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Endocrinopathy in thalassaemia major

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McIntosh, N. (1976). *Archives of Disease in Childhood*, **51**, 195. **Endocrinopathy in thalassaemia major.** Pituitary, adrenal, and pancreatic functions were investigated in 9 patients with thalassaemia major. 9 a.m. plasma ACTH values were 148–480 pg/ml (normal range 15–70 pg/ml). Cortisol and growth hormone response to insulin-induced hypoglycaemia was normal in all. 24-hour urinary excretions of 17-ketosteroids and 17-hydroxycorticosteroids were normal. There was normal cortisol response to intramuscular injection of ACTH. In a physiological adrenal stimulation test there was a significantly smaller response to each physiological dose of tetracosactrin. 4 patients had diabetic glucose tolerance tests—none are clinically diabetic. The mean plasma glucose utilization constant ($K_{gl} = 2.02$) is significantly smaller than normal. Plasma insulin response both in the oral and the intravenous glucose tolerance test was significantly smaller than normal.

The data were consistent with severe and widespread impairment of endocrine function and a plausible explanation would be iron deposition in endocrine organs. It is suggested that pituitary hyperfunction of ACTH secretion is due to target organ unresponsiveness which can be shown in its early stages only by a physiological test of the adrenal cortex. Skin pigmentation in thalassaemia seems to be due to the melanophore-stimulating effect of this raised plasma ACTH.

Soon after the first report of thalassaemia major (Cooley and Lee, 1925), it was realized that in many cases cause of death was related to iron load, and this was identical clinically and pathologically with that seen in idiopathic haemochromatosis (Erlandson, Brilliant, and Smith, 1964; Fink, 1964). In both conditions pathological studies have shown haemosiderin deposition in liver, spleen, heart, kidney, in most endocrine organs, but not in the skin (Ellis, Schulman, and Smith, 1954). Transfusion haemosiderosis shows the same distribution, but heavier deposition, in the reticulo-endothelial system, almost certainly due to the different site of haem release (Fink, 1964). The increased iron load in thalassaemia is due to blood transfusions, one unit of blood containing approximately 200 mg of iron. It has been noted, however, that there is often a discrepancy between transfused iron load and the degree of haemosiderosis in thalassaemia. Erlandson *et al.* (1962) showed that patients with a number of haemolytic anaemias had increased gastrointestinal iron absorption, and this together with the iron therapy given to some patients for 'anaemia', seemed to account

in thalassaemia major for the increased iron that had not been transfused.

Stunting of growth in thalassaemia major is almost invariable after the first decade, but the cause remains unknown. It has been ascribed to the chronic hypoxia associated with severe anaemia, and certainly the height of these children can often be increased by high-transfusion regimens (Wolman, 1964). Hormonal insufficiency may be at least a contributory cause, suggested by the findings of massive haemosiderosis in endocrine glands at necropsy. The present investigation was undertaken to determine the extent to which the endocrine glands are affected functionally in prepubertal thalassaemia major.

Methods and patients

The age, sex, and transfused iron load of the 9 patients with thalassaemia major diagnosed by blood film and haemoglobin electrophoresis are shown in Table I. The transfused iron load was calculated on the basis of 200 mg of iron in each unit of citrated blood used (one unit contains 120 ml sodium citrate and 420 ml of blood). Cases 2 and 8 have only recently come under our care and have had no prior chelation therapy. For at least 5 years all our other cases have received

TABLE I

Age, sex, and details of iron load in 9 patients with thalassaemia major

Case no.	Age (years)	Sex	I.V. iron load (200 mg/unit)	Iron excreted with blood (mg)	Iron excreted with daily desferrioxamine (g)	Approx balance of iron (g)
1	14	M	30g	3·8g	7·7	+19
2	12	M	approx 33g	0	0	+33
3	12	F	1·2g	0	0	+1·2
4	11	F	20g	325	3·6	+16
5	10	F	20g	430	6	+13·5
6	10	M	23g	800	5	+17
7	9	F	22g	450	9	+12·5
8	6	M	12g	0	0	+12
9	5	M	6g	96	0	+5

chelation intravenously with each blood transfusion, and the 5 older children have also had daily intramuscular injections of desferrioxamine B.

