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Biochemical and Endocrinological Studies in Parasite-infested Patients with and without Infantilism

By

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The pituitary adrenal axis was assessed by estimation of the basal cortisol level and of the adrenal reponse to ACTH stimulation and to insulin hypoglycaemia in 5 bilharziasis patients with a similar infestation.

The basal cortisol level was normal in both groups and the adrenals responsed normally to both ACTH and hypoglycaemia, a conclusive evidence of a normal adrenal axis.

Urinary total and differential oestrogen values were equally elevated in all patients with or without infantilism with no significant difference between them. 17 KS excretion was below normal in all cases, whereas 17 OH-CS excretion was in the normal range. Urinary gonadotrophins were negative in 4 out of the 5 cases with infantilism, while only in one out of the 8 cases with no infantilism.

Undernutrition and excess oestrogens, as possible aetiopathogenetic factors in the production of infantilism are discussed and a pituitary origin of the defect is postulated.

Parasistim and in particular infestation with bilharziasis during childhood can adversely affect somatic and sexual development, and a condition of parasitic infantilism may ensue. The underlying pathomechanism is obscure.

There is much controversy concerning the mode by which protracted undernutrition can delay development. It has been suggested by Talbot and Sobel [19] to be the result of a general body cell defect, whereas Mullinos and Pomerantz [12, 13] reported that undernutrition produces a condition of pseudohypophysectomy, and Goth et al. [10] showed that protein deficiency depresses all pituitary hormones. Ershoff [8] and El-Ridi et al. [6], however, showed that the endocrinopathy is primarily a defect in the pituitary hormones and not in their production.

In a previous report, El-Sheikh [7] investigated the hypothalamo-pituitary-adrenal function in parasitic infantilism by using the metyrapone test; but this test examines only one component of the endocrine axis and not the functional status of the entire system.

This paper deals with the other trials at throwing further light on the problem by studying the pituitary-adrenal as well as the pituitary-gonadal axises in such patients.

Material and Methods

Thirteen male farmers suffering from bilharzial hepatic fibrosis, of whom five had clinical parasitic infantilism, formed the material of the present study. The patients were studied clinically and subjected to routine liver function tests, faecal, urine and blood analysis. Estimation of total and fractional urinary oestrogen was carried out by a modification [1, 12] of Miller's method. Total urinary gonadotrophins were estimated biologically by the mouse test [3]; urinary 17-ketosteroids by the method of Callow [5] with some modification [2], and urinary hydroxycorticosteroids by the method of Porter and Silber [15, 18].

The pituitary suprarenal axis was tested on the basis of the plasma cortisol index in response to insulin hypoglycaemia and to ACTH administration. The insulin tolerance test was started between 9 and 10 a.m. after an overnight fast and the subjects were kept at rest in the horizontal position for at least half an hour. An indwelling needle was inserted and blood samples were taken then and half an hour later. The lowest level of plasma steroid reached was considered the basal reading. A control sample was obtained for basal plasma cortisol and blood sugar levels. Insulin (0.1 μ/kg body wt.) was then given intravenously and samples were obtained at 20, 30, 60, 90 and 120 min. following the injection. All samples were subjected to glucose estimation while the 20, 30 and 120 min. samples were used for cortisol estimation; the highest level measured was used for calculating the increment of response to hypoglycaemic stress. Plasma adrenal corticosteroids were measured fluorometrically by the method of Spencer Peet et al. [19].

One week after the insulin tolerance test, the response to ACTH was studied as follows. A heparinized blood sample was taken early in the morning before giving the patient an intramuscular injection of 0.4 mg depot ACTH. Blood samples for cortisol estimations were taken 8 hrs and 24 hrs after the injection. The test was carried out in five patients, on the day following the insulin tolerance test and was repeated one week later.

Results

The clinical and laboratory findings in the 5 patients with parasitic infantilism have been compared with those of the 8 patients with normal somatic and sexual development. Results are shown in Tables I to IV.

