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THE ASSOCIATION OF PITUITARY HYPOFUNCTION WITH CHRONIC DIARRHOEA

A REPORT OF TWO CASES

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Panhypopituitarism is a rare disease and the majority of cases which do occur are either secondary to postpartum haemorrhage or to surgical removal of the gland. It is, however, well-known that features of the condition may occur in persons who are grossly malnourished. A striking point in such cases has been the reversion to normal once the general nutrition has been improved and for this reason such subjects have been labelled as examples of 'functional hypopituitarism'.

The present paper describes two cases of panhypopituitarism in whom chronic diarrhoea with malnutrition antedated the onset of the endocrine disorder. In both subjects the pituitary failure seemed to be severe and irreversible. Because of the variety of such an association, it seems worth while reporting these two cases in detail.

CASE REPORTS

Case 1

A male patient aged 54 years was admitted to the Johannesburg General Hospital in February 1953 with a history of weakness and tiredness over the previous 12 years. He was well until 1941, when he took part in the retreat from Burma. During this period he developed severe diarrhoea, which was diagnosed as being due to both amoebic and bacillary infections of the bowel. He was treated in hospital for several months and, although the diarrhoea cleared up, his general condition remained poor and he was sent back to England. There he was diagnosed as suffering from anaemia but there was no response to a variety of haematinic agents. Over the next years, his condition remained stationary and, although weak, he was able to carry on a sedentary occupation. Apart from the major complaint there were several other changes which the patient noted after the original illness in Burma. He became impotent, was very sensitive to cold, and had to shave only once or twice a week, previously having been of normal hirsuties. These symptoms had persisted up to the time of his admission to hospital.

On examination, he was pale and the skin of the face was finely wrinkled. Facial hair was sparse. Axillary hair was absent and there was very little pubic hair. The pulse rate was 67 per minute and the blood pressure was 120/65 mm. Hg. Nothing abnormal was noted in either the cardiovascular or respiratory systems and nothing abnormal was noted on palpation of the abdomen. The penis was normal in size but the testes were soft and atrophic.

Laboratory data. Packed cell volume 32%, haemoglobin 11·1 g.%, red-cell count 3,760,000 per c.mm. Leucocytes 3,400 per c.mm. (neutrophills 71%, monocytes 6%, lymphocytes 22%, eosinophils 1%, basophils *nil*). Blood electrolytes normal. Modified Ide test negative. X-rays of chest and skull normal. Electrocardiogram normal. Oral sugar tolerance curve (50 g. of glucose)—fasting 69 mg.%, ½ hour 106 mg.%, 1 hour 110 mg.%, 1½ hours 100 mg.%, 2 hours 80 mg.%. Insulin sensitivity test (5 units insulin intravenously)—basal 96 mg.%, ¼ hour 59 mg.%, ½ hour 34 mg.%, 1 hour 41 mg.%, 1½ hours 46 mg.%, 2 hours 51 mg.%. Basal metabolic rate 20%. Robinson-Kepler test positive (factor 8). 17-ketosteroids in 24-hour specimen of urine 2·1 mg. (measured as dehydroisoandrosterone).

Progress. A diagnosis of panhypopituitarism was made on the clinical findings together with the results of the laboratory tests. Replacement therapy was begun with small doses of methyltestosterone, desoxycorticosterone acetate and thyroid extract. Subsequently cortisone was added to the regime. Response to treatment was excellent. There was a marked increase in energy, libido and potency returned, and the blood count gradually reverted to normal. This improvement has been maintained over the ensuing 4½ years.

Case 2

A married European female aged 46 years, with no children, was first admitted to another unit in the Johannesburg General Hospital in January 1956. The major complaints were abdominal pain and intermittent diarrhoea for 10 years. In the 7 months before admission, the diarrhoea had been particularly severe, with the passage of up to 10 motions daily. The stools were sometimes watery and yellow, while on other occasions they were bulky and offensive. The diarrhoea was accompanied by cramplike generalized abdominal pains. Over the 7 months the weight had fallen from 120 lb. to 60 lb. Just before admission to hospital she had noticed some swelling of the ankles.