Urinary iron excretion was measured by the method of Fielding and Brunström (1964). During transfusion urine was collected from the start until 6 hours after the finish of the transfusion, and 2 g desferrioxamine B was given with each unit of blood. In patients receiving 500 mg desferrioxamine B intramuscularly daily, 24-hour urinary iron excretions were measured in the intertransfusion period.

An intravenous insulin test was performed using 0·1 unit/kg of soluble insulin (Roth *et al.*, 1963). All patients had biochemical evidence of hypoglycaemia, in most cases accompanied by clinical symptoms. Growth hormone responses were measured by radioimmunoassay (Hartog *et al.*, 1963), and cortisol responses by the fluorimetric method of Mattingly (1962). Plasma ACTH levels were measured by the radioimmunoassay technique described by Berson and Yalow (1968) using a modification by Mukherjee and Swyer (1972), the antibody being specific against N terminal 1-24 ACTH and synthetic human 1-39 ACTH.

24-Hour urinary excretions of 17-ketosteroids (17 KS) and 17-hydrocorticosteroids (17 OHCS) were estimated by the MRC recommended method (Gray *et al.*, 1969). An intramuscular ACTH stimulation test was performed (Friedman, 1967). After blood was taken at 9 a.m. for cortisol estimation, 40 units of Acthar gel (Armour Pharmaceutical Company Ltd, England) was given intramuscularly, and a second cortisol level was measured at 5 hours. A graded dose tetracosactrin stimulation test was performed on subjects whose pituitary corticotrophin secretion had been previously suppressed by 2 mg dexamethasone 6-hourly for five doses. The cortisol response was measured to 31·25 ng, 62·5 ng, 125 ng, 250 ng, and 250 000 ng intravenous tetracosactrin as described by Landon *et al.* (1967).

An oral glucose tolerance test was performed on fasting patients given a 50 g glucose load. Glucose and insulin levels were measured in venous blood at 0, 15, 30, 60, 90, and 120 minutes. Intravenous glucose tolerance tests were performed on rested, fasted patients with a glucose load of 500 mg/kg, body weight given

over 2 minutes as described by Lundbaek (1962). From the decline in glucose concentration in the blood a glucose utilization constant, Kgl, was obtained (Lundbaek, 1962; Loeb, 1966). The response in insulin levels was also measured. All glucose estimations were performed by an automated glucose oxidase method (Gutteridge and Wright, 1968). Insulin was measured by a double antibody radioimmunoassay (Hales and Randle, 1963).

Results

Pituitary. The results of the intravenous insulin stress test showed normal response of both growth hormone and cortisol, suggesting functional integrity of the hypothalamo-pituitary-adrenal axis. Table II shows those values, and also the 9 a.m. plasma ACTH levels which are three or four times above the normal values of Besser *et al.* (1971) and of Mukherjee and Swyer (1972) using the same antibody.

Adrenal. Table III and Fig. 1 show that the results of 24-hour production of 17 KS metabolites are normal and those of the 17 OHCS metabolites are high normal for age. The ACTH stimulation tests (Table III) showed a normal or high resting cortisol level with a good response to stimulation in all but Cases 2 and 3. In Case 2 the test was repeated with a similar normal resting level and no response to stimulation. Results of the graded dose tetracosactrin stimulation test are also shown in Table III. In Fig. 2 the rise in cortisol above the fasting level is plotted against the dose of tetracosactrin given in subjects whose pituitary glands have been previously suppressed with dexamethasone. At each dose except the maximum there is a smaller response ($P < 0\cdot002$) in the thalassaemic patients than in the normal group of Landon *et al.* (1967).

