TWO SIBLING CASES WITH LIPOATROPHIC DIABETES

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Hansen and McQuarrie (1940) reported a rare case with the main features "hepatomegaly, glycosuria and lack of subcutaneous fat tissue". Lawrence (1955) described another case, paid attention to its similarity to McQuarrie's patient and named the disease lipoatrophic diabetes.

Lipoatrophic diabetes is a fascinating and very rare syndrome and if it is fully worked out and understood, it will make a great contribution to the relation of carbohydrate and fat metabolism. However, this disease has been rare and has not yet been reported in our country, except one case of Ishigaki et al. (1963) of our department. We have studied two sibling cases with the same syndrome. We have been able to show that it is probably due to a hypothalamic lesion. Our two cases, therefore, will be presented in some detail, and some of the most important theoretical problems will be discussed.

CASE REPORTS

Case 1

Our first patient H.S. was a 10-years-old girl, the eldest of five siblings and all of these five siblings were alive. The consanguineous marriage or congenital anomaly was not found in this family tree of these cases. The family history did not show diabetes or metabolic disease except for her brother (case 2). She was a full term baby after a normal gestation. The del-
Ivery was uneventful. She weighed 3,000 g at birth and had definite signs of her disease; thin and bony with a wrinkled face and a lack of subcutaneous fat.

Since her birth she has remained emaciated in spite of her good appetite. From early infancy she has shown a generalized lipoatrophy, giving her an athlete appearance. The abdomen has been protruding. Dentition began in 6 months, walking in one year and 6 months, speech in 2 years, after her birth, respectively.

When she suffered from pneumonia in 2 years of her age, she was found ill with rickets, from which she recovered by the administration of vitamin D, but has had no serious illness in all her life. From 4 years of her age, a brownish pigmentation of the skin has developed gradually, especially at her neck, and axillary and pubic area. The similar pigmentation has appeared also on her face from 6 years of age. Her height was a little taller than an average girl of the same age. Her scholastic record was middle in her class. Her intelligence appeared to be entirely normal. She was first seen at Tohoku University Hospital, Sendai, on October 6, 1963, with the chief complaints of generalized lipoatrophy and abnormal pigmentation.

Physical examination: On admission, her height was found to be 140.5 cm and her weight 37.5 kg. The skin was dry with creases and folds, and marked hyperpigmentation, especially noticeable on her face, neck and in the skin fold of the axillae. Subcutaneous fat tissues were absent, with prominent veins (Fig. 1). She had neither anemia nor jaundice. Thyroidal gland was not enlarged. The labia majora and clitoris were moderately hypertrophic. She was just beginning to show the budding of the breast. Systolic murmur was audible on the apex and on the left sternal margin. The lungs were clear to percussion and auscultation. The abdomen was protruding. The liver was large and firm with a smooth surface, and could be felt 8 fingers below the costal margin. Spleen and kidneys were not palpable. Ascites did not exist. The funduscopic examination did not reveal any abnormalities.
Laboratory examinations: On admission, following data were obtained: hemoglobin 17.3 g per 100 ml, red blood cell count 4.57 million per cu. mm, and leukocyte count 7.5 thousands per cu. mm with 57% neutrophils, 32% lymphocytes and 10% monocytes. Urine urobilinogen was positive at a dilution of 1:200. Albuminuria was not found. Millon’s reaction was positive in urine. Occult blood test was negative in stools. Serum total protein was 7.8 g % with an albumin of 3.22 g %. Serum γ-globulin was 2.46 g %. Erythrocyte sedimentation rate was 11 mm per hr., and the result of a serologic test for syphilis was not reactive. Serum bilirubin was within normal limits, and bromsulfalein test showed 2.5% retention of the dye in 45 mins. The results of a battery of empirical liver function tests were: alkaline phosphatase 24.5 K.A. units; thymol turbidity 9.0 units; zinc sulphate turbidity 25.2 units; GOT 53 units; GPT 95 units, and cephalin cholesterol flocculation (−). Sugar in the urine was excreted about 30 g per day and the fasting blood sugar was varied from 138 to 350 mg per 100 ml. Ketone bodies were not found in the urine. The values to serum electrolytes were normal as follows: Na 145.5, K 4.3 and Cl 100.0 mEq per l, and Ca 11.39, and P 5.40 mg per 100 ml. The blood non-protein nitrogen was 18.7 mg %.

