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Adrenal Response to ACTH in Patients with Prader-Willi Syndrome, Simple Obesity, and Constitutional Dwarfism

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In 1956 Prader, Labhart, and Willi first described a group of patients who presented with 'floppiness' at birth and later became obese, dwarfed, and mentally retarded, and some had impaired glucose tolerance tests. Further articles followed (Prader and Willi, 1961; Laurance, 1961, 1967; Forssman and Hagberg, 1964; Evans, 1964; Hooft, Delire, and Casneuf, 1966).

Laurance gave a detailed description of the syndrome. The features which he considered characteristic were obesity, mental retardation, hypogonadism, hypotonia, shortness of stature, prominent forehead, almond-shaped eyes, *retroussé* nose, small fish-like mouth, short hands and feet. All of them were floppy at birth and some of them showed a diabetic type of glucose tolerance test. Laurance concluded that the adrenal function was normal in these patients, but Forssman and Hagberg reported a reduced response to ACTH. In the present paper we report a comparison of the plasma cortisol response to ACTH in 22 subjects, 6 of whom were children showing the features of Prader-Willi syndrome as described above. Of the remainder, 6 were children with constitutional short stature, 4 were children with simple obesity, and 6 were healthy adolescents with no known metabolic disease. Evidence is also presented from the results of long-term ACTH (3 days) in 2 cases of Prader-Willi syndrome that the urinary 17-OHCS output parallels their plasma cortisol response.

Materials and Methods

Plasma cortisol was estimated by the fluorimetric procedure of Rudd, Sampson, and Brooke (1963). The output of 17-OHCS in the urine was measured as Porter-Silber chromogens, employing a modification of the colorimetric procedure of Silber and Porter (1954). Urinary steroid data are expressed in terms of body weight, in view of the close correlation of steroid excretion rates with this body parameter under basal conditions (Tanner *et al.*, 1959), and under conditions of adrenocortical stimulation with ACTH (Prezio *et al.*, 1964).

ACTH test. Short-term and long-term tests were carried out.

(1) *Short-term.* Plasma cortisol levels were measured before and after a single injection of ACTH. The test was conducted in the following manner.

A venous sample of heparinized plasma was obtained at 10 a.m. (basal); 40 I.U. ACTH (Organon Zinc) were then given intramuscularly and further blood samples were obtained at 2, 4, and 6 hours after the injection of ACTH (Jenkins, Pilkington, and Rosenoer, 1960).

(2) *Long-term* (3-day ACTH test). 17-OHCS were measured before and after three consecutive days of adrenocortical stimulation with ACTH. The procedure adopted was similar to that described by Clayton, Edwards, and Renwick (1963). A baseline 24-hour urine was collected on the first day. 20 I.U. ACTH (Crookes Gel) were then given intramuscularly twice daily (6 a.m. and 6 p.m.) for 3 consecutive days, and 24-hour urine samples were collected on each day. The creatinine content of each urine was measured as an index of accurate daily collection.

Results

The clinical findings in the 6 children with Prader-Willi syndrome (Cases 17 to 22) are shown in Table I. The plasma cortisol responses obtained in the four groups are shown in Table II. Table III shows the age and body parameters of the patients with constitutional shortness of stature (Cases 7-12), and simple obesity (Cases 13-16). Our normal controls were 6 healthy young adults (Cases 1–6), 3 male and 3 female of normal height and weight whose ages ranged from 16½ to 19 years, mean 18 years. As an index of a normal response to ACTH, the mean responses

