1.53	-0.26	+3.03	+2.50	-0.48	
39	M	+	0.10	0.10	1.40	-1.99	-0.83	—	-0.83	-0.60	
40	M	+	0.03	0.18	9.97	-2.50	-1.31	-1.06	+0.20	+0.50	
41	M	+	0.04	0.10	0.50	-0.50	-0.80	—	—	+0.40	

\*Overtreated or undertreated till time of referral.

paired sets of data. The height SDS for bone age at present was compared with the midparental height SDS using the line of identity between the two.<sup>5</sup>

## Results

The clinical data of the patients are shown in the table. All had 21 hydroxylase deficiency and all but four were salt losers. The present age ranged from 0.6 to 22.8 years. Nine patients had completed puberty and five had attained final height.

Of 41 patients, 32 (patients 1–32) were referred after the newborn period and nine (patients 33–41) were treated from birth in our department.

Of the patients referred, eight had been over-treated with high doses of steroids and had growth retardation, cushingoid features, and delayed bone age and seven had been undertreated with low doses of steroids and had sexual precocity and advanced bone age at the time of referral. Two others have been found to have partial growth hormone insufficiency during follow up and have been treated additionally with daily subcutaneous growth

hormone. Three of the non-salt losers presented between 7 and 9 years of age with either signs of virilisation or precocious puberty and advanced bone age. Compliance was poor in three patients. The remaining nine patients were in good control as reflected by their normal growth.

Of those who were treated from birth, only one patient was non-compliant and had advanced bone age. The rest were in good control and only two of these patients required a further admission to hospital after the initial diagnosis had been established and treatment instituted. Present height SDS for chronological age ranged from  $-1.60$  to  $-0.26$  and for all those in whom bone age data were available, prognosis of final height was good.

Height SDS for chronological age at time of presentation to this hospital and values at present are shown in fig 1a. Height SDS for bone age are compared in a similar way in fig 1b. There were no significant changes between any of the values. In other words, the treatment regimen had been successful in maintaining normal growth from the time of its institution.

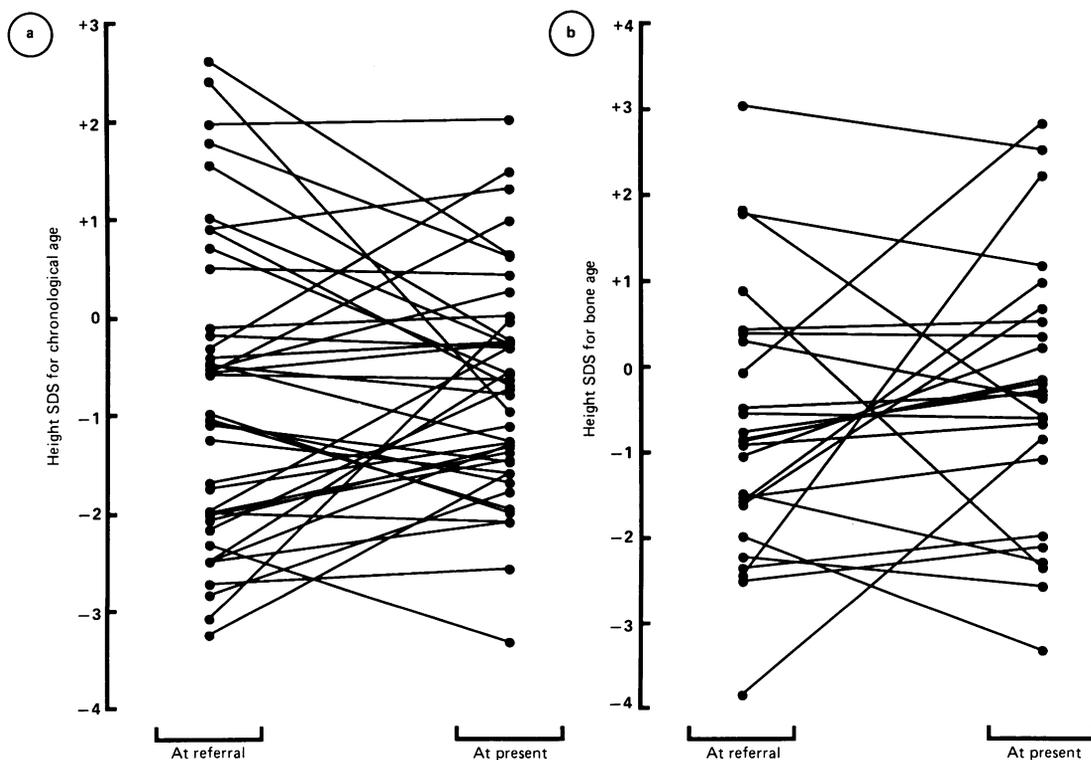


Fig 1 (a) Height SDS for chronological age at referral and at present; (b) height SDS for bone age at referral and at present.

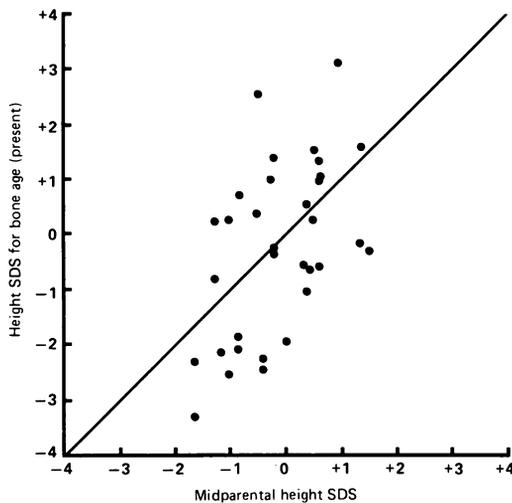


Fig 2 Comparison of height SDS for bone age at present with midparental height SDS.