Fig. 2. Glucose tolerance test in 2 cases of lipoatrophic diabetes
Serum total cholesterol was 225, total lipids 715.1, neutral fat 176.1 and phospholipids 235.3 mg per 100 ml. The heparin-induced lipoprotein lipase activity in serum was -32.5% at 15 mins. (normal value is from -10 to -20%), and non-esterified fatty acid 3.9 mEq per l (normal value is 0.4-1.0 mEq per l). The total amino-acid in the urine was excreted 138.6 mg per 24 hrs. and its fraction was normal. Glucose tolerance test showed a diabetic type as shown in Figure 2. The results of fat absorption test were normal as shown in Figure 3. Steatorrhea and creatorrhea were not demonstrated.

Her basal metabolic rate was +21%, the radioactive iodine uptake of the thyroid 54.5% in 24 hrs. and the serum protein-bound iodine concentration 7.8 mcg %. The urinary neutral 17-ketosteroids were 3.0 mg per 24 hrs. and the 17-hydroxycorticosteroids 1.02 mg per 24 hrs. The increase in 17-hydroxycorticosteroids after ACTH administration was normal. The cortisol secretion was 17.4 mg per 24 hrs. The urine estrone, estradiol and estriol were normal. Gonadotropin measured by the mouse uterine weight method slightly elevated in the urine, but growth hormone estimated by the method of immunoassay was normal in plasma. X-ray film showed advanced bone age compatible with 11.5 years of age. The plasma insulin estimated by the method of immunoassay was normal.
The electroencephalogram showed random irregular slow wave activity of 5-7 cycles per sec. dominating all leads. By sleep activation, there showed sporadic burst of high voltage slow wave of 4-7 cycles per sec. in all leads and sporadic positive spiky wave in midline areas. This was regarded as a hypothalamic lesion but with no asymmetry and no episodic activity.

A biopsy specimen of the skin revealed definite fat depletion of the subcutaneous tissue. The skin was hyperkeratotic and pigmented; in addition, a number of small superficial papillomas were noted in the axillae, and diagnosed as acanthosis nigricans (Fig. 4).

Clinical course after admission: On the standard diet, 60 units of NPH insulin per day had no effect for diabetes, when all injections were stopped, the glucose excretion did not rise, her weight was not lost, and hyperglycemia invariably existed. However, the temporary changes in the size of the liver and discoloration of the skin pigmentation were observed.

Case 2

Our second patient S.S. was a 4-years-old boy, the fourth among the first case’s siblings. He was born following a normal gestation, full term. His birth weight was 3,180 g. His abdomen has been similarly protruding as the first case. He showed a generalized lipoatrophy. Dentition began in 9 months after his birth. He walked unaided at 2 years of age. He never learned to talk, and his hearing did not appear to deteriorate. Recently, he was found to have X-formed legs. Recently black brownish pigmentation of the skin has developed. He was first seen at Tohoku University Hospital, Sendai, on October 6, 1963, with his sister (case 1), with the chief complaints of generalized lipoatrophy and protruding abdomen.

Physical examination: On admission, his height was 93.5 cm, and weight 15.0 kg. The pulse was 82 per min. and blood pressure 114/60 mm Hg. His face showed a characteristic feature of this disease, but his pigmentation was more slight than his elder sister. Subcutaneous fat was lacking over the entire body (Fig. 5). Neither anemia nor jaundice was observed. The head was of normal shape. His lower limbs showed an X-formed shape. The lymph glands and the thyroid gland were not enlarged. Systolic murmur was slightly audible on apex on auscultation. The abdomen was protruding. The liver reached 4.5 fingers and the spleen 1.5 fingers, below the costal margin. Kidneys were not palpable. There was no ascites. Genitalia were normal.

