TWO CASES OF SIMMONDS'S DISEASE DUE TO POST-PARTUM NECROSIS OF THE PITUITARY GLAND

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We report the following cases for several reasons. Every patient with Simmonds's disease presents a fascinating picture of deranged pituitary function which cannot be paralleled by operating on animals; the symptoms and response to treatment are very instructive from both the theoretical and the practical aspects. An important practical point is that the underlying pathology in these patients may not be suspected until many years of ill-health have elapsed, and it is probable that there are many more patients suffering from varying degrees of pituitary failure from this cause than are suspected. We feel very strongly that the title "Simmonds's disease" should be restricted to this type of case due to post-partum necrosis of the pituitary as described in Simmonds's original article.

Case 1

The patient, a married woman aged 42, had had ten normal pregnancies. Thirteen years previously the tenth pregnancy was followed by a severe post-partum haemorrhage. She was not admitted to hospital until 13 days after

delivery, when she was transfused with 2 pints (1.14 litres) of blood. Lactation was not established, all pubic and axillary hair was lost, and no further menstrual period occurred. Her intelligence was low, and for many years she remained in a state of poor health without seeking medical advice. Six months before the present admission to hospital she went to her doctor because of "anaemia." She was admitted in January, 1949, for investigation of anaemia and weakness.

On examination she had a puffy myxoedematous face, her skin was very dry, inelastic, and pale with a yellow tint suggesting carotinaemia. Her expression was dull and apathetic. Pubic and axillary hair was absent. Internal and external genitalia were atrophied. Her pulse was feeble, temperature subnormal, and blood pressure 90/? mm. Hg. She was not wasted.

Fig. 1 shows the more important investigations that were undertaken during the course of observation. Others were as follows. Kepler test, 23 (evidence of adrenal failure). Blood count after readmission (December 20, 1949): Hb, 60%; red cells, 3,700,000; white cells, 4,000 (polymorphs 58%, lymphocytes 34%, monocytes 6%, eosinophils 2%). Examination of urine and blood urea revealed nothing abnormal. E.C.G. showed normal tracings of low voltage. A radiograph of skull revealed nothing abnormal. A fractional test meal showed the presence of free hydrochloric acid.

The history and the physical examination rendered the diagnosis of Simmonds's syndrome almost certain, but two investigations were undertaken which confirm a diagnosis of anterior pituitary dysfunction—the determination of the 17-ketosteroids in the urine and the response to a test injection of insulin. The 17-ketosteroid result was confirmatory of the diagnosis, only a trace of this substance being found in the 24-hour specimen of urine. An insulin sensitivity test was then undertaken. As the condition of the patient was not very good, only one-third of the calculated dose of insulin—that is, 1½ units—was injected intravenously. Within half an hour the patient felt faint, sweated, and

FIG. 1.—Case 1. Details of investigations and treatment.

became unconscious. The test was discontinued; the pulse was not perceptible, and the blood pressure fell to 60 mm. Hg.

Energetic treatment with glucose, adrenaline, and adrenal cortical extract ("eucortone") was started at once, but the patient remained semiconscious, confused, with a barely perceptible pulse and a systolic blood pressure between 60 and 74 mm. Hg for a fortnight. The blood-sugar figures were as follows: fasting, 33 mg. per 100 ml.; 5 minutes after insulin injection, 31 mg.; 15 minutes, 17 mg.; 30 minutes, 22 mg. No further samples were taken owing to the serious condition of the patient. Unfortunately the test dose of insulin was given before the results of the fasting blood sugar had been received from the laboratory, otherwise the test would not have been undertaken.

The treatment is recorded in Fig. 1. It will be seen that for the first few days, owing to lack of supplies, the dose of eucortone was only 10-20

Fig. 2.—Case 1. Photograph showing absence of axillary and pubic hair and poor mammary development.

ml. daily; thereafter it was raised to 60 ml. A few injections of testosterone propionate were given, but these had to be discontinued because they induced restlessness. Thyroid gland (dry) 1/5 gr. (13 mg.) was tried on three successive days, but caused diarrhoea and a fall of blood pressure, so it could not be continued. The patient improved gradually, and at the beginning of March treatment with "doca" was substituted for eucortone, and later 200 mg. of doca was implanted and the patient was discharged in fairly good condition taking 5 g. of salt extra, with 10 mg. of methyl testosterone sublingually, which now had no ill effect. When seen in the out-patient department one month after discharge she was well; thereafter she ceased attendance.

The patient was readmitted in December, 1949, unconscious; no history was obtainable. The pulse and blood pressure were imperceptible. A vein was exposed; no blood could be obtained, but a glucose-saline drip was given with intravenous injections of 10 ml. of eucortone every four hours. She regained consciousness in a few hours and gradually improved. In January, 1950, 200 mg. of doca was implanted, and in March 100 mg. As the patient could not tolerate thyroid gland, thyrotropic hormone was given in doses of 200 units every other day for five weeks; the only changes noticed were that the skin became less dry and the hair of the head improved in appearance.