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TABLE II
Pituitary function tests in thalassaemia

Case no.	Insulin stress test						9 a.m. plasma ACTH (pg/ml)
	Glucose (mg/100 ml)		Growth hormone (μ U/ml)		Cortisol (μ g/100 ml)		
	Fasting	Lowest	Before	After	Before	After	
1	75	25	7	35	11	30	148
2	60	25	15	43	28	35	480
3	50	20	33	77	11	22	
4	115	65	24	108	28	13	245
5	65	25	11	39	13	33	253
6	80	40	18	7	18	31	270
7	90	45	41	10	13	21	190
8	85	70	9	77	11	30	
9	70	35	45	11			200

Normal values of Besser *et al.* (1971) (19) 15–70 pg/ml (in young adults)

TABLE III
Adrenal function tests in thalassaemia

Case no.	24-hour urinary excretion/mg		ACTH stimulation test (cortisol μ g/100 ml)		Insulin tolerance test (cortisol μ g/100 ml)		Graded dose tetracosactrin stimulation test (ng/dose of tetracosactrin)					
	17 KS	17 OHCS	Before	After	Before	After	Resting	31.25	62.5	125	250	250 000
	(Cortisol in μ g/100 ml)											
1	3.6	12.1	13	38	11	30	2.0	2.0	2.4	1.6	7.8	26.0
2	4.1	10.8	20	18	28	35	2.0	2.4	2.8	4.0	4.6	13.4
3	1.8	4.8	20	24	11	22	3.2	2.0	3.0	2.2	10.8	17.0
4	1.9	8.8	30	44	13	28	3.2	—	8.8	11.0	16.6	21.1
5	1.4	3.8	35	69	13	33	2.0	3.6	2.8	8.0	16.4	35.0
6	2.4	6.2	25	53	18	31	8.0	7.8	5.0	4.6	17.0	39.0
7	2.5	8.9	9	53	13	21	7.0	6.0	5.8	6.2	13.6	32.0
8	1.0	4.2	11	48	11	30	2.8	3.4	5.2	6.2	8.0	14.4
9	1.8	4.8	16	76								

17 KS, 17-ketosteroids; 17 OHCS, 17-hydroxycorticosteroid.

Pancreas. Table IV gives the results of oral and intravenous glucose tolerance tests and the glucose utilization constants (Kgl). Figs. 3–5 compare the results of this study with previously published series. P values are given for each comparison. In the results of the oral glucose tolerance tests, Cases 1, 2, 5, and 6 can be seen to have chemical diabetes (Milner, 1969). Comparing the thalassaemic children as a group with normal children of Etienne, Lasfargues, and Laplane (1961), glucose levels are significantly higher at zero minutes, 30 minutes, and 120 minutes in the thalassaemics. The series of Etienne *et al.* (1961) has been used as a comparison because values are specifically on venous as opposed to capillary blood samples. Fig. 4 compares the plasma insulin values with those obtained in normal children by

Milner (1969). The difference is highly significant at all times except for the 120-minute sample. Table V compares the peak insulin values of our patients with normals, juvenile diabetics, and growth-retarded children published by Karp, Laron, and Doron (1973). The secretion pattern does not differ significantly from the values of juvenile diabetics ($P > 0.1$).

The glucose utilization constants Kgl (Table IV) in the intravenous glucose tolerance test are low (mean \pm SE 2.02 ± 0.22) compared to the values of Loeb (1966) (mean \pm SE 2.66 ± 0.19 ; $P < 0.05$). Cases 4 and 6 are exceedingly low and equivalent to diabetic values. Fig. 5 shows the insulin results and compares these to normals of Crockford, Harbeck, and Williams (1966). Glucose levels (Table IV) are only significantly higher at 5 and 20