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TABLE I

Details of 6 Cases with Prader-Willi Syndrome

	Case 17	Case 18	Case 19	Case 20	Case 21	Case 22
Age (yr.)	14 10/12	13 10/12	13 8/12	8 11/12	12 11/12	8
Sex	F	M	M	M	F	F
Height (cm.)	132·7	128·9	148·6	127·6	146·7	120·7
Height age (yr.)	9½	8 4/12	12 4/12	8 4/12	12	7¼
Weight (kg.)	73	60·78	84·36	29·48	65·3	39
Weight age (yr.)	18+	17¼	18+	10 4/12	18+	12½
Birthweight (g.)	2720	2948	3117	2260	2806	2514
Floppy at birth	+	+	+	+	+	+
Muscular hypotonia	+	+	+	+	+	+
Mental retardation	+	+	+	+	+	+
Obesity	+	+	+	+	+	+
Short stature	+	+	+	—	+	+
Typical facial appearance	+	+	+	+	+	+
Cryptorchidism in males		+	+	+		
Delayed secondary sexual development	+	+	+		+	
Skeletal abnormalities	?	+	+		+	
Diabetic type glucose tolerance test				+		+

TABLE II

Plasma Cortisol Levels after ACTH

Case No.	Age (yr.)	Sex	Baseline	Hours after ACTH		
				2 hours	4 hours	6 hours
Group 1 (normal adolescents)						
1	19	M	14·0	27·3	33·3	33·3
2	18	M	14·7	32·0	36·0	43·3
3	19	F	15·4	34·7	38·5	40·0
4	17½	F	11·3	34·7	46·6	44·0
5	18	M	7·0	21·0	30·1	29·4
6	16½	F	15·4	32·9	47·6	55·1
Mean ±2 SD			13·0±6·6	30·4±10·8	38·7±14·2	40·9±18·0
95% limits			(6·4–19·6)	(19·6–41·2)	(24·5–52·9)	(22·9–58·9)
Group 2 (children of short stature)						
7	5½	M	9·0	25·5	29·0	
8	8	M	10·0	42·0	36·0	40·0
9	9	M	11·9	31·0		41·0
10	9 7/12	M	12·2	29·6	37·6	38·1
11	5½	F	7·0	29·5		32·0
12	8½	F	17·0	39·2	43·0	47·4
Mean			11·2	32·8	36·4	39·7
Group 3 (children with obesity)						
13	11	F	18·0	37·4	38·3	38·3
14	2½	F	9·2	32·2	40·5	41·1
15	11 7/12	M	8·0	27·4	29·2	33·7
16	14 7/12	M	10·0	43·7	47·8	—
Mean			12·0	35·2	39·0	39·3
Group 4 (children with Prader-Willi syndrome)						
17	14 10/12	F	11·2	14·8	23·0	23·0
18	13 10/12	M	14·7		20·0	
19	13 8/12	M	5·8	25·3	25·3	
20	8 11/12	M	13·7	35·8	43·7	44·7
21	12 11/12	F	16·5	19·5	26·2	27·5
Mean			12·4	23·4	27·6	31·7

TABLE III

Cases with Short Stature (7–12), and with Obesity (13–16)

Case No.	Age Years	Age Months	Sex	Height (cm.)	Weight (kg.)	Height Age Years	Height Age Months	Weight Age Years	Weight Age Months
7	5	6	M	87·6	11·8	2	3	1	7
8	8	0	M	101·6	14·7	4	1	2	9
9	9	0	M	111·8	19·5	6	0	5	8
10	9	7	M	121·9	22·7	7	3	7	3
11	5	6	F	87·6	11·6	2	4	1	11
12	8	6	F	108·6	16·3	5	2	4	7
13	11	0	F	139·7	54·3	10	6	13	5
14	2	6	F	102·9	19·1	4	4	6	0
15	11	7	M	149·2	66·9	12	6	18+	
16	14	7	M	128·3	43·8	8	6	13	6

(±2 SD) found for the young adults 4 hours after ACTH have been used, and they were for this normal graph 38·7±14·2 μg. cortisol/100 ml. plasma.

Individual values obtained at 4 hours in the children with constitutional dwarfism were within the normal limits. Similar responses were obtained for the patients with simple obesity. The obese children compared with the children with constitutional short stature showed slightly higher, but statistically insignificant mean values. When individual values for the children with Prader-Willi syndrome were compared to the normal controls at 4 hours after ACTH, 2 of the 5 patients (Cases 17 and 18) showed a response outside the 95% confidence limits, 2 had responses at the lower limits of normal (Cases 19 and 21), and 1 had a normal response (Case 20).

