Hyperglycaemic Non-Ketotic Coma Following Surgically Treated Acromegaly in a Non-Diabetic*

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SUMMARY

Extremely severe, hyperglycaemic, hyperosmolar, non-ketotic coma occurred in a 47-year-old, apparently non-diabetic, acromegalic woman shortly after having her pituitary adenoma removed. She was totally unconscious, shocked, anuric, grossly dehydrated and in status pilepticus but she recovered, and has remained non-diabetic, with diminished adrenal response and growth hormone levels returning to normal. Her plasma insulin response to glucose is excellent.

The factors that precipitated this syndrome in this patient are obscure to us.

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The condition designated 'hyperglycaemic hyperosmolar non-ketotic coma' raises many questions regarding aetiology and pathogenesis. It occurs typically in middle-aged, often overweight, mild diabetics, perhaps particularly in non-White races.[1,2] It has been recorded in children,[3-6] in insulin-dependent diabetics[7-9] and in association with severe burns,[10,11] acute and chronic pancreatitis,[1,12-14] pancreatic carcinoma,[15] thyrotoxicosis,[16] administration of various diuretics,[17,18] corticosteroids,[4,12,19-21] and diphenylhydantoin,[22] haemo- and peritoneal dialysis,[23] heat stroke,[24] and other severe illnesses, especially overwhelming sepsis.[15]

The extremely severe case to be described occurred in unexpected circumstances—within a week of operation for the removal of a pituitary adenoma in a presumed non-diabetic woman suffering from acromegaly.

CASE REPORT

The patient was a Coloured female aged 47 years, normal weight 51·75 kg and height 152·5 cm. She had no family history of diabetes and was childless.

During November 1968 the patient was admitted to the neurosurgical ward with bitemporal hemianopia and the clinical features of typical acromegaly, having had symptoms of the latter for the past 10 years. She was found to be hypertensive, but apparently not diabetic (a single random blood-sugar level was low and glycosuria was not present). The pituitary fossa was enlarged, the presence and extent of the tumour were confirmed by further studies and it was removed through a right frontal craniotomy.

Histology revealed a chromophobe adenoma and radiotherapy was started. The patient became moderately thirsty and developed some nocturia, which improved after a few days. The field defect improved and the patient was discharged, 10 days after operation, on tri-iodothyronine 0·02 mg a day and hydrocortisone acetate 12·5 mg *t.d.s.*

One week after discharge she was readmitted to a medical ward in deep coma. She had by then received 560 rads to the pituitary fossa. On her fourth day at home she had suddenly found herself enormously thirsty, with half-hourly nocturnal polyuria. She drank several litres of fluid—mostly plain water and a drink made by diluting a commercial concentrated fruit juice. She had consumed about 200 g of sugar a day in this manner for 3 days before passing into coma.

She was now totally unconscious, flaccid but twitching, severely dehydrated with hypotension (50/0 mmHg), tachycardia (140/min) and tachypnoea (32/min), without features of acidosis.

Initial Investigations

Urine contained 2+ protein, 4+ sugar and a trace of ketones. Her blood was thick like syrup, with haemoglobin concentration 11·5 g/100 ml, ESR 26 mm/h (Westergren), serum ketones present in trace amounts, glucose 1 480 mg and urea 116 mg/100 ml; sodium 149, potassium 4·9, chloride 97 and total CO_2 22·4 mEq/litre; osmolality 408 mOsm/litre (freezing point osmometer).

During the first 12 hours she received: 10 litres of half-strength normal saline, 700 units of soluble insulin, 13 g of potassium chloride and 400 mg of hydrocortisone.

After this time her fits had stopped, she was responding to painful and vocal stimuli, her blood sugar was now 157 mg/100 ml, sodium 146 and potassium 3·6 mEq/litre. Although she was apparently well rehydrated, her serum osmolality was still high, now being 333 mOsm/litre, and so a further 6 litres of hypotonic fluid were infused. Improvement was gradual, constant and maintained. After 2 weeks insulin and hydrocortisone medication was stopped and an oral sulphonylurea given; this was discontinued a week later, after which her fasting blood sugar levels were 80 - 95 and postprandial 100 - 106 mg/100 ml. She was discharged on full diet, with no antidiabetic therapy, and no hormones.

Follow-up

March 1969: The patient was readmitted, off all therapy, and in excellent health: Blood pressure 150/100 mmHg; haemoglobin 12·6 g/100 ml; urine normal; serum electrolytes and ECG normal; thyroid status normal (Table I).

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Her growth hormone level was raised (14 ng/ml fasting) but not increased by hypoglycaemia (Table I). Her urine concentrating power was normal (Table I) and her blood cortisol level was normal in the fasting state, but not raised by hypoglycaemic stress, nor by lysine vasopressin (Table I).

Glucose tolerance was normal but possibly abnormal when the test was augmented with cortisone (Table I). Plasma immunoreactive insulin response to glucose was excellent (Table I and Fig. 1).