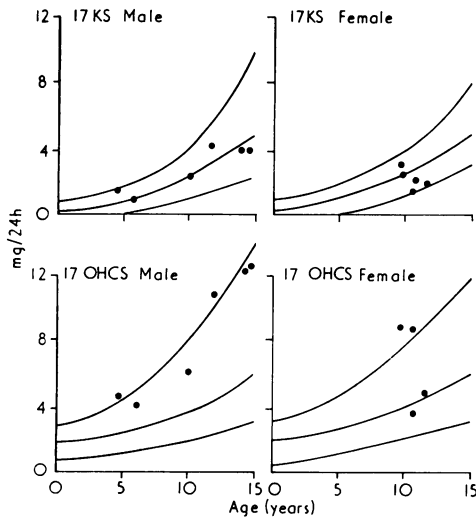


FIG. 1.—24-hour production of 17-ketosteroid (17 KS) and 17-hydroxycorticosteroid (17 OHCS) metabolites. Lines represent mean $\pm 2SD$ of normals, from Borth, Linder, and Riondel (1957). Each ● represents one thalassaemic case.

minutes, despite the exceedingly poor insulin response throughout.

Discussion

Despite the fact that iron loading in haemochromatosis is well known to produce endocrino-

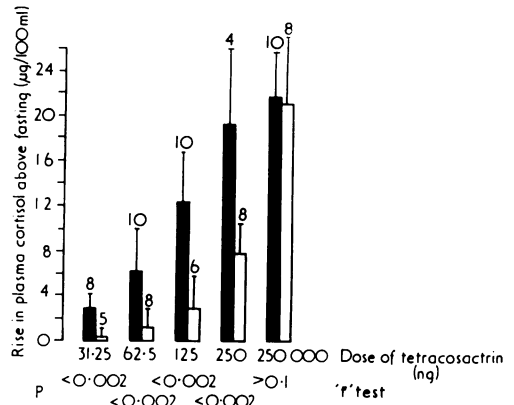


FIG. 2.—Physiological adrenal stimulation test. The increase in plasma cortisol from the fasting level is plotted in the dexamethasone-suppressed subjects given 5 increasing doses of I.V. tetracosactrin. The solid columns show mean $+2SE$ of Landon *et al.* (1967) for normal adults. The open columns shown mean $+2SE$ of our thalassaemic children. The number over each column is the number tested. Probability values are shown beneath ('t' test).

pathy, studies of endocrine function in thalassaemia, another iron loading disease, are few. Bannerman *et al.* (1967) were the first to report a case of thalassaemia intermedia with multiple pathology at the age of 41 years, with involvement of endocrine organs. Kuo, Zaino, and Roginsky (1968) were the first to report a series, investigating 7 patients aged from 6 to 23 years, finding low basal urinary

TABLE IV
Pancreatic function tests in thalassaemia

Case no.		Oral glucose tolerance test (min)						I.V. glucose tolerance test (min)								Plasma glucose utilization constant (Kgi)
		0	15	30	60	90	120	0	5	10	20	30	40	50	60	
1	Sugar (mg/100 ml)	80	120	165	215	185	160	—	275	240	205	175	160	150	130	1.2
	Insulin ($\mu U/ml$)	1	12	13	1	10	2	—	57	32	13	12	17	20	16	
2	Sugar	75	180	160	205	180	100	100	—	245	165	110	80	80	70	2.3
	Insulin	—	—	—	—	—	—	—	6	17	23	9	5	2	—	
3	Sugar	80	90	85	75	85	90	70	190	170	110	90	55	40	50	2.1
	Insulin	4	16	18	—	16	17	1	13	11	2	1	—	1	—	
4	Sugar	—	—	—	—	—	—	—	295	275	235	210	170	165	145	1.25
	Insulin	—	—	—	—	—	—	—	—	40	32	28	22	22	19	
5	Sugar	90	120	—	125	140	135	85	270	235	160	115	100	85	85	2.3
	Insulin	0	175	11	8	23	4	15	110	74	24	7	19	9	8	
6	Sugar	100	143	205	190	175	180	90	275	245	210	180	160	140	110	1.26
	Insulin	7	5	17	28	26	31	4	18	16	8	—	10	3	1	
7	Sugar	65	100	110	115	—	95	95	260	230	150	110	90	95	105	2.5
	Insulin	5	14	25	21	—	10	15	129	53	13	2	1	3	7	
8	Sugar	100	135	130	95	115	90	75	275	215	180	—	100	—	85	2.2
	Insulin	1	12	13	1	10	2	1	7	5	3	—	1	—	1	
9	Sugar	80	130	140	110	—	95	90	235	196	130	75	60	60	70	3.1
	Insulin	5	19	26	8	—	14	25	200	—	—	21	11	—	—	

