SPONTANEOUS HYPOGLYCAEMIA ASSOCIATED WITH EPILEPSY; SUBTOTAL PANCREATECTOMY

BY

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Reports of cases of spontaneous hypoglycaemia treated by partial pancreatectomy are uncommon in this country, although American literature contains numerous accounts of the surgical treatment of pancreatic hyperactivity. The case herewith reported is of interest in that the symptoms of hypoglycaemia were associated with epilepsy, which confused the clinical picture in the earlier stages of the illness. Although, most unfortunately, the patient succumbed from pulmonary infarction, he lived long enough to demonstrate the remarkable improvement which followed subtotal pancreatectomy.

Case History

In 1922 the patient, then aged 41, had his first fit. He had just begun his morning's work when without warning he fell on his face unconscious. He understood that he lay quite still, was uncertain if he bit his tongue, but remembered having "wetted his trousers." He was taken home unconscious. His doctor said that his heart was in a bad state and that he smoked excessively. During the same day he had three further fits, with twitching movements all over the body, and believed that he remained unconscious for some seven hours in all.

A doctor again examined him that evening and the following day. He then referred him to one of the larger London teaching hospitals. Here his skull was x-rayed in three positions and a blood test taken. Bromide and luminal (phenobarbitone) were prescribed. Following this the fits recurred, but gradually they became less frequent. After some five years of treatment he enjoyed an interval of about two years with freedom from fits, and so gave up attending the hospital for three months. Cessation of treatment was, however, followed by a recurrence of the fits, and so he resumed his attendance at the hospital and continued the treatment until the outbreak of war, when he was transferred to the Metropolitan Hospital with a diagnosis of epilepsy.

On Oct. 19, 1939, he first attended the general medical out-patients department of the Metropolitan Hospital. He was seen by the house-physician, who considered the symptoms to be compatible with the diagnosis of idiopathic epilepsy. The patient was therefore treated with phenobarbitone, gr. 1 (65 mg.) b.d. On April 19, 1941, he stated that he felt well and was working, and had remained free from fits for two years while taking the tablets.

On Jan. 24, 1942, he first reported the occurrence of peculiar attacks unlike his fits. He had had six of these attacks in the previous two weeks, four occurring on the same day. In the attacks he saw "something terrible coming towards him"—so terrible that he was unable to describe it. He felt, however, that it concerned the Germans, and explained that he had been a prisoner of war for nine months in the 1914-18 conflict, which had greatly upset him, as, though he had often thought that he might be killed, he had never contemplated being a prisoner. After this feeling of "terrible fear" he experienced a peculiar sensation in the stomach, but found that if he gripped the bench hard this might pass off, leaving him very weak; otherwise he would collapse suddenly without further warning. After these attacks, for 24 hours he felt choking in the throat, was unable to speak easily, and wished to cry. He then stated that these "attacks" had been occurring for the past eighteen years as well as the fits, which he had previously described. At first they had occurred at intervals of two or three months, but in the last six months more frequently, and he noted that he tended to have several attacks one month and then a period of freedom. These attacks would occur at any time of day, but were more frequent before midday. He himself had noticed no relation between the attacks and the times of his meals or of his work. His work involved heavy manual labour, and his wife had often said that he should not go to work without more food. He continued on phenobarbitone, but on July 11, 1942, reported seven of these attacks occurring on one day, and was therefore referred by the house-physician for a further opinion.

On July 15 he was first seen by one of us (N. G. H.), and a tentative diagnosis of hypoglycaemic attacks was considered. Admission

was arranged to the West End Hospital for Nervous Diseases for further investigation.

Habits.—The patient was a french-polisher. He drank on the average one pint (568 ml.) of beer and smoked 1/2 oz. (14 g.) of tobacco daily. His usual meals were as follows: 6.30 a.m.: A cup of tea and one piece of bread-and-jam. 9.30 a.m.: Breakfast at work—a cup of tea, and a sandwich of bread and bacon. 1 p.m.: A meat or fish dish with bread, followed by pudding or a sweet 3.30 p.m.: A cup of tea and a piece of cake. 6 p.m.: 1 pint of ale 7 p.m.: His main meal—e.g., a chop and vegetable, followed by a sweet or pudding.

Condition on Examination.—He was admitted to the West End Hospital on Aug. 10, 1942. Weight 8 st. 11 lb. (55.7 kg.), his previously highest known weight having been 9 st. 4 lb. (59 kg.). He was well developed and his general nutrition good. He appeared younger than his age. Full neurological examination proved normal. With the exception of some slight emphysema and a few rhonchi in the chest, a comprehensive examination also proved normal. The B.P. was 140/90 and the pulse rate 65-80 and regular. On examination the urine was normal.