The results showed that

(1) all patients with long-standing grave parasitism, whether infantile or not and regardless of the presence of hepatic disturbances, display undernutrition;

(2) most patients had mixed parasitic infection; long-standing bilharziasis ravaged all the victims;

(3) age estimated on the basis of body measurements and bone age, lagged much behind the actual age; body measurements were all equally inferior but proportionate;

(4) all infantile cases showed subnormal but proportionate body measurements, absence of secondary sexual characters and sex organs of infantile or prepubertal size;

(5) the level of intelligence was below normal at the actual age in all cases;

(6) liver function was deranged in 9 cases, and there was hypoalbuminaemia in 9 cases;

(7) patients in both groups had a normal basal cortisol level;

(8) patients in both groups had a

normal adrenal response to ACTH stimulation and to hypoglycaemic stress.

(9) there was no significant difference between the two groups in basal cortisol level and in response to ACTH, but the infantile cases displayed a significantly more intensive response to insulin hypoglycaemia.

Discussion

The study of the pituitary adrenal axis in bilharzial patients with stunted growth coupled with failure to attain sexual maturity, i.e. parasitic infantilism, showed a normal basal secretion of cortisol and a normal response to both insulin hypoglycaemia and exogenous ACTH. This allows the conclusion that the pituitary adrenal axis is not deranged in patients with protracted bilharzial infestation which is often accompanied by undernutrition. The low urinary 17-ketosteroids (17 KS) in the presence of normal 17-hydroxy steroids (17-OH-CS) was also in favour of a normal adrenal cortex.

The present results are in accord with those of Lamy et al. [11], who failed to demonstrate significant changes in adrenal function in patients with undernutrition, but do not agree with the findings of several other authors [6, 7, 13] who used indirect parameters for the assessment of the pituitary-adrenal axis.

The failure of the adrenals to respond to ACTH stimulation when given on the second day after the hypoglycaemic stress may suggest a hypofunction of adrenals which becomes evident under the effect of successive stresses.

A comparison of the patients with infantilism presumably caused by protracted parasitism since childhood with patients having the same parasitism but without infantilism, revealed no significant differences either in the basal cortisol level or in the response of the adrenals to ACTH ($p < 0.2 > 0.2$ and > 0.3, respectively). However, insulin hypoglycaemia induced a significantly more intensive adrenal response in the first group ($p < 0.01$).

In the 17-KS level there was a significant difference between the patients with infantilism and the group without infantilism ($p < 0.01$). It has to be noted that a lack of Leydig's cells was revealed by testicular biopsy in cases with infantilism [8]. All our patients whether with or without infantilism displayed high urinary oestrogen values [1, 9].

Malnutrition which is known to depress all pituitary trophic hormones including naturally gonadotrophins and somatotrophin could have been regarded as an operating factor in the infantilism. However, in spite of the fact that undernutrition affects the whole of the endocrine system and all the pituitary functions, our cases of parasitic infantilism showed a normal adrenal function and a normal ACTH output. This, as well as the fact that most but not all the infantile cases displayed undernutrition, would argue against this possibility.

TABLE I

Cases of bilharzial hepatic fibrosis with

No.	Age	Wt.	Height	Span	Estimated age (yrs)	Genital	Secondary sex characteristics	Liver size (fb)	Spleen size (fb)
			Upper limb to low limb						
1	12	32	125.5 (1.0)	135	0.8	Infantile	Absent	+4	+2 Bilh.
2	21	65	164 (1.0)	185	12.0	N	N	+3	+6
3	40	60	155 (1.1)	155	40.0	N	N	+3	+7
4	31	63	160 (1.0)	175	31.0	N	N	N	+3
5	14	39	140 (0.9)	146	12.0	Infantile	Absent	+4	+2
6	15	30	140 (0.9)	137	11.0	Infantile	Absent	+3	N
7	21	39	146 (1.08)	141	12.0	Prepubertal	Absent	+4	+2
8	35	64	164 (1.0)	164	35.0	N	N	N	+8
9	25	53	176 (1.1)	178	25.0	N	N	N	+8
10	10	50	128.0 (1.08)	130	10.0	N	N	+5	+3
11	15	31	145 (1.0)	156	11.0	Infantile	Absent	+5	Huge
12	20	51	169 (1.0)	169	20.0	N	N	+3	+4
13	55	60	189 (1.0)	189	55.0	N	N	N	+3

