Short Reports

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Linear Growth In Treated Congenital Adrenal Hyperplasia

The former high mortality rate (about 20%) in the salt-losing type of congenital adrenal hyperplasia led to a period of excessive cortisone therapy. Rappaport, Cornu, and Royer (1968) found that, as a result of such overtreatment, children who had significant growth retardation during the first 2 years of life did not show catch-up growth later. We have therefore evaluated the effects of various cortisone dose schedules on the linear growth of cases to elucidate the causes of growth failure.

Review of Cases

The heights were recorded on centile charts (Tanner and Whitehouse). Bone ages (left wrist) were read from the Greulich and Pyle atlas. Height age (HA) is the age at which the height lies on the 50th centile line.

(a) **Salt-losing type.** 27 of 35 cases treated and followed for the first 2 years of life or longer grew within the 3rd–97th centiles for height. 8 cases grew below the 3rd centile. They are presented in the Table and also discussed below. Only Case 3 has shown catch-up above the 3rd centile lines.

Cases 1, 2, and 3 had a meningocele, hiatus hernia, and ureteric and vesical calculi, respectively. They had become cushingoid due to excessive therapy. Case 3 has shown catch-up after 3 years of age and is now growing on the 25th centile line.

Cases 4, 5, and 6 were initially treated elsewhere and had been cushingoid. The latter two are now showing some catch-up but are still below the 3rd centile line.

Cases 7 and 8 grew normally for 6 months and 1 year, respectively. They showed growth failure but did not become cushingoid. Their height is still below the 3rd centile.

(b) **Simple virilizing type.** For comparison, those cases first treated before 2 years of age were reviewed. None grew below the 3rd centile, but the series is small. 5 additional cases were treated late, i.e. at 10, 6½, 6¼, and 5 years, but, nevertheless, achieved adult heights of 164, 166, 158, 154, and 158 cm, respectively. In the latter 2 cases, therapy was stopped after puberty. Four years later their 24-hour urinary 17-ketosteroids (17KS) were 67 and 47 mg, respectively. Therapy was restarted to suppress adrenal overactivity.

Discussion

Bergstrand (1966) reported normal growth rates in 28 children adequately treated from early infancy. Rappaport *et al.* (1968) reported growth failure in children who received excessive cortisone therapy during infancy, i.e. doses above 35 mg/m^2 per day. Aceto *et al.* (1966) reported that some children with the simple virilizing type of disorder who were untreated had not shown the expected abnormal growth acceleration during the first 4 years of life.

The daily oral dose of cortisone usually recommended is twice the cortisol production rate (CPR) of 12 $\pm$ 3 mg/m^2 per 24 hr, i.e. 18–30 mg/m^2 (Migeon, 1968). The cortisone doses for children growing along the 50th centile for height and weight have been calculated and reported previously (Raiti and Newns, 1970).

(a) **Salt-losers.** The 27 children who grew normally received cortisone doses which are compatible with the calculated requirements (on a surface area basis). However, during the first year of life, the doses given exceeded the calculated dose requirement. This did not appear to affect their ultimate growth in that they continued to grow on or above the 3rd centile. Cortisone in total doses of 15 mg/day appears to be adequate for the first 2 years of life. This dose permits good growth rates and also minimizes the number of impending adrenal crises due to repeated minor illnesses or stresses at this time of life.

Cortisone given in 2 or in 3 equally divided doses did not produce significant differences in growth rates. Because of its short half-life, it is generally recommended that cortisone be given 8-hourly in equal doses so as constantly to suppress pituitary ACTH secretion.

Eight cases (Table) did not grow satisfactorily. All received cortisone doses in excess of 36 mg/m^2 per 24 hours, i.e. CPR $\times$ 3, and 6 had been cushingoid. All showed retarded bone ages. Only 4 of these 8 patients are now receiving oral cortisone doses compatible with the expected requirements, 2 of whom have already shown catch-up, one up to the 25th centile. All 8 patients

still have delayed bone ages, indicating that the suppressive effects of cortisone are still evident. One important reason for growth failure, therefore, is excessive therapy for the patient's needs.