Investigations.—The C.S.F. showed a pressure of 140 mm., no cells, a slightly raised protein of 70 mg. per 100 ml., no excess of globulin, and a normal colloidal gold curve. The Wassermann and Meinelke flocculation tests in both blood and fluid were negative. Skiagrams of the skull and pituitary fossa were normal. Skiagrams of the suprarenal region showed no abnormality.

Blood-sugar examinations on Aug. 12 (patient on normal full diet previously) gave the following results. Glucose-tolerance curve:—Fasting, 53 mg. per 100 ml. After 50 g. of glucose: 1/2 hour, 109 mg.; 1 hour, 133 mg.; 1½ hours, 32 mg.; 2 hours, 32 mg. per 100 ml. (Urine specimens fasting and at 1 and 2 hours contained no sugar.)

Aug. 18.—The patient was ordered a diet containing 400 g. carbohydrate a day. Food was taken every two hours by day, and, if waking, in the night.

Aug. 19.—Glucose-tolerance curve:—Fasting, 52 mg. per 100 ml. After 50 g. glucose: 1/2 hour, 80 mg.; 1½ hours, 63 mg.; 2 hours, 72 mg. per 100 ml.

Aug. 31.—Blood sugar on waking in morning, 39 mg.; 2 hours after midday meal, 75 mg. per 100 ml.

Sept. 7.—At 6.30 a.m. the patient had a full breakfast of cereal, milk, and sugar, 2 slices of bread-and-butter and jam, and tea. At 9.15 a.m. he developed an attack, and the blood sugar was found to be 56 mg. per 100 ml. Glucose (50 g.) was then given, and half an hour later the blood sugar was 72 mg. per 100 ml.

A blood count on Aug. 24 showed: Hb, 102%; red cells, 5,260,000; C.I., 0.97; white cells, 7,200. Blood sedimentation rate (Wintrobe, 100 mm. col.), 2 mm. in 1 hour. An electro-encephalogram taken on Sept. 1 (by courtesy of Dr. Dennis Hill) showed the following results: Dominant rhythm, 10 per second—voltage 50 microvolts; regularity good; no abnormal rhythms; stable on hyperventilation. Conclusion: within normal limits.

While the patient was in hospital a number of severe hypoglycaemic attacks were observed, which were not relieved by a diet of 4,000 calories over a period of five weeks. In view of this and of the results of the clinical investigations, and also of the progressive nature of the illness, it was decided to explore the pancreas for an islet adenoma, and, if such were not found, to perform a subtotal pancreatectomy.

Operation (McN. L.).—On the morning of the operation the blood sugar was 66 mg. per 100 ml. The patient's blood was Group A. An upper transverse abdominal incision was made an inch below the ninth costal margin. The rectus muscles were divided by diathermy and the abdomen was opened. The stomach was displaced upwards, and the lesser sac was opened by an incision through the gastro-colic omentum, and the mesocolon was divided. By this means efficient exposure of the pancreas was obtained. A careful search failed to reveal an adenoma, so it was decided that a subtotal pancreatectomy should be performed. A splenectomy was carried out in order to obviate troublesome haemorrhage from the splenic vein, which is normally partially embedded in the pancreas. The tail and body of the pancreas were then mobilized, and about three-quarters of the gland removed with a diathermy knife and immediately fixed for histological examination. The raw surface was oversewn with mattress sutures. After insertion of a rubber drain the abdominal wall was closed in layers. After the operation the patient was somewhat shocked, but recovered from the anaesthetic. His condition steadily improved until the following day, when he suddenly collapsed and died, twenty-five hours after the operation. The blood sugar the morning after the operation rose to 130-140 mg. per 100 ml. (The details of this reading were destroyed by enemy action.)

Necropsy (Dr. Carnegie Dickson).—The abdominal wound was reopened and the intestines found to be distended with flatus. There

was only a slight accumulation of blood-stained fluid in the flanks and in the bed of the spleen. No evidence of fat necrosis was seen. Careful investigation of the mesentery of the bowel, retroperitoneal tissues, and elsewhere showed no accessory pancreas in which an adenoma might have developed. No adenoma was found in the remaining part of the pancreas. The liver was normal apart from moderate fatty degeneration and some venous congestion. Both kidneys showed some cloudy swelling; otherwise there was nothing of note. Both suprarenals were normal. The lungs showed a very patchy congestion, some of which was due to areas of multiple infarction. There was no acute pneumonic consolidation. The pituitary gland and thyroid both appeared normal. The heart and aorta were normal. *The Brain:* The leptomeninges showed a very distinct degree of fibrous thickening over the hemispheres, especially over the vertex, where the convolutions were distinctly narrowed and atrophied. Exaggeration of the sulci in the region of the thickened leptomeninges was as pronounced as in many cases of advanced general paresis.