The hyper-oestrogenaemia present in both groups could have a hepatic origin analogous to that reported in severe liver disease [1, 4, 9]; it is known to act through an inhibition of the anterior pituitary trophic hormones. If this condition is induced early in life, it may lead to severe hypogonadism or even infantilism.

Again, the finding of a low 17-KS associated with normal 17-OH-KS in the present series would substantiate

and without parasitic infantilism

Additional parasitic infestation	Blood counts	Liver function tests					State of nutrition
		Serum bilirubin	Serum proteins		Zinc S. turbidity	Thymol turbidity	
			Total	A/G ratio			
Ascaris in stools	Anaemia Eosinophilia	0.20	7.00	0.92	12	8	Fair
—	Anaemia Eosinophilia	0.30	8.00	1.80	10	8	Fair
—	Normal	0.75	6.75	1.44	11	5	Fair
		0.84	7.60	1.10	5	2	Fair
Ancylostoma	Anaemia Eosinophilia	0.10	7.20	0.80	8	3	Moderate under-nutrition
Ascaris	Anaemia Eosinophilia	0.57	5.40	0.61	6	4	Poor
Ancylostoma	Anaemia Eosinophilia	0.75	5.50	0.43	6	3	Poor
Ancylostoma	Anaemia Eosinophilia	0.20	8.00	0.66	12	9	Fair
—	Normal	1.30	6.40	1.51	15	9	Fair
	Normal	0.50	7.80	0.26	13	6	Fair
Ancylostoma	Normal	0.50	7.00	0.54	13	6	Poor
—	Anaemia	0.65	8.00	0.33	14	5	Fair
—	Anaemia	0.15	6.50	0.43	11	6	Fair

a gonadal origin of the defect; yet excess oestrogen is known to inhibit corticosteroid biosynthesis, with a subsequent reduction of urinary 17-KS output [21].

Hyperoestrogenism was undoubtedly an operating factor but could not be the sole one, as some cases in the present series had minimal hepatic damage and some had none whatever.

TABLE II

Plasma cortisol response to ACTH

No.	Age	Basal cortisol µg per 100 ml	8 hours		24 hours	
			µg per 100 ml	increase percent	µg per 100 ml	increase or decrease per cent
		A. Cases with infantilism				
1	12	20.0	28	40	16	— 20
5	14	12.0	32	166.6	42	+250
6	15	12.0	16	31.1	14	+ 14.7
7	21	19.0	29	52.6	21	+ 10.5
11	15	18.0	26	44.4	18.5	+ 2.8
	Mean	16.24	26.2	+66.94	22.3	51.6
	SE ±	± 1.72	±2.7	±15.06	±5.06	± 7.3
		B. Cases without infantilism				
2	21	29.3	51	70.6	16	— 45.4
3	40	24.0	48	100	56	+141.6
4	31	15.5	28	80.6	18	+ 16.1
8	35	12.0	23	91.6	14	+ 16.6
9	25	18.0	22	22.2	20	+ 11.1
10	10	21.0	28	33.3	23	+ 9.5
12	20	13.3	16.6	24.7	11	— 17.3
13	55	29.2	37.3	24.7	32	+ 9.6
	Mean	20.28	31.73	44.7	23.75	+ 17.7
		± 2.4	±4.4	±10.17	±5.13	± 15.99
Significance		$p < 0.2$	$p > 0.3$	$p > 0.2$	$p > 0.8$	$p > 0.3$

It has been reported that children have LH and FSH gonadotrophins long before puberty and a marked increase above prepubertal level was noticed at puberty and was correlated with the early stages of pubertal development [16, 17, 22]. There is much controversy about the role they play in prepubertal age; an effect on growth has been postulated.