An additional reason for persistent growth failure could be that constant cortisol dose schedules suppress not only pituitary ACTH secretion, but also growth hormone release to physiological (though not to pharmacological) stimuli. Such growth hormone deficiency would also produce growth failure and bone age retardation. For these few cases, it might be advisable to vary the cortisone dose according to the expected circadian rhythm for cortisol, i.e. give larger doses in the evening or early morning and smaller doses during the day. Diurnal cortisol fluctuations are normally found after 1 year of age and the mature circadian rhythm for cortisol is established by 3 years of age (Franks, 1967). We stress, however, that most cases grow satisfactorily when they received cortisone in equal doses, 2 or 3 times a day.

The growth suppression, once induced, persists for a long time, but need not be irreversible (as shown by the 2 cases mentioned above). Such cases need less cortisone. Their urinary 17KS can be permitted to rise slightly above the usually accepted limits for age, or their 11-oxygenation index (Edwards, Makin, and Barratt, 1964) can be permitted to approach the upper limit of normal, provided that the bone age does not advance beyond the chronological age.

(b) **Simple virilizing type.** None of these cases grew below the 3rd centile and none had been cushingoid. Prednisone, when given in equivalent doses, sometimes has shown a greater suppressive effect on stature. We prefer cortisone as the drug of choice.

The 5 patients first treated after 5 years of age achieved acceptable adult heights, i.e. above 153 cm.

TABLE

Cortisone Dosage Received by 8 Cases of Salt-losing Congenital Adrenal Hyperplasia, with Growth Failure

Case No.	Chronological Age (yr)	Height (cm)	Weight (kg)	Height Age (yr)	Bone Age (yr)		Cortisone (mg/m^2 per day
1	6/12	62	6·2	3/12	—	Cortisone 10 mg b.d.	60
	16/12	73	8·9	10/12	1	Cortisone 7·5 mg t.d.s.	50
	2–3/12	78	9·8	13/12	15/12	Cortisone 5 mg t.d.s.	32
	2–9/12	80	10·3	1–3/12	—	Cortisone 5 mg t.d.s.	30
2	6/12	63	6·8	4/12	—	Cortisone 7·5 mg t.d.s.	100
	11/12	67	8·4	7/12		Cortisone 7·5 mg t.d.s.	62
	1·9/12	74	10·0	1		Cortisone 7·5 mg t.d.s.	48
3	8/12	68	7·0	6/12	—	Cortisone 10 mg b.d.	54
	1	72	7·6	9/12	—	Cortisone 10 mg b.d.	50
	2	77	10·0	1	15/12	Cortisone 10 mg b.d.	43
	3–6/12	91	15·9	2½	3	Cortisone 10 mg b.d.	32
	6–6/12	114	21·0	6	5½	Cortisone 10 mg b.d.	24
4	1–6/12	67	7·0	6/12	3/12	Prednisone 7·5 mg b.d.	—
	2–3/12	76	8·5	1	2	Prednisone 7·5 mg t.d.s.	—
	4–9/12	90	11·8	2½	3	Cortisone 7·5 mg t.d.s.	40
	5–3/12	95	12·7	3	—	Cortisone 7·5 mg t.d.s.	39
5	2–4/12	77	10·0	1	15/12	Cortisone 5 mg t.d.s.	31
	4–6/12	92	14·6	2¾	2–10/12	Cortisone 5 mg t.d.s.	24
	5–6/12	100	18·3	3¾	—	Cortisone 5 mg t.d.s.	20
6	2	73	9·6	10/12	—	Cortisone 12·5 mg b.d.	54
	3–2/12	87	10·5	2½	—	Cortisone 12·5 mg b.d.	50
	6–3/12	103	18	4½	5	Cortisone 12·5 mg b.d.	35
7	1	65	6·4	6/12	—	Cortisone 7·5 mg t.d.s.	64
	2	75	8·4	1	15/12	Cortisone 7·5 mg t.d.s.	50
	3	85	11	2	—	Cortisone 7·5 mg t.d.s.	43
	4	90	12	3½	—	Cortisone 7·5 mg t.d.s.	40
	6	101	14·8	4	—	Cortisone 7·5 mg t.d.s.	35
8	1	69	8·3	9/12		Cortisone 7·5 mg t.d.s.	54
	2–6/12	80	10	1½	1½	Cortisone 7·5 mg t.d.s.	47
	3–3/4	86	13	2½	1½	Cortisone 5 mg t.d.s.	26
	5	94	15·1	3–2/12	2	Cortisone 5 mg t.d.s.	23