In the systematic history it was noted that the patient had been pregnant 3 times but on each occasion the infant was stillborn. Postpartum blood loss had not been excessive and she had regular menses for 10 years after the birth of the last child.

She became menopausal at the age of 42.

On physical examination the striking feature was gross emaciation. The tongue was smooth and red. The extremities were cold and there was some peripheral oedema of the lower limbs. The blood pressure was 150/90 mm.Hg. and nothing abnormal was noted in either cardiovascular or respiratory systems. The abdomen was distended with gas and there was a smooth 3-finger hepatomegaly.

Laboratory data. Haemoglobin 13·8 g.%. Leucocytes 9,300 per c.mm. Sedimentation rate (Westergren) 30 mm. in 1 hour. Urine analysis—glucose 4+positive, albumin absent, nothing of significance seen on microscopic examination. Glucose tolerance test (50 g. orally)—fasting 118 mg.%, 1 hour 160 mg.%, 1½ hours 200 mg.%, 2 hours 170 mg.%. serum calcium 4·5 mEq./l., serum inorganic phosphorus 5 mg.%, blood urea 11 mg.%, serum proteins 5·1 g.% (albumin 2·4, globulin 2·7), prothrombin index 100%. Stool examination—macroscopically grey, semi-solid and offensive, microscopically fat globules and muscle fibres present. No pathogenic organisms isolated. Fat balance—21·8g. excreted in 24 hours on diet containing 100 g. of fat. Duodenal intubation—No tryptic activity present. Serum protein-bound iodine 3·3 micrograms %. 17-ketosteroids in 24-hour specimen of urine 2·4 mg. (measured as dehydroisoandrosterone). Follicle-stimulating hormone in 24-hour specimen of urine more than 48 mouse units (normal 12-24 mouse units). Skeletal survey normal. X-rays abdomen—calcification in position corresponding to body and tail of pancreas.

Progress. A diagnosis of severe chronic pancreatitis was made. The steatorrhoea was regarded as being secondary to a deficiency of exocrine secretions and the diabetes as a manifestation of insulin lack. Therapy was started with a high-protein diet, vitamin supplements and a pancreatic extract. In addition, daily insulin (15 units soluble and 15 units protamine zinc) was required in order to stabilize the diabetes. On this treatment the patient gained weight, the diarrhoea subsided to some extent and she felt symptomatically better. She was finally discharged on maintenance therapy 2 months after admission.

Second admission. The patient was readmitted 5 months later, in February 1957, because of an exacerbation of the diarrhoea and for stabilization of the diabetes. There was some doubt whether therapy had been properly followed while she was out of hospital and whether insulin had been taken regularly. Physical findings were similar to those on the previous admission.

Relevant laboratory data: Haemoglobin 11·6 g.%. Urine analysis—glucose 4+ positive. Glucose tolerance test (50 g. orally)—fasting 270 mg.%, ½ hour 312 mg.%, 1 hour 350 mg.%, 2 hours 450 mg.%, 3 hours 472 mg.%, 4 hours 362 mg.%. Serum proteins—total 5·4 g.%, (albumin 1·4, globulin 4·0). 'Liver function' tests—thymol turbidity 5·5 units, zinc sulphate turbidity 16·8 units, alkaline phosphatase 12·2 King-Armstrong units. Total serium lipids 337 mg.%, total serium cholesterol 138 mg.%, serum calcium 5·1 mEq./l. Gastric analysis—histamine-fast achlorhydria.

Progress: Although there had been no major change in the clinical picture, it was felt that some deterioration had occurred. The protein deficit was more marked and the derangement in liver function tests suggested that the malnutrition had caused hepatic degeneration which might be either fibrosis or fatty infiltration. The glucose tolerance test was also more disturbed than on the previous admission. Therapy was begun again and the response was fairly adequate. However, although the diarrhoea became less troublesome, the patient did not gain weight on this admission. Diabetic control was again achieved on a total daily dosage of 30 units of insulin. The patient was discharged again after 1 month in hospital.

Third admission. The patient was first seen by the authors on her third and final admission to hospital in April 1957, only 2 weeks after the previous discharge. While at home she had developed severe diarrhoea and swelling of the legs. Upper abdominal pain, which was cramplike in nature, had also been a feature. During this period she had not taken any insulin.