Fig 2 shows the association between height SDS for bone age at present and the midparental height (target height) SDS. Of 33 sets of values available, 18 were either above or close to the line and 15 below the line. The 18 patients whose values lay above or close to the line were those treated with early emphasis on growth management. Five of these 18 were overtreated from one to three years of life before referral. One patient has already achieved a final height appropriate to target height. The remaining 17 patients will probably attain a final height at or above the target height if they remain in good control. Of the 15 whose values were below the line, four patients had attained final heights below midparental heights; they belonged to the categories of either overtreatment for a prolonged period or undertreatment with late referral. The remaining 11 patients will probably attain a final height below the target height. Of these, four were patients who were undertreated and had advanced bone age at the time of referral, one was overtreated for eight years and had growth retardation at the time of referral, two were late diagnosed congenital adrenal hyperplasia with advanced bone age, and four had poor compliance.

### Discussion

The aims of management in congenital adrenal hyperplasia are to maintain normal health, to suppress the effects of excessive androgen secretion,

to maintain a normal growth velocity, to undergo normal puberty, and to achieve a final height as close to target height as possible. Undersuppression of adrenocorticotrophic hormone leads to increased height velocity and advanced bone age; oversuppression leads to the reverse and the recommended replacement dose of cortisol in congenital adrenal hyperplasia for optimal growth effects is 20–25 mg/m<sup>2</sup>/day.<sup>7</sup> There is surprisingly little individual variation but there is a differing effect of treatment with glucocorticoids between patients.<sup>8</sup> In salt losers, adequate replacement with fludrocortisone and salt in the newborn period is crucially important for maintenance of good health and optimal control because insufficient mineralocorticoid treatment results in hypovolaemia, hyponatraemia, hyperkalaemia, and a raised plasma renin activity, which leads to loss of glucocorticoid control.<sup>9</sup> It is often not appreciated, however, that fludrocortisone not only exerts mineralocorticoid effects but also has appreciable glucocorticoid effects.<sup>10</sup> The dosage of fludrocortisone should be matched to surface area and the glucocorticoid contribution must be remembered before an increase in the dose of cortisol is instituted. At puberty, the rise in sex steroid secretion, increased growth velocity, and rapidly changing surface area require appropriate parallel increases in glucocorticoid and mineralocorticoid dosages to prevent loss of androgen control and consequent rapid acceleration in bone age.

As the object of treatment is to suppress adrenocorticotrophic hormone drive and not simply to replace cortisol and fludrocortisone, the ideal method for assessing individual dose should be to titrate the concentration of glucocorticoid against the adrenocorticotrophic hormone concentration and mineralocorticoid against plasma renin activity.<sup>11</sup> In practice, however, interpretation of the adrenocorticotrophic hormone concentration is difficult because of the circadian variation and measurement of plasma renin activity is affected by diet and postural factors.<sup>12</sup> Monitoring by single random plasma measurements of 17-OH progesterone has been shown to be unreliable as an index of therapeutic control with glucocorticoids as there is a pronounced circadian rhythm.<sup>13 14</sup> With episodic fluctuations in the secretion of the steroid and the timing of sample collection with respect to the last dose of cortisol, there is great difficulty in the interpretation of the values. Serial measurements of 17-OH progesterone in plasma, capillary blood, and saliva have been used to assess control and nomograms have been employed to interpret the daily profiles.<sup>15 16</sup>

The disadvantages of monitoring by biochemical

steroid indices are manifold. Such studies measure adequacy of control over a short period of time only. As serial sampling of saliva and capillary blood is usually undertaken at home, the validity of the technique is dependent on the reliability of the patient. Anticipation of sampling might also lead to good short term compliance with medication, which may not necessarily apply to the long term results. Infrequent sampling gives erroneous results because of the circadian rhythm and fluctuation in the secretion of steroids.

Obsession to achieve biochemical perfection often over-rides the realisation of the importance of accurate measurements of stature and assessment of growth velocity and skeletal maturity. Attempts to achieve 17-OH progesterone concentrations within the range for normal individuals by increasing or decreasing the dose of cortisol leads to oscillations between overtreatment and undertreatment, both of which are deleterious to growth.<sup>7</sup> From our data, it can be seen that this was a frequent error in the management of congenital adrenal hyperplasia, but overtreatment during the infantile component of growth is probably less hazardous in compromising height prognosis, provided the situation is rectified over the course of the childhood component of growth.<sup>17</sup> Undertreatment, on the other hand, almost always compromises final height because an advanced bone age can rarely be recovered.

Results from the study of congenital adrenal hyperplasia by Winter and Couch showed the median height to be the 25th centile.<sup>1</sup> Thus as a group, these patients were generally shorter than their peers. This has also been the experience in the study by DiMartino-Nardi *et al.*<sup>2</sup> In both of these studies, monitoring was by frequent assessments of serum 17-OH progesterone, testosterone, and plasma renin activity but more emphasis was placed on these than on growth velocity. We submit that if the desired end result is normal growth the best method of monitoring treatment is to concentrate on this rather than on biochemical indices. This requires particularly close follow up during periods of rapid growth in infancy and puberty and frequent adjustment of medication at such times.

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