Mean = 2.02

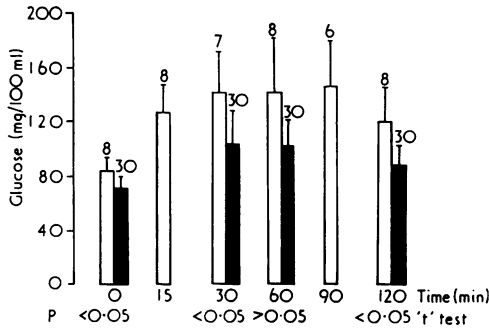


FIG. 3.—Glucose values (mg/100 ml) on venous blood fasting and at periods after a 50 g glucose load. Mean +2SE of normals are shown in solid column (Etienne *et al.*, 1961) and mean +2SE for thalassaemic patients shown in open columns. The number over each column is the number of patients tested. Probability values ('t' test) are shown beneath.

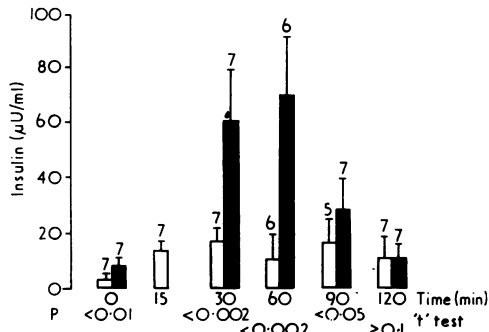


FIG. 4.—Insulin values (µU/ml) fasting and at periods after a 50 g oral glucose load. Mean +2SE of normals aged 5–15 years (Milner, 1969) are shown in solid columns. Mean +2SE for thalassaemic patients are shown in open columns. The number over each column is the number of patients tested. Probability values ('t' test) are shown beneath.

17-ketosteroid levels and a poor response to metyrapone, but a normal insulin stress test. Canale *et al.* (1974) investigated endocrine function in 20 patients with thalassaemia major. 10 were prepubertal, and in these no abnormality of thyroid, pituitary, or adrenal function was noted. Of 10 cases aged 13 to 27 years, 9 had low urinary 17-ketosteroid production, though in fact commensurate for height and bone ages. Urine and plasma hydroxycorticoid levels were normal, as was urine aldosterone. Growth hormone response to insulin was normal in all.

They concluded that only 3 transfused patients

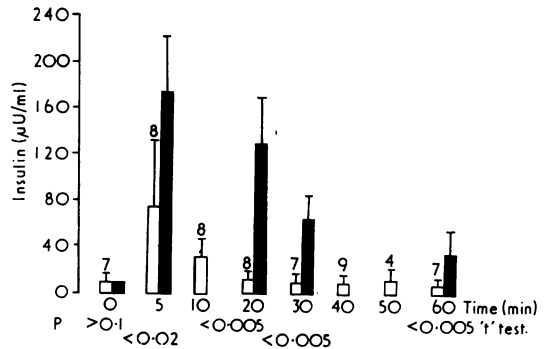


FIG. 5.—Plasma insulin values before and at intervals after 500 mg/kg intravenous glucose. Solid columns show mean +2SE of thalassaemia patients and open columns mean +2SE of young adults of Crockford *et al.* (1966). Number over open columns indicates the number of patients studied. Probability values ('t' test) are shown beneath.