On physical examination the patient was found to be mentally torpid and very cachectic. The skin was fine and atrophic and a scaly erythematous rash was noted on the trunk and extremities. Spider naevi were present on the forehead and upper chest. The tongue was red and smooth and there was cheilosis at the angles of the mouth. Marked oedema of the legs was present, extending up to the sacrum and vulva. The breasts were atrophic and both axillary and pubic hair were very scanty. No abnormality was noted in the cardiovascular, respiratory and central nervous systems. It was observed that the patient was extremely intolerant to cold and this, coupled with the fine skin and scanty secondary sex hair, raised the possibility that pituitary hypofunction was contributing to the clinical picture.

Laboratory data: Haemoglobin 10·0 g.%, microscopically the red cells showed a tendency to macrocytosis. Urine analysis—*nil* of significance. Glucose tolerance curve (50 g. orally)—fasting 100 mg.%, 1 hour 135 mg.%, 1½ hours 153 mg.%, 2 hours 140 mg.%. Starch tolerance test (50 g. of starch)—fasting 83 mg.%, 1 hour 105 mg.%, 1½ hours 92 mg.%, 2 hours 92 mg.%. Blood urea 19 mg.%, serum proteins 4·5 g.% (albumin 1·1, globulin 3·4). Blood electrolytes—sodium 135 mEq./l., potassium 3·1 mEq./l., calcium 4·1 mEq./l., inorganic phosphorus 2·4 mg.%. Serum cholesterol 120 mg.%, serum protein-bound iodine 2·4 micrograms%. 17-ketosteroids (measured as dehydroisoandrosterone) in 24-hour specimen of urine—0·26 mg. Follicle-stimulating hormone, assay of 24-hour specimen of urine, 6-12 mouse units.

Progress. Despite replacement therapy with intravenous fluids and large doses of oral pancreatic extract, the patient went steadily downhill and died after 2 weeks in hospital. At the time of death the clinical diagnosis was one of chronic pancreatitis with panhypopituitarism in addition.

Autopsy Findings (18 hours after death). The body was emaciated and there was generalized pallor. Oedema was present in both lower extremities and the vulva. The breasts were atrophic. The heart was not enlarged (weight 250 g.); all the valves were competent and healthy: there was slight dilatation of the left ventricle, with thickening of the endocardium; an organized myocardial infarction was present in the interventricular septum; there was a severe degree of atheroma with calcification in the coronary arteries and in the aorta. The smaller arteries showed the presence of arteriosclerosis. The liver was slightly diminished in size (weight 1250 g.); its surface was granular; on section, diffuse cirrhosis and fatty change were noted. The pancreas was grossly diminished in size; it was 4 inches long and ½ inch broad; on section, well marked atrophy and fibrosis were noted; the ducts were dilated and contained white calculi. Central nervous system: the arteries of the circle of Willis showed the presence of atheroma. Endocrine system: the thyroid gland was normal in size; a small adenomatous nodule was present. The pituitary gland was about normal in size; on section an irregular area of dull lustreless yellow colour was seen, occupying about one quarter of the anterior lobe and extending in an irregular manner across the anterior lobe from border to border. The suprarenals showed no macroscopic evidence of abnormality. The parathyroid glands were smaller than normal.

Histopathology. Sections of the pancreas showed advanced fibrosis of the interstitial tissue with a well-marked dilatation of the ducts; a minimal amount of parenchyma was seen, viz. occasional clusters of acini, representing portions of lobules, and in the tail of the gland isolated fragments of islet tissue embedded in dense fibrous tissue; these features are those of chronic cystic pancreatitis. Sections of the liver showed the presence of severe fatty infiltration and diffuse hepatic fibrosis. Section of the heart confirmed the presence of an organized myocardial infarction. Section of the thyroid showed the gland to be in the resting stage. Section of the pituitary showed the presence of necrosis in the anterior lobe; this necrosis was seen in two areas in the posterior portion of the anterior lobe, one on either side of the pars intermedia; the one area of necrosis was about twice the size of the other and together they involved about one quarter of the anterior lobe; they extended from the periphery into the interior of the lobe and were roughly wedge-shaped with their broad bases situated on the periphery of the gland; this distribution is in keeping with avascular necrosis. Sections of the parathyroid glands showed parenchymal atrophy and lipomatosis.