Histology.—An extensive series of sections of the pancreas stained for islet tissue showed nothing suggestive of hyperplasia or tumour. Complete histological examination of the other organs, including the brain, was not possible owing to the destruction of the specimens by enemy action.

Discussion

The normality of the pancreas in this case is noteworthy. The very full pathological examination, including the search for accessory pancreatic tissue, excluded the possibility of an islet adenoma having being missed at operation.

A lesion of the hypothalamus in the region of the paraventricular nuclei might explain the picture, as Barris and Ingram (1936) have shown in cats that this may cause permanent hypoglycaemia and increased sensitivity to insulin. A similar mechanism is possibly the basis of obesity and hypoglycaemia following some cases of encephalitis.

Hypoglycaemia itself may also produce lesions in the brain consisting of widespread degeneration and necrosis of the nerve cells with corresponding glial proliferation. It has been thought that this is due to the failure of the vital oxidative processes from lack of glucose, probably reinforced by vasomotor disturbances. In the 6 cases described by Lawrence, Meyer, and Nevin (1942) this mainly affected the cerebral cortex, caudate nucleus, and putamen, and to a less extent the cerebellum. It is therefore unfortunate that it was not possible to examine the brain in detail.

The epilepsy of late onset was possibly associated with the hypoglycaemia, as a low blood sugar may induce fits in a patient not normally epileptic, while resistant cases of epilepsy are sometimes found to have low blood-sugar levels.

Whatever the aetiology of this case, however, the severity of the attacks and their failure to respond to dietetic treatment (Whipple and Frantz, 1935) would almost certainly have caused a fatal coma, and so operation was fully justified.

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OCCURRENCE OF OVULATION AND CAUSES OF STERILITY IN METROPATHIA HAEMORRHAGICA

BY

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This note records evidence of ovulation in a typical case of metropathia haemorrhagica and suggests that the sterility associated with this condition can be due to causes other than an anovulatory cycle.

Case Report

The patient, aged 40, has five children, the youngest 11 years old. She was admitted for menorrhagia and metrorrhagia of three years' duration, a temporary remission of symptoms having followed curettage two years ago. Since the onset of irregular periods her cycle has been 7 to 8 days' bleeding, usually excessive, the intervals varying from 28 to 35 days, while periods of bleeding up to six weeks' duration have occurred latterly. Subtotal hysterectomy revealed a cystic right ovary about 3 cm. in diameter, the left ovary being normal.

Pathological Findings.—Macroscopic section showed moderate symmetrical enlargement of the uterus due to myohyperplasia, with a thickened haemorrhagic endometrium about 6 mm. in thickness in the fresh specimen. Two small intramural fibroids were also present. Rather more than half-way down the posterior wall a small endometrial polyp-like structure projected about 4 mm. into the uterine cavity, and a portion of endometrium and myometrium including this small mass was sectioned. The gross morbid anatomical characteristics were thus consistent with the clinical diagnosis of metropathia haemorrhagica.

Histology.—The curettage made two years ago followed a fortnight of continuous bleeding and the scrapings were post-menstrual, showing no progesterone activity. In the present specimen (see Fig.)

Photomicrograph showing mass of degenerate chorionic villi and adjacent oestrogenic endometrium. Stained Heidenhain's iron haematoxylin.

the myometrium showed no abnormality, apart from the fibromyomata, while the endometrium presented an extremely interesting picture. It was of "mixed" type, a very few glands showing early secretory activity, while the majority were in the oestrogen phase, some with cystic dilatation. In glands where secretory activity is evident this is often limited to a few cells, the remainder presenting an even and regular luminal border. What appeared macroscopically to be an endometrial polyp proved to be a mass of degenerate chorionic villi, lying mostly outside the endometrium and projecting into the uterine cavity. The penetration of trophoblast into the endometrium was limited to a depth of approximately 0.5 to 1 mm. Decidual reaction was pronounced in the stroma, and the hypertrophied decidual cells showed the intermingling with numerous lymphocytes which is characteristic of early pregnancy. In general, the stromal picture was in marked contrast to the glandular picture.

Discussion

The endometrial glands in the above case present evidence of a prolonged oestrogen phase, although the partial onset of