October 1969: During the final assessment she was found to be well and her feet were smaller by 1½ sizes.

The abovementioned tests were repeated (Table II) and the only important changes were that her growth hormone levels were now lower and still unresponsive; and the glucose tolerance curve was lower and flatter.

A third glucose tolerance test was performed after discharge and was again normal (Table III).

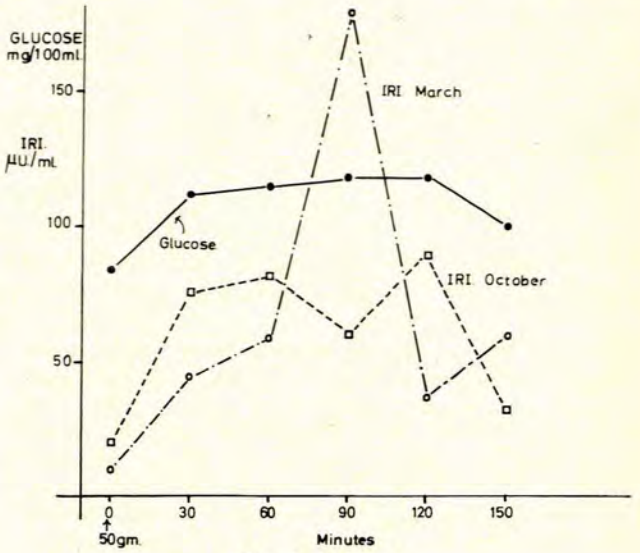

Fig. 1. See text.

Final Endocrine Status

The final assessment was as follows:

1. Normal thyroid function; normal basal adrenal function but absence of adrenal response to insulin hypoglycaemia, lysine vasopressin or Metopirone.
2. Growth hormone levels returning to normal but unresponsive to both hypoglycaemic stimulation and hyperglycaemic suppression.
3. Normal glucose tolerance with excellent insulin response and impaired cortisone/glucose tolerance.

TABLE I. ENDOCRINE STUDIES, MARCH 1969

Thyroid function

^{131}I uptake 35% at 24 hours.
Rbc uptake ^{131}I - T_3 12·5%; PBI 6.5 μg %.

Follicle-stimulating hormone (24-hour urine)

Positive at 6 mouse uterine units.

Insulin hypoglycaemia test (0·1 units/kg intravenously)

	at 0	20	40	60	minutes
Plasma glucose	72	32	34	50	mg/100 ml
Plasma cortisol	14	14	14	13	μg/100 ml
Plasma HGH	14	12	10	9	ng/ml

Metopirone test

Urinary 17-oxogenic steroids per 24 hours, preceding, during, and following metopirone: 3·6, 5·3, 6·6 mg.

Lysine vasopressin test (10 units intramuscularly)

	at 0	30	60	minutes
Plasma cortisol	12	5	12	μg/100 ml

Urine concentrating ability (after overnight fast)

Plasma osmolality	291	mOsm/litre
Urine osmolality	518	mOsm/litre

Glucose tolerance

		at 0	30	60	90	120	150	minutes
50 g oral standard	Plasma glucose	84	112	115	119	11	101	mg/100 ml
	Plasma IRI	10	45	57	185	37	60	μU/ml
+ 100 mg cortisone	Plasma glucose	90	166	217	208	198	156	mg/100 ml
	Plasma IRI	20	57	127	172	140	90	μU/ml

TABLE II. ENDOCRINE STUDIES, OCTOBER 1969

Thyroid function

^{131}I uptake 16% (6 hours), 31% (24 hours).
Rbc uptake of ^{131}I - T_3 13%; PBI 6·0 μg/100 ml.

Insulin hypoglycaemia test

	at 0	20	40	60	minutes
Plasma glucose	64	25	25	25	mg/100 ml
Plasma cortisol	10	10	10	12	μg/100 ml
Plasma HGH	6	4	3	3	ng/ml

Metopirone test

Urinary 17-oxogenic steroids 2·5 mg per 24 hours basal; 8·8 mg per day after metopirone.

Lysine vasopressin test

	at 0	30	60	minutes
Plasma cortisol	21	28	24	μg/100 ml

Glucose tolerance (50 g oral)

	at 0	30	60	90	120	150	minutes
Plasma glucose	76	81	70	58	50	45	mg/100 ml
Plasma IRI	22	76	82	60	95	32	μU/ml
Plasma HGH	4	4	3	3	3	3	ng/100 ml

TABLE III. OUTPATIENT GLUCOSE TOLERANCE (NOVEMBER 1969)

	at 0	30	60	90	120	minutes
Standard test: (capillary blood) glucose	**86**	**96**	**142**	**142**	**126**	**mg/100 ml**
Cortisone-primed: glucose	**109**	**122**	**182**	**215**	**197**	**mg/100 ml**

Assessment of Case

A probably non-diabetic acromegalic patient became completely comatose within a few days of discharge from hospital following removal of her pituitary adenoma. She was extremely hyperglycaemic, grossly dehydrated, shocked, totally anuric and in status epilepticus. She recovered full health after strenuously appropriate therapy, though with a defective adrenal response to stressful stimuli. She is not diabetic at present and maintains normal glucose tolerance and insulin response.