DISCUSSION

The interest of the two cases reported here is the probable association between malnutrition due to chronic diarrhoea and the subsequent hypofunction of the anterior pituitary.

In both the cases this hypofunction seemed to be due to organic rather than functional changes in the gland. This was more clearly demonstrated in case 1, in whom unequivocal signs of irreversible panhypopituitarism developed after a period of prolonged and severe diarrhoea. Despite remission of the diarrhoea the patient's general condition did not improve and he developed weakness, impotence, intolerance to cold, loss of secondary sex hair and a mild refractory anaemia. Biochemical tests, made several years after the onset of the condition, confirmed the presence of pituitary hypofunction and there was a dramatic response to end-organ replacement therapy.

It has been well recognized that pituitary hypofunction can develop in any state of malnutrition. Thus it has been described in starvation, in anorexia nervosa, and secondary to steatorrhoea. However, the striking feature of most reports has been the return to normal once the nutrition has been improved. For example, although Jacobs[1] found a loss of libido, thinning of axillary and public hair and some degree of testicular atrophy in American prisoners of war in a Japanese camp during World War II, these changes were found to be reversible after as long as 40 months of starvation. The same seems to be true in anorexia nervosa. In 1939 Sheldon[2] pointed out that such cases develop a 'functional' type of Simmonds' disease. He felt that a lowering of food intake may lead to a decrease in anterior pituitary function and may thus mimic the findings associated with organic pituitary disease.

There is both clinical and experimental evidence to suggest the validity of such a thesis. For instance, in 1930 Mason and Wolfe[3] found atrophy of the genital system in female rats following on chronic malnutrition and they were able to reverse these changes with pituitary implants. In addition, Weiner (quoted by Hultgren[4]) reported that anoestrus in starving guinea-pigs could be abolished by hypophyseal extracts.

Of special interest are those cases of hypopituitarism which have been reported in association with diarrhoea. In 1939 Bauer[5] drew attention to the endocrine changes in sprue and suggested that these were due to the concomitant nutritional deficiency. More recently (1952) Hubble[6] reported a case of adult coeliac disease presenting features quite similar to those in case 1. The patient was a female, aged 38 years, who had suffered from repeated attacks of diarrhoea since childhood. Menstruation had been irregular before it ceased one year prior to examination. The physical findings included pallor and scanty pubic axillary hair. The daily excretion of 17-ketosteroids had dropped from 5 mg. 1 year previously to 2·5 mg., while gonadotrophins and oestrogens were absent in the urine. The condition seems to have been functional rather than organic since menstruation subsequently returned when the patient was kept on a gluten-free diet, and urinary oestrogens and gonadotrophins are now normal. However, it still remains possible that chronic diarrhoea with malnutrition may, in isolated instances, lead to irreversible pituitary damage. A probable example of such a case is one reported by Salamon and Lascano[7] in 1942. They found evidence of Simmonds' disease in a male patient who had suffered from steatorrhoea for 5 years. At autopsy there was a diffuse sclerosis of the gland and 2 foci of ischaemic necrosis. In addition, atrophy of the thyroid and testes was present.

From these findings it appears as if the dividing line between functional and organic pituitary damage is not always a clear one. Perloff *et al.*,[8] in 1954, after reviewing the literature came to the conclusion that functional hypopituitarism differs from the organic variety in only two respects. Firstly, the syndrome can be abolished by re-feeding and, secondly, recognizable changes in the structure of the anterior lobe of the pituitary are either absent or slight. Actual histological changes in the pituitary following on malnutrition have, in fact, been reported by a number of workers. In 1948 D'Angelo *et al.*[9] were able to demonstrate an arrest of cellular mitosis, vacuolization of cytoplasm, loss of staining reactions, and a reduction in the number of cells in starving rats. In addition, Gillman and Gillman[10] have reported the presence of cellular changes and small destructive foci in the anterior pituitary lobes of subjects dying from starvation.