The patient was discharged in March, 1950. The myxoedematous appearance had not changed, and the skin remained dry. She was anaemic; iron had not been well tolerated, and difficult veins precluded the use of iron intravenously. Since discharge she has remained well, and has been able to do some housework and shopping. The raising of the haemoglobin level still remains a problem.

Case 2

The patient, a married woman aged 48, had had five pregnancies between 22 and 17 years previously. A post-partum haemorrhage occurred after the second and fifth

pregnancies. Amenorrhoea has been present since the last pregnancy, and since then she has never felt quite well. She has attended the doctor for the last five years on account of "gastric complaints" and "anaemia." She was admitted to hospital on August 27, 1949, in a semi-comatose condition, into which she had lapsed three days before.

On examination she was mentally confused; her face was myxoedematous, her skin was dry and pale, the hair of the scalp was dry, and pubic and axillary hair and eyebrows were missing. Internal and external genitalia were atrophied. Petechiae were present on shoulders and ankles. The patient was not wasted. Her temperature and pulse were subnormal. Her blood pressure was 90/55 mm. Hg. A blood count showed: Hb, 90% (red cell count not done); white cells, 5,300 (polymorphs, 58%, lymphocytes 34%, monocytes 5%, eosinophils 2%, basophils 1%); blood urea, 19 mg. per 100 ml.; blood sugar, 62 mg. per 100 ml.; serum chloride, 565 mg. per 100 ml.; serum sodium, 334 mg. per 100 ml. The urine was normal. An E.C.G. showed normal tracings of low voltage.

The mental symptoms and stupor suggested hypoglycaemia; intravenous glucose brought an improvement, but mental confusion persisted. Further consideration suggested the diagnosis of Simmonds's disease because of the history and the physical resemblance to Case 1. Eucortone, 5 ml. daily, was given and the confusion cleared at once, and the general condition thereafter improved. Estimation of 17-ketosteroids in the urine showed only 0.5 mg. for 24 hours, confirming the diagnosis. In view of the previous experience the insulin tolerance test was not done. Thyroid gland, 1/2 gr. (32 mg.), was given twice, but this small dose was not tolerated; the blood pressure fell to 80/60 mm. Hg. and that treatment was discontinued. Subsequently the patient improved gradually on an extra 5 g. of salt, with 10 mg. of methyl testosterone sublingually. On discharge in November, 1949, she still looked myxoedematous, but was able to do light work. Since then she has been living a normal life and her health has been maintained by implants of doca and methyl testosterone sublingually.

Interesting Points Resulting from the Chemical Investigations

In Case 1 the blood cholesterol was high owing to secondary myxoedema, but fell during treatment. The sodium and chlorides were at first low, improved on treatment with salt and doca to normal level, and had to be restricted later owing to development of oedema. The potassium level was normal. Total serum protein (Case 1) was normal, but the A./G. ratio was reversed: albumin 2.5%, globulin 3.8%. This is unexplained. Hypochromic anaemia was present, the eosinophils were 1%, 2%, and nil in three counts. This type of anaemia is also found in hypothyroidism, and is noted by Escamella and Lissner in a number of verified cases. All blood-sugar estimates were low. It is interesting to note that the ketosteroid estimation rose after treatment.

Comment

The interest of these patients lies in the fact that the pituitary gland had been so seriously disturbed that the production of thyrotropic, gonadotrophic, and adrenocorticotrophic hormones was severely reduced. They both showed features of myxoedema with subnormal temperature, slow pulse rate, intolerance to cold, and lowered B.M.R. The lack of gonadotrophic influence was shown by the cessation of menstrual periods at an early age, the subsequent sexual involution, and the absence of sexual hair. The lack of adrenocortical hormone was shown by the low blood pressure, low blood-sugar level, and by the low ketosteroid production. With

such severe damage treatment is necessarily difficult. It has been found that pituitary extracts are of no value.

The great value of adrenal cortical extract and salt was conclusively shown by our patients. Certainly Case 1 and probably Case 2 would have died without it. In the first patient the injection of insulin precipitated an adrenal crisis, on the verge of which she must have been living for a long time. This test illustrated only too clearly the danger of giving a dose of insulin in patients with severe degrees of pituitary failure. If the diagnosis can be made without the test it is clearly much safer not to do the latter. In Case 2 there was the same underlying mechanism, though not so severe. Both patients recovered a fair degree of health with adrenal cortical hormone and later doca. It was possible to substitute doca implants for the whole adrenal extract, provided sufficient was implanted. This suggests that doca must have more widespread action than just the regulation of sodium and potassium balance, which in these patients was not grossly upset so far as the chemical investigations show. The level of the blood sugar was not raised by treatment.