These patients may not have shown excessive growth during early childhood as observed by Aceto *et al.* (1966). After therapy was stopped, 2 cases showed the expected adrenal overactivity (high urinary 17KS). Treatment must, therefore, be continued.

The present management for all types of congenital adrenal hyperplasia was recently reviewed (Raiti and Newns, 1970). The criteria for diagnosis have not altered (Raiti and Newns, 1964).

Summary

Twenty-seven of 35 cases with the salt-losing type and all 10 with the simple virilizing type grew within the 3rd-97th centile for height. 8 of the salt-losers grew below the 3rd centile; all had received excessive cortisone, and all had delayed bone ages.

The total daily cortisone replacement dose should be based on the expected cortisol production rate for body size, and should not exceed twice this rate, which is 12 mg/m^2 per 24 hr. No difference in growth pattern was found when cortisone was given either in 2 or 3 equally divided doses. During the first two years of life, a minimum cortisone dose of 15 mg/day is recommended (in divided doses), even though this exceeds the calculated requirement.

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Effect of Gonadotrophin Therapy on Testicular Volume and Sexual Development in Adolescent Boys with Hypogonadotrophic Hypogonadism

Most of the recent reports on gonadotrophin therapy of eunuchoidism deal with its effect on adult hypogonadotrophic males, with particular emphasis on the restoration of spermatogenesis. Studies of the adolescent age group, including serial measurements of testicular volume, are few (Johnsen, 1966; Lytton and Kase, 1966; Crooke, Davies, and Morris, 1968). This report was designed to evaluate the effect of human chorionic gonadotrophin (HCG), singly and in combination with human menopausal gonadotrophin (HMG), on testicular volume and on secondary sexual characteristics in a group of adolescent hypogonadotrophic boys.

Patients and Methods

Six adolescent patients with hypogonadotrophic hypogonadism were treated with HCG and HGM for periods ranging from 3 to 25 months. Endocrine evaluation revealed isolated gonadotrophin deficiency in 5 and associated insufficiency of ACTH, TSH, and GH in one patient (Case 6). All periodically underwent a complete physical examination which included body measurements and evaluation of sexual development. Testicular volume was estimated by means of an 'orchidometer', i.e. a series of ellipsoids of known volume (Prader, 1966; Zilka and Laron, 1969). The diameter of the penis and its extended length were measured in millimetres with a slide caliper. Sexual hair was scored by arbitrary signs, and 6 stages were graded from — to ++. Skeletal age was estimated according to the Atlas of Greulich and Pyle (1960). Urinary 17-ketosteroids were assayed by the method of Peterson and Pierce (1960). Determination of urinary gonadotrophins in terms of mouse uterine units was performed by a modification of the method described by Albert (1955).

Treatment. HCG, given as a source of ICSH activity, was administered intramuscularly twice weekly. Case 1: 2000 IU/wk for 6½ mth; Case 2: 2000 IU/wk for 3 mth and 3000 IU/wk for 16 mth; Case 3: 1000–5000 IU/wk for 30 mth and 10,000 IU/wk for 7 mth; Case 4: 3000 IU/wk for 3 mth and 5000 IU/wk for 16 mth; Case 5: 5000 IU/wk for 15 mth; Case 6: 3000 IU/wk for 8 mth. HMG (Pergonal—500*), given as a source of FSH activity, will be referred to in terms of

*Pergonal-500: lyophilized HMG from human menopausal urine prepared by Instituto Farmacologico Serono, Rome, Italy, marketed in Israel by Ikapharm. One ampoule contains 75 IU FSH and 75 IU ICSH.