TABLE V
Oral glucose tolerance test

Peak insulin values (µU/ml)	Mean	SD	SE	No.
Thalassaemic patients	21	6.8	2.6	7
Normals	131	42	6	48
Juvenile diabetics	25	10	2	15
'Growth-retarded' (1973)	50	38	6	36

Note: Thalassaemic values significantly lower than 'normals' and 'growth-retarded' (P <0.002), and not different from diabetics (P >0.1).

showed loss of endocrine function after 20–24 years of transfusion, and suggested that the dysfunction could be due to end organ fibrosis. Lassman *et al.* (1974) investigated 8 transfusion-dependent thalassaemics aged 5–31 years, 2 of whom were known to have insulin-dependent diabetes mellitus. 4 others in the series were shown to have impaired glucose tolerance. 2 postpubertal patients had abnormal metyrapone tests, and gonadal failure was thought to be secondary to pituitary hypofunction. The present study investigated only prepubertal thalassaemics, a group in which it has been suggested in published reports that endocrine abnormality is absent.

Our finding of raised resting 9 a.m. ACTH levels is important as it substantiates the results of adrenal function tests. Slate grey pigmentation was recognized to be very common in thalassaemia major soon after the original description of the disease, and indeed pigmentation is recorded in all the cases described by Lassman *et al.* (1974). It usually appears in the first decade of life and be-

comes progressively more intense. Despite lack of stainable iron on histology (Ellis *et al.*, 1954) this pigmentation has usually been assumed to be due to iron deposition. From the present study it seems likely that the pigmentation is similar to that in Addison's disease and results from increased circulating ACTH, the first 13 amino acids of which are identical with melanophore-stimulating hormone (Lee, Lerner, and Buettner-Janusch, 1961). The patient in this study who subjectively was most deeply pigmented did in fact have the highest level of resting 9 a.m. plasma ACTH.

The usual tests of adrenal function showed little impairment of function. In Cases 2 and 8 there was no response to intramuscular ACTH and this could have been because the adrenal gland was always working at maximum rate to produce the normal circulating cortisol levels. Using the more physiological graded dose adrenal cortical stimulation test (Landon *et al.*, 1967) highly significant suppression of function was shown in the physiological range with a normal reserve of function. This could explain why there was an increase in the circulating levels of plasma ACTH, the increased levels being required to produce normal adrenocortical response. Ethical reasons prevent normal values being available for children in this test, but since completion of this study normal adult values have been obtained in younger children with thalassaemia major (McIntosh, 1976).

Highly significant impairment of pancreatic function was shown. Not only were 4 of the oral glucose tolerance tests shown to be diabetic in type, but also the peripheral glucose utilization seen in the intravenous glucose tolerance was poor. High Kgl values have been shown prepubertally by Loeb (1966) but in our patients, who were all prepubertal, the values were generally low, and in Cases 1, 4, and 6 they were in the diabetic range. The poor glucose tolerance was shown clearly to be related to highly significant impairment of insulin secretion, very low levels being found after oral or intravenous stimulation. Similar ethical considerations make insulin values in response to oral and intravenous glucose loads unavailable in the paediatric age group. The normal adult values quoted are probably satisfactory, indeed the youngest patient in the series had an exceedingly high response, but the data must be interpreted with some caution.

Thus in our patients β cell pancreatic function and adrenal cortical function are both shown to be depressed, though the latter was shown only using a very sensitive test. The depression of function was seen in a virtually untransfused patient as well

as in those severely iron loaded. If one postulates iron deposition as the aetiology (as seems likely with the parallel of haemochromatosis) it may be that gastrointestinally absorbed iron is more damaging than intravenously loaded iron. Even the 6-year-old patient had a poor insulin response to oral glucose load, so damage occurs early in life, and we should become even more intensive in our use of chelation therapy.

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