HYPOTHERMIC MYXOEDEMA

A Report of the Successful Use of Triiodothyronine

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Severe constipation and hypothermia progressing to hypothermic coma are known complications of myxoedema. The occurrence of hypothermia is recognized to be an indication for urgent treatment with the most rapidly acting thyroid preparation available, l-triiodothyronine. There are only two cases of hypothermic myxoedema coma which have been successfully treated with triiodothyronine reported in the English literature (Macdonald, 1958; Surtees and Ginsberg, 1958), and there is no accepted régime for the dosage and mode of administration of this drug.

A further case of myxoedema with hypothermia which was successfully treated is here reported, with details of the dosage of triiodothyronine used. The patient is also of interest in that she originally presented with sub-acute obstruction of the large bowel due to faecal impaction, the result of severe constipation, and at this time, four weeks before the occurrence of hypothermia, the diagnosis of myxoedema was missed.

Case Report

The patient, a widow of 79, was referred to hospital in October 1958 as an emergency, complaining of abdominal pain. Until four months before she had been constipated, since when she had had frequent fluid motions and had occasionally been incontinent of fluid faeces. In the past four months she had had a poor appetite, and in the previous two days had had abdominal colic, each episode of pain being followed by, and relieved by, the passage of flatus.

For several years she had been breathless on effort and had had swelling of the legs, and for eighteen months she had been having mersalyl injections twice weekly. She had had one child: the pregnancy had been normal, with no post-partum haemorrhage, and followed by normal lactation.

On examination the temperature was 97° F., pulse 74 per minute, regular, respiration rate 20 per minute, and blood pressure 190/105. She was fully conscious, alert and co-operative, and her voice was not obviously abnormal. The scalp hair was thin: the skin was dry, thin and scaly,

but warm. Apart from pitting oedema up to the knees there were no signs of heart failure, and the heart and lungs were normal. The abdomen was grossly distended and tympanitic. There were no signs of free fluid and no organs or abnormal masses were palpable. She was incontinent of fluid faeces, and per rectum hard faecal masses were felt. Bowel sounds were not heard at first, but were noticed two hours after admission. A straight X-ray of the abdomen showed gross gaseous distension of the colon, but no fluid levels.

The haemoglobin was 60 per cent., blood urea 60 mg. per 100 ml. The serum electrolytes were normal, and a catheter specimen of urine was free of albumen.

A diagnosis of sub-acute large bowel obstruction was made: the house surgeon suggested that the patient looked myxoedematous but in view of her mental alertness, normal pulse rate, and warm, though dry, skin, this was not acted upon, and a laparotomy was done for relief of the intestinal obstruction. A general anaesthetic was given without incident and a preliminary sigmoidoscopy was attempted but the view was completely obscured by faeces. At laparotomy large masses of faeces were found in the sigmoid and descending colon and there was a volvulus of the transverse colon. This was corrected and a manual removal of faeces performed per rectum before the anaesthetic was ended.

She made a good immediate post-operative recovery. A week later chlorothiazide treatment was started because of the leg oedema, and this was continued after her discharge, three weeks after the operation, to a convalescent home. Apart from a rise in temperature to 99.2° F. for two days following the operation her temperature varied from 97° F. to 98° F., and it is recorded in her post-operative notes that she was lethargic, with poor appetite, and that one enema had to be given because her bowels had not been opened for one period of five days.

Four days after discharge, on a very cold November day she was sent back from the convalescent home as she had become gradually slower, increasingly reluctant to move, and was

said to have neither eaten nor drunk 'anything' since her arrival there.

On examination then she was drowsy: although she could be roused her reactions were very slow, and she was quite unable to give any history. Her voice, which had been normal so shortly before was hoarse, croaking and deep. The pulse was 66 per minute, regular, respiration rate 12 per minute, and the oral temperature, taken with a low reading thermometer, varied from 93.2° F. to 94.6° F. The skin was dry and scaly, and felt very cold. The scalp hair was dry and scanty, as previously noticed, and both her axillary and pubic hair were very sparse. The facies, however, were not pathognomonic of myxoedema.

The heart sounds were normal: there was pitting oedema of the legs but no other signs of heart failure, and the lung fields were clear.

The tongue was dry and furred and hard faecal masses were palpable per abdomen and per rectum. The cranial nerves and upper limbs were normal, but the knee and ankle jerks were absent.

A clinical diagnosis of myxoedema with hypothermia and impending coma was made: an E.C.G. then done showed low voltage T waves in the standard limb leads and in V6 consistent with myxoedema.

Treatment was started with 1-triiodothyronine, 20 µg. by mouth (swallowed), four hourly, cortisone acetate 50 mg. by mouth six hourly, and parenteral prophylactic penicillin. She was nursed in a standard hospital bed, and no attempt was made to warm her up by applying external heat.