Laboratory findings: Peripheral blood hemoglobin was 13.1 g per 100 ml, red blood cell count 4.71 million per cu. mm and leukocyte count 13.8 thousands per cu. mm. The blood picture
was essentially normal except for an increasing lymphocytosis, which reached 52% of the total white cells. Urine urobilinogen was positive at a dilution of 1:100, but albumin and sugar negative. Occult blood test was slightly positive in the feces. Microscopical examination showed visible ascarid-eggs and several starch granules, and no visible excess of unsplit or split fats; hence no evidence of external pancreatic deficiency. Serum total protein was 8.14 g % with an albumin of 3.39 g per 100 ml. Millon's reaction was strongly positive in urine. The amino acid in urine was 145 mg and its fraction was normal. Erythrocyte sedimentation rate was 7 mm per hr., and the result of a serologic test for syphilis was not reactive. Serum total bilirubin was less than 1 mg per 100 ml. Bromsulfalein test showed 1.0% retention of the dye in 45 mins. The results of liver function test were as follows: alkaline phosphatase 65.0 K.A. units; thymol turbidity 6.2 units; zinc sulphate turbidity 20.8 units; GOT 64; GPT 66; and cephalin cholesterol flocculation (−). Routine serum electrolytes were within normal limits: Na 135.0, K 5.0, Cl 110.0 mEq. per l, respectively. Serum calcium was 12.7 mg and P 4.5 mg per 100 ml. The fasting blood sugar was 80 mg %. The results of glucose tolerance test were normal as shown in Figure 2. The blood non-protein nitrogen was 17.8 mg per 100 ml. Serum total lipid was 638.7, neutral fat 159.2, phospholipid 182.5 and total cholesterol 158.0 mg per 100 ml. The results of fat absorption test were normal as shown in Figure 3. Steatorrhea and creatorrhea were not demonstrated. The heparin-induced lipoprotein lipase activity in serum was −32.5% at 15 mins. and non-esterified fatty acids 1.1 mEq per l. There was no clinical evidence of fatty diarrhea and no microscopic or chemical evidence of lack of fat absorption from the intestine. Fat-analysis of the dried feces showed a normal percentage of total fat and normal proportion of split to unsplit fat.

His basal metabolic rate was impossible to estimate for his low intelligence. The 131I uptake was 47.6% in 24 hrs. and the serum protein-bound iodine concentration was 7.8 mcg %.
Radiography of the entire bony system, including the limbs showed rickets. The urinary neutral 17-ketosteroids were 0.54 mg per 24 hrs, and the 17-hydroxycorticosteroids were 2.35 mg per 24 hrs. The increase in 17-hydroxycorticosteroids after ACTH administration was normal. The growth hormone was normal in urine. The plasma insulin estimated by the method of immunoassay was normal. His chest X-ray showed an elevated diaphragm.

An electroencephalogram showed a paroxysmal burst of bilateral synchronous high voltage slow waves of 6 to 7 cycles per sec. in almost every area, particularly predominant on the midline. This was thought to be compatible with thalamic or hypothalamic lesion, but these findings were more slight than in case 1.

The section of the skin showed a normal amount of fat in the cells of the sebaceous glands, but no subcutaneous fat could be seen. The unusual feature of his type was not the facial atrophy but the ultimate complete absence of subcutaneous fat, which was confirmed by biopsy (Fig. 6).

Clinical course after the admission: His rickets was recovered by the administration of enormous amount of vitamin D (600,000 units). The other treatments were not performed.