From these various findings reported by other workers, it seems reasonable to suppose that case 1 in the present paper represents an example of a rare but real entity—irreversible pituitary damage initiated by a period of severe diarrhoea with associated malnutrition. The interpretation of case 2, however, is more difficult. This patient had suffered from chronic pancreatitis with diabetes, steatorrhoea and protein deficit for several years. Clinically she showed the features of pituitary insufficiency as evidenced by extreme intolerance to cold, hoarseness, loss of secondary sex hair and anaemia. In addition, the diabetes showed a striking amelioration in the last few weeks of life. Glycosuria disappeared and the sugar-tolerance curve returned towards normal. At this stage she became so sensitive to the effects of insulin that it was discontinued and serial laboratory studies demonstrated an appreciable fall in serum protein-bound iodine and in the urinary excretion of follicle-stimulating hormone and 17-ketosteroids. At autopsy 30% of the anterior pituitary was found to be necrosed.

It is possible that the pituitary necrosis present in case 2 was secondary to the chronic malnutrition. However, it is well recognized that it may have been related to the diabetes from which she suffered. This association has been recorded by a number of investigations,[11-14] In a review in 1956 of 7,326 autopsies in adults, Brennan *et al.*,[15] found that some degree of pituitary necrosis was present in 2·0% of diabetes subjects as opposed to an incidence of 0·2% in non-diabetics. On the basis of such studies, diabetes mellitus has been estimated as a cause of between 1% (Escamilla and Lisser, 1942)[13] and 8% (Plaut, 1952)[16] of cases of pituitary failure.

In case 2 it is therefore impossible to dogmatize on the relative roles played by malnutrition and diabetes in the genesis of the pituitary hypofunction. It seems probable that both were involved. It is also not easy to relate the amount of pituitary necrosis revealed at autopsy to the undoubted clinical evidence of severe pituitary hypofunction. In 1949 Sheehan and Summers [14] showed that 75% or more of the pituitary must be destroyed before clinical manifestations of hypofunction appear. However, these findings relate to cases of postpartum haemorrhage in whom the remainder of the gland was healthy. In case 2 this was almost certainly not so, for the function of the gland had been depressed by chronic malnutrition. On such a background the occurrence of limited necrosis was probably sufficient to cause the changes in endocrine function which were evident on the patient's last admission.

Of these changes the alteration in glucose tolerance was perhaps the most striking. The endocrine antagonism between the pituitary and pancreas is well established. For

example, it has been found that the diabetes produced in dogs by extirpation of the pancreas can be ameliorated by the removal of the anterior pituitary. Such dogs are hypersensitive to insulin and brief fasting produces severe hypoglycaemia.[17-19] Young,[20] also found that diabetes could be produced in dogs given large amounts of pituitary extract over long periods.

In effect, case 2 represented an example of the Houssay phenomenon in man. Although examples of such cases are rare, Harvey and de Klerk[21] in an excellent review of the subject in 1955 analysed 11 cases reported in the literature and added 3 of their own. It has been possible to find reference to a further 7 cases[22-27, 15] which, with the present example make a total of 22 reported cases. The condition usually involves individuals who have had diabetes mellitus for a considerable time and is usually caused by infarction of the anterior lobe of the pituitary gland. One of the first manifestations is hypoglycaemia with extreme sensitivity to administered insulin. Within a month or two signs of thyroid, adrenal and gonadal insufficiency begin to appear. The diabetes is ameliorated rather than cured and the glucose-tolerance curve usually remains diabetic in type.

SUMMARY

Two cases are reported in which the presence of severe malnutrition, associated with chronic diarrhoea was followed by evidence of permanent pituitary damage. This is best illustrated in case 1, where replacement therapy produced an excellent and lasting response. Case 2 was found to have pituitary necrosis at autopsy. Aetiological factors may well have been chronic diarrhoea and malnutrition, although the presence of diabetes mellitus might also have played a role.

Attention is drawn to the scanty reference in the literature to organic pituitary damage occurring in cases of malnutrition associated with chronic diarrhoea.

The relation between diabetes and pituitary necrosis is briefly reviewed.

The possible endocrine link-up between organic and functional hypopituitarism as seen in malnutrition, anorexia nervosa, starvation, and chronic diarrhoea is discussed.

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