Twelve hours later there had been no clinical improvement (temperature 94° F., pulse 60 per minute, respiration rate 11 per minute), and investigations then done were as follows: Hb. 75 per cent., blood urea 37 mg. per 100 ml., serum cholesterol 370 mgm. per 100 ml., serum electrolytes in meq. per litre Na, 129, K, 3.0, Cl, 68, and CO₂, 34. The urinary chlorides were 3.0 g. per litre and the urinary albumen was 2.5 g. per litre. The electrolyte levels in the blood suggested the presence of a respiratory acidosis, with hypochloraemia and hypokalaemia probably caused by chlorothiazide. She began to vomit, and as it was not possible to give further thyroid hormone by mouth all oral treatment was stopped, and an intravenous infusion started of normal saline with 20 µg. of triiodothyronine, 100 mg. of hydrocortisone, and potassium chloride added to each litre. After one litre of this had been given over the next twelve hours there was a noticeable improvement. Although her voice was still hoarse and husky she was talking more, and was more alert. The pulse was 70 per minute and regular, respiration rate 12 per minute but

the temperature was still only 94° F. The serum electrolytes were unchanged, and the urinary chlorides still only 3 g. per litre. As the vomiting had now stopped oral treatment was restarted, with 20 µg. of triiodothyronine sublingually every eight hours, cortisone acetate 175 mg. per day in divided doses, with, in addition, a daily injection of 40 units of corticotrophin gel. The intravenous saline-potassium infusion was continued in an attempt to correct the hypochloraemia and hypokalaemia. On the next (the third) day her improvement continued: the temperature was then 95° F., the blood urea 27 mg. per 100 ml. and the serum electrolytes, in meq. per litre were Na, 123, K, 3.3, Cl, 79, and CO₂, 29. On the fourth day the temperature rose to 96.4° F., the pulse was 78 per minute, and respiration rate 14 per minute. Her voice remained hoarse, but she was much more alert, and her mental reactions were brisker. The corticotrophin was stopped, the cortisone reduced to 150 mg. daily, and the triiodothyronine reduced to 20 µg. every twelve hours. She was by this time drinking and eating well, and therefore the intravenous transfusion was stopped, and oral salt and potassium supplements given.

She continued from then on to make a steady recovery. By the 28th day her voice had become completely normal, and the E.C.G. had returned to within normal limits. The corticosteroids were gradually reduced and discontinued on the 24th day. Starting on the 28th day she was gradually changed from 20 µg. of triiodothyronine b.d. to 0.1 mg. 1-thyroxine b.d. This change was effected over fourteen days; the triiodothyronine being continued for the first fortnight of thyroxine administration as the latter takes from ten to fourteen days to exert its maximum action.

Daily serum electrolyte determinations were not done, but six weeks after admission they were all within normal limits, i.e. in meq. per litre Na 143, K, 5.3, Cl, 96, CO₂, 28. Blood urea 44 mg. per 100 ml., and serum cholesterol 190 mg. per 100 ml.

Discussion

Karhausen and Zylberszac (1955) reported the case of a woman with myxoedema who presented in a similar way to the present one. She died in hypothermic myxoedema coma following a six months' illness, the main features of which were increasing lethargy and severe constipation. The constipation was so marked that before her ultimate hospital admission in a pre-comatose state a diagnosis of intestinal obstruction had been made. The constipation in the present case had allowed faecal impaction to occur and to cause volvulus of the transverse colon: although con-

stipation is a classical symptom of myxoedema, it must be rare for it to progress to the extent of needing a laparotomy for its management.

The problems of treatment of the hypothermia occurring in myxoedema arise in the dosage and mode of administration of the thyroid hormone used, whether to apply external warmth, and in the use or not of the corticosteroids.

The thyroid preparation with the quickest action is l-triiodothyronine. It was isolated in 1951 by Gross and Pitt Rivers: on the basis of the minimal effective dose it is five times as potent as l-thyroxine. After a single oral dose an effect can be detected within four hours, a maximal effect occurs at four days, and all effect has disappeared after ten days. Comparative figures for l-thyroxine are a noticeable effect in four days, maximal effect in ten-fourteen days, and disappearance of all effect after one month, whereas thyroid sicca does not even begin to exert its action for from three to four weeks (Goodman and Gilman, 1955). It is this rapidity of onset of action which makes triiodothyronine so valuable in the treatment of myxoedema with hypothermia. In terms of equivalent doses, based on the actual increase in basal metabolism produced by these three drugs, 1 gr. of thyroid sicca, 0.1 mg. of l-thyroxine and 20 μ g. of l-triiodothyronine are equivalent.