Two patients with Prader-Willi syndrome were also studied after ACTH stimulation for 3 days (Cases 17 and 22). In Fig. 1 values of 17-OHCS obtained for these 2 children are shown with the mean excretion rate obtained in 12 children with short stature and 4 children of normal stature in early puberty.

The 2 patients with Prader-Willi syndrome failed to produce an adequate 17-OHCS excretion after the prolonged stimulation with ACTH. Case 17 also had a poor response to ACTH in the short-term test.

Discussion

Investigations of the function of the pituitary and adrenal cortex have given normal results in most cases (Laurance, 1967), but in Forssman and Hagberg's patient there was a poor response to ACTH. The results reported here show that in some patients with Prader-Willi syndrome a

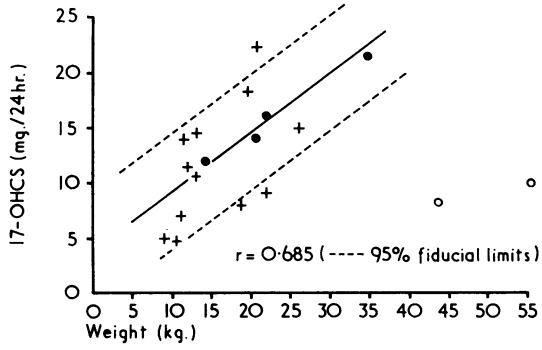

FIG. 1.—*Mean (3-day) responses to ACTH.* + = *short children;* ● = *normal stature (early puberty);* O = *Prader-Willi syndrome.*

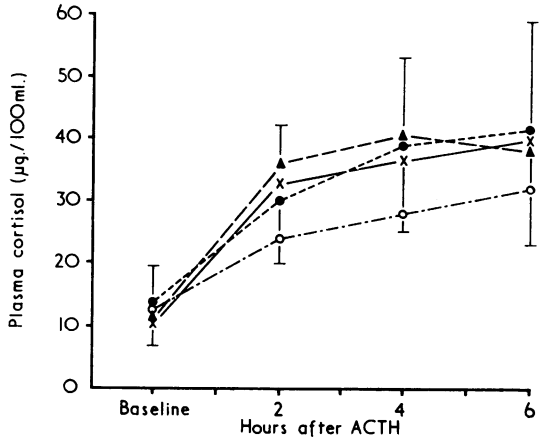

FIG. 2.—*Plasma cortisol levels in the 4 groups after ACTH stimulation.* ● = *normals (±2 SD);* ▲ = *obesity;* × = *short children;* O = *Prader-Willi syndrome.*

partial failure of adrenal response is present. 3 out of the 6 children with Prader-Willi syndrome had a poor response to ACTH, and when the results are compared with those obtained in children with short stature or simple obesity, these responses are still abnormal. It appears then that neither shortness of stature nor obesity are the factors responsible for the inadequate responses.

The children with Prader-Willi syndrome were, on average, heavier than the children in the other two groups, and the possibility therefore exists that since a fixed dose (40 I.U.) of ACTH was used for adrenal stimulation, when plasma cortisols were measured, a submaximal dose might have contributed to the reduced responses. We feel that this explanation is unlikely, however. The dose of ACTH employed was that suggested by Jenkins (1961), who showed that 40 I.U. produced an adequate plasma cortisol response in normal adults at 4 hours. In addition, the 2 children with Prader-Willi syndrome who were re-investigated using the 3-day stimulation test did not show any evidence of a normal increase in 17-OHCS output, despite the fact that a total dose of 120 units of ACTH was used.

Summary

Adrenal function in 6 children with Prader-Willi syndrome was evaluated. 2 of 5 had a poor cortisol response to short-term ACTH stimulation. Further studies using a long-term ACTH test with measurement of 17-OHCS urinary excretion in 2 of the children confirmed that adrenal function was deficient.

Neither adiposity nor shortness of stature appeared to be directly concerned in this defective adrenal response to ACTH stimulation, because similar tests applied to 6 children with constitutional short stature, 4 children with simple obesity, and 6 healthy adolescents gave normal results.

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