Most of the more recently reported cases have been treated mainly with testosterone by mouth, injection, or implant; the very good effect of doca in our patients is worth stressing. In patients with secondary myxoedema it has been previously noted that thyroid gland may not be tolerated. This was the case in our patients, and patients who show signs suggesting myxoedema should be examined for other signs of pituitary hypofunction before thyroid gland is given. As in the case of insulin, thyroid gland may be a dangerous drug in these patients even in a very small dose, and should be given with great caution. It had a very adverse effect with both patients. It is to be noted that adequate blood transfusion for treatment for the initial post-partum haemorrhage had not been given. In Case 1 a small transfusion was given 13 days after the haemorrhage. In Case 2 no blood was administered. It would seem likely that adequate prompt transfusion of such cases would prevent the development of this sequel.

Summary

Two patients with characteristic history and physical signs of anterior pituitary gland failure following post-partum necrosis of the gland are presented.

Both showed symptoms of adrenal crisis and responded to treatment by adrenal extract and salt. Both are being maintained in fair health by implants of doca and methyl testosterone by mouth.

On April 16 Professor E. J. Cohn, of Harvard University, demonstrated at Cornell University Medical School an interesting machine which processes blood as fast as it is drawn from the donor, according to a *New York Times* report. The machine, which is portable, made of plastic materials, and can be sterilized, prepares plasma at the rate of 0.5 ml./sec., or over three pints an hour. Blood flows direct from the vein over an exchange resin, which removes calcium and so prevents clotting, is then cooled, and passes into a small continuously running centrifuge which separates cells and plasma. Prothrombin is then removed from the plasma by a second resin which absorbs it, and a zinc glycine solution is added to precipitate fibrinogen and gamma globulins, which are centrifuged off. The remaining plasma protein (largely albumin), after removal of the zinc, is frozen, sterilized by exposure to an electron beam, and is then ready for storage or use.

Medical Memoranda

Phlegmonous Enteritis Occurring After Strangulated Femoral Hernia

This unusual sequela of a strangulated hernia seems to be worthy of record.

Case Report

A married woman aged 40 was admitted to hospital on May 4, 1950, as a case of strangulated femoral hernia of six hours' duration. She had vomited twice and was experiencing colicky abdominal pain. Clinical examination at the time of admission confirmed the presence of a tender irreducible right femoral hernia. The abdomen was slightly distended and auscultation revealed hyperactive peristalsis. Operation was undertaken within two hours of admission.

First Operation.—A Lotheissen-type operation was performed. The sac contained a firmly incarcerated loop of small bowel, the upward delivery of which could be effected only after division of Gimbernat's ligament. The affected bowel, 1-2 in. (2.5-5 cm.) in length, was deeply congested, but, following delivery from the sac, on application of a hot swab it rapidly regained its normal colour. Normal lustre and contractability were present, and the bowel accordingly was adjudged viable. The sac was excised and a repair effected with interrupted sutures of No. 7 nylon.

The patient made an uninterrupted recovery and was discharged from hospital on May 18. At no time during her stay in hospital was there any complaint of pain or diarrhoea, and no evidence of incipient intestinal obstruction.

On May 19—that is, the day after her discharge home—she was readmitted with a history of 14 hours' central abdominal pain accompanied by nausea and vomiting. On admission she was obviously ill. Her temperature was 99.5° F. (37.5° C.) and the pulse rate 110. Her tongue was dry and furred. Abdominal examination showed slight generalized distension with rebound tenderness and guarding in the central abdominal zone and in the right iliac fossa. Auscultation showed hyperactive peristalsis. Rectal examination gave no useful information. A diagnosis of intestinal obstruction was made, and laparotomy was performed some two hours after admission.

Second Operation.—On May 19 the abdomen was opened through a lower right paramedian incision, a quantity of clear straw-coloured fluid escaping on opening the peritoneal cavity. At about 2 ft. (61 cm.) from the ileo-caecal junction a segment of ileum, presumably that portion of the bowel which had previously been incarcerated in the femoral hernial sac, was found to be the site of a phlegmonous induration. The portion of gut affected was some 4-6 in. (10-15 cm.) in length, almost twice the length of the gut originally incarcerated in the hernial sac. Its colour was dusky red and it was mottled in appearance. It was considerably thickened and rubbery in consistence. The adjacent mesentery was oedematous and palpably thickened. The area was fairly sharply demarcated from normal ileum, which was collapsed distal to and moderately distended proximal to the lesion. An interesting feature was the complete absence of any plastic peritonitis such as might have been expected under such conditions. A diagnosis of localized phlegmonous enteritis was made, and about 20 in. (50 cm.) of bowel was resected. Continuity was restored by a side-to-side anastomosis and the abdomen closed without drainage.

After operation the patient developed paralytic ileus, which necessitated the use of continuous aspiration and intravenous saline therapy for five days. Bowel function returned normally on the seventh day, and she then had a protracted but