DISCUSSION

Of the 36 cases of hyperglycaemic non-ketonic coma we have seen at Groote Schuur Hospital, this patient seemed to be by far the most ill and to have the least chance of survival.

It seems strange that she should have presented with an acute diabetic syndrome only *after* the diabetogenic stimulus of acromegaly had been alleviated. The questions to be considered are, foremost, why she, apparently a non-diabetic, developed such a condition; assuming she had temporary insulin insufficiency, why did ketosis not occur; and why did she go into status epilepticus?

The first and most important question we are unable to answer. The syndrome has occurred in other patients after the use of pharmacological doses of corticosteroids, but in our patient this dose was within the physiological replacement range. She appears to be non-diabetic, and even further protected from hyperglycaemia by her degree of postoperative hypopituitarism. The raised blood sugar readings on cortisone GTT are of doubtful significance on account of her age,[25] though it is possible that this test indicates a submerged diabetic state. Her capacity for immunoreactive insulin (IRI) release is now excellent—unfortunately we do not have records of her IRI levels in the acute phase, but we can presume them to have been low. The syndrome *has* occurred in non-diabetics, but only when artificially produced by means of actually infusing glucose into the blood circulation or peritoneal cavity, or of stuffing a burned subject with carbohydrates. The sugar in our patient's fruit drinks may have accentuated the hyperglycaemia but cannot have initiated it.

A deficiency of antidiuretic hormone (ADH) would increase diuresis and contribute to dehydration, and indeed she did have evidence of transient diabetes insipidus for a few days after the operation, but this did not continue and she had no evidence of ADH lack when tested in 1969.

It is conceivable that a remnant of tumour was left at operation and subsequently infarcted with a sudden and transient release of growth hormone which could account for a temporary diabetic state (suggested by Dr Graham Joplin of London). This would not explain the lack of ketosis.

A patient of Kolodny and Sherman[8] developed hyperglycaemic coma 4 weeks after pituitary stalk section, but the circumstances were different from those of our case. He was a young, chronic, severe, juvenile-type diabetic, whose operation was performed to alleviate his advancing retinopathy. An episode of severe ketoacidosis had occurred 6 weeks before operation. It may be that in this case the ensuing hypopituitary state had prevented ketosis from occurring (see below). A very similar case has been reported from Mexico.[9]

That hypophysectomy tends to prevent ketosis in insulin-lack diabetes has been known since the famous experiments of Houssay and Biasotti.[26] The Houssay dogs eventually died, not from ketoacidosis, but from insulin-lack. In the absence of growth hormone lipolysis would be reduced—but in our patient we know that the resting growth hormone level was high and not suppressed by hyperglycaemia. Plasma growth hormone levels have been found to be raised in severe diabetic ketoacidosis[27,28] but were no higher than the basal level in our patient. Growth hormone deficiency cannot therefore be considered to be a reason for the lack of ketoacidosis in our case. A deficiency of ACTH may also reduce lipolysis and so presumably be one factor in the lack of ketosis in these two cases. However the great majority of hypoadrenal diabetics are certainly not protected from ketoacidosis.

We suppose it must be allowed that our patient was possibly releasing sufficient insulin to prevent ketosis but not enough to prevent hyperglycaemia. Since we have now found patients with the hyperosmolar syndrome but zero IRI and ILA in their blood we do not really like this hypothesis but cannot disprove it in this case.

The neurological features of coma and epilepsy are presumably related to the osmotic gradient between blood and brain cell and/or to the extreme viscosity of the blood itself in this and some other cases of the hyperosmolar syndrome. In this syndrome the stimulus to cerebral discharge is not smothered by the depressant effect of ketone bodies.

We attribute her recovery to the massive fluid replacement with half-strength saline, sufficient insulin and careful monitoring of the serum potassium level. The hydrocortisone may have assisted in controlling the shocked state, especially since we know that her adrenal response to stress is deficient. The prognosis of the hyperosmolar syndrome in general has been poor but seems to be improving. Thus 7 of our first 10 cases died,[35] but only 1 of our last 12. This we attribute largely to the lavish employment of hypotonic saline solutions and the realization that the serum potassium level is apt to fall more precipitously than during the treatment of ketoacidosis.

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APPENDIX

Glucose: Venous plasma (except where indicated), Auto-Analyzer, Hoffman method.
Plasma 'cortisol': Fluorescence method of Mattingly.
IRI: Hales and Randle method[29] as modified by Radio Chemical Centre, Amersham Data Sheet 5616.
HGH: Morgan and Lazarow method,[30] using Wilhelmi HGH H 5968C as standard and tracer.
Other methods were standard laboratory procedures.

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*Includes previous references to dialysis and hyperosmolar coma.