Urinary gonadotrophins were negative in 4 and equivocal in one of the 5 cases of parasitic infantilism, while only in one of the cases with no infantilism. Their lack was naturally responsible for the failure of sexual development and pointed to a defective pituitary function.

Could the gonadotrophins be also responsible for the defective somatic development or was there a deficiency of somatotrophin as well? The question will only be settled when a method of growth hormone immunoassay will be available.

TABLE III

Plasma cortisol response to insulin hypoglycaemia

No.	Age	Blood sugar		Plasma cortisol	
		min. value mg per 100 ml	fall per cent	max. value µg per 100 ml	max. rise above basal value
		A. Cases with parasitic infantilism			
1	12	38.0	31.8	32.0	14.0
5	14	32.0	50.0	26.0	17.4
6	15	50.0	57.0	32.0	19.7
7	21	80.0	38.0	54.5	27.7
11	15	41.0	56.0	32.5	19.3
	Mean	48.2	46.5	35.4	19.62
	SE±	± 8.46	±6.87	±4.92	±2.237
		B. Cases without infantilism			
2	21	35.0	46.0	38.0	12.0
3	40	50.0	45.0	33.3	12.3
4	31	85.0	40.0	30.0	9.5
8	35	59.0	31.0	25.0	10.0
9	25	40.0	55.0	28.0	10.0
10	10	25.0	67.0	24.6	5.8
12	20	28.0	57.0	20.0	5.5
13	55	50.0	45.0	33.0	12.0
	Mean	46.5	48.25	28.98	9.63
	SE±	± 6.27	±3.93	±4.18	±0.948
		$p < 0.8$	$p > 0.8$	$p > 0.4$	$p < 0.01$

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TABLE IV

Urinary oestrogens; 17-ketosteroids and hydroxysteroids, and gonadotrophins

No.	Age	Oestrogens				Corticosteroids mg/24 hr.		Gonadotrophins
		E^1	E_2	E_3		17-Keto-steroid	17-OH-CS	
					A. Cases with infantilism			
1	12	4.0	6.2	2.8	13.0	1.00	3.2	Negative
5	14	3.8	6.6	3.8	14.2	0.75	4.1	Equivocal
6	15	3.0	5.0	3.9	11.9	0.19	4.6	Negative
7	21	4.0	12.0	4.0	20.0	1.40	5.2	Negative
11	15	1.8	4.6	2.8	9.2	0.23	3.6	Negative
	Mean	3.33±	6.85±	3.44±	13.46±	0.714±	4.14±	
	SE±	0.42	1.33	0.43	1.51	0.216	0.235	
					B. Cases without infantilism			
2	21	6.2	8.0	3.5	17.7	1.20	3.2	Positive
3	40	5.2	9.2	5.2	19.6	0.90	4.3	Positive
4	31	6.5	8.5	4.5	19.5	1.50	5.1	Positive
8	35	6.2	7.2	7.3	20.9	2.00	6.4	Positive
9	25	5.5	5.0	2.8	13.3	0.93	2.3	Equivocal
10	10	2.5	3.0	1.9	7.4	1.50	4.2	Equivocal
12	20	7.0	10.0	3.0	20.0	1.10	3.7	Negative
13	55	8.0	7.5	3.7	19.2	2.85	5.2	Positive
	Mean	5.8±	7.3±	3.9±	15.95±	1.497±	4.3±	
	SE±	0.574	0.591	0.59	3.2	0.23	0.14	
Significance		$p < 0.5$	$p < 0.2$	$p < 0.5$	$p < 0.8$	$p < 0.01$	$p > 0.4$	

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