Macdonald (1958) and Surtees and Ginsberg (1958) have both reported the successful use of triiodothyronine in the treatment of hypothermic myxoedema. Macdonald employed doses of 80 μ g. intravenously at twelve hourly intervals for three doses: Surtees and Ginsberg began treatment with one dose of 100 μ g. intravenously, then 40 μ g. orally twelve-hourly for two doses, and then 40 μ g. orally daily. On this régime the patient was resuscitated from coma, but died from a myocardial infarction one month later.

Anderson and Hausman (1956) noted the onset of angina, with death two days later, after a man aged 49 had 50 μ g. of triiodothyronine given intravenously in the treatment of his hypothermic myxoedema coma. Dyson and Wood (1956) used large doses intravenously—1,200 μ g. and 1,000 μ g.—in a patient with myxoedema coma. There was a noticeable response to these doses, with rise of body temperature, return of consciousness, and restoration of the E.C.G. to normal, with no anginal pain and no cardiac irregularities, but unfortunately the patient died a few days later from bronchopneumonia. Although large doses (1,000 μ g. and over) have been given with immediate safety (Asper *et al.*, 1953; Rawson *et al.*, 1953; Dyson and Wood, 1956), there are reports that these may cause serious cardiac arrhythmias. Thus Dyson and Wood

mention the occurrence of atrial fibrillation and congestive cardiac failure following 1,000 μ g. intravenously, and they suggest that doses of 100 μ g. intravenously, repeated if necessary in twelve hours, will probably be adequate, and should not be exceeded.

Malden (1955) reported the resuscitation of a patient with myxoedema who was admitted in coma, with hypothermia, but in whom the C.S.F. protein was 150 mg. per 100 ml. After treatment with external warmth, corticosteroids and oral l-thyroxine, 0.3 mg. daily, the patient gradually recovered consciousness after three weeks, and was then found to have increased reflexes on the left side, suggesting that a cerebrovascular accident had probably occurred, and that the coma was not due solely to hypothyroidism. There is no other case recorded of l-thyroxine having successfully rescued a patient from hypothermic myxoedema coma, although Summers (1953) reported a case of myxoedema in pre-coma successfully treated with heroic doses of l-thyroxine: 1.0 mg. six hourly, i.e. the equivalent of 40 grains of thyroid sicca per day. The patient was a man of 59 who, following a twelve months' illness marked by increasing dryness of the skin and dislike of cold was found on admission to be myxoedematous. His cerebration was slow and became progressively more sluggish until four days later he was semi-stuporous; his temperature ranged from 96° F. to 98° F. He responded to oral l-thyroxine 1.0 mg. six hourly and cortisone, and there was a gradual return to consciousness over the next few days. However, in the winter of the same year, four months later, he was readmitted in pre-coma with a temperature of 83.5° F. Treatment was again given with l-thyroxine and cortisone, but this time it had no effect, and he died in coma two days later.

Use of Corticosteroids

There is evidence that adrenal cortical function is depressed by primary hypothyroidism. Hubble (1955) gives figures showing that the urinary ketogenic steroid excretion (being the end product of hydrocortisone metabolism) is lowered in congestive heart failure, cirrhosis, and myxoedema. Hill (1950) showed that some patients with myxoedema have a delayed and at times inadequate response to corticotrophin, and that this response is corrected by thyroid. Summers (1956) studied the effect of a small dose of cortisone—25 mg. daily—on five patients with severe myxoedema for one month, before any thyroid was given. He found that, within two days the cortisone produced a marked quickening of mental processes but that it had no effect on

the physical or biochemical state of the myxoedema. He commented that 'The appearance of extremely active and busy patients who apparently still remained myxoedematous was most remarkable'; and suggested that corticosteroids may be of therapeutic use in those patients with myxoedema where drowsiness is marked, and the development of coma is feared. Corticosteroids were part of the successful régime used by Macdonald (1958) and by Dyson and Wood (1956), and their success together with the evidence outlined above prompted the use of cortisone in the present case.

External Warmth

Opinions vary as to the effectiveness of applying external warmth to patients with myxoedema coma. Macdonald considered this to be unphysiological, and pointed out that of the three such cases he treated with triiodothyronine and corticosteroids the only one to survive did not have external heat applied. It is however recognized that patients with panhypopituitarism who develop hypothermic coma should be so treated (Sheehan and Summers, 1952).

The present patient was not 'warmed up' artificially, and this may have contributed to her recovery.

Summary

A woman of 79 was operated on for sub-acute

large bowel obstruction caused by faecal impaction due to severe constipation, the result of unrecognized myxoedema. Four weeks after the operation, in a period of very cold weather she developed hypothermia, and became almost comatose. Her body temperature and mental state were restored quickly to normal, and her myxoedema cured with l-triiodothyronine and corticosteroids. Previous reports of this treatment régime are reviewed.

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