HISTOLOGICAL FINDINGS OF THE LIVER

Histopathological findings

Case 1 (Fig. 7): At diagnostic laparoscopy the absence of mesenteric fat was striking. Microscopic examination of the liver showed a well-marked nutritional cirrhosis (Gall, 1960), with considerable deposition of fibrous tissue along the portal tracts and heavy fat infiltration of liver cells. Profound alteration in the structure of the liver was found. Most liver cells on paraffin slides were vacuolated. They had either a single voluminous vacuole or smaller, numerous ones. The vacuole content was identified by its staining reaction as neutral fats.

Case 2 (Fig. 8): A surgical biopsy of the liver was performed in case 2. A marked infiltration existed throughout the hepatic parenchyma. Fibrosis was observed in the portal area and central vein region, resulting in production of irregular hepatic lobules which may be called "nutritional cirrhosis" according to Gall (1960). Fatty infiltration was very marked, and sporadic formation of large vacuoles measuring up to 80 μ in diameter was found. It was also noted that hepatic cells were swollen and vacuolized.

Histochemical findings

Histochemical examination was performed in detail only in Case 2. In the frozen section stained by Sudan III, fat was found as large-vacuolar and fine-granular droplets within hepatic cells. Both of them were sudanophilic but not uniformly stained. The large-vacuolar type was stained with the color ranging from orange red, pale orange to negative, while the fine-granular type was brown-colored. But these droplets were ascertained to be the same substance by the following histochemical methods of fat staining. Gray to black color was obtained with Nile blue. Gray to black color was found with osmium. Polarized microscopic examination revealed that the picture of double refraction seen in majority of portions showed to be crystallization without a cross picture. All of them became negative-double-refractive by the warming process, but became positive again by the cooling process. Therefore, these results did not always offer sub-
Fig. 6. Section of the skin in Case 2 (H.-E.) ×100
Fig. 7. Photomicrograph showing section of the liver with fatty infiltration and cirrhotic changes in Case 1 (H.-E.) ×100
Fig. 8. Photomicrograph showing section of the liver with fatty infiltration and cirrhotic changes in Case 2 (H.-E.) ×100
Lipoatrophic diabetes is an extremely rare syndrome and its familial incidence has not yet been reported in Japan. In other countries, Hall et al. (1936), Bardinelli (1954), Donohue and Uchida (1954), Seip (1959) and Brubaker et al. (1964), have reported the sibling cases who were accompanied with generalized lipoatrophy and hepatomegaly. The condition usually begins in childhood and is characterized by (1) generalized subcutaneous lipoatrophy, (2) diabetes mellitus resistant both to insulin and to the development of ketosis, (3) abnormal cutaneous pigmentation like acanthosis nigricans, (4) hepatomegaly and splenomegaly and (5) hyperlipemia sometimes with cutaneous xanthomata.

Many hypotheses have been proposed to explain the pathogenesis of lipoatrophic diabetes. The basic defect of this syndrome seems to consist of diminished storage of subcutaneous fat.

Carbohydrate and protein provide a relatively small storage and fat is laid down not only from dietary fat but also from excess carbohydrate, which is probably the major source of depot fat in man.

It is clearly accepted that insulin plays an important role in the storage of ingested carbohydrate as glycogen in the liver and muscles. That insulin may be equally necessary for the change of carbohydrate into depot fat is neither recognized nor clearly known but is strongly supported by recent experimental studies. Insulin prevents lipemia only when it controls hyperglycemia.

Namely, it is suggested in this syndrome that a large proportion of ingested carbohydrate does not go straight into fat depot, but produces fatty enlargement of the liver and subsequent portal cirrhosis, because of the impairment of fat storage in subcutaneous tissue. In the absence of a fat depot the full end-action of insulin obviously cannot take place, and this would explain the hyperglycemia and diabetes confirmed in this complete lipoatrophy.

The disturbance of carbohydrate metabolism of lipoatrophic diabetes differs from that of ordinary diabetes in the extreme resistance to insulin, in the absence
such animals, the vaginal cornification was not abolished by ovariectomy, being independent of estrogenic stimulation.

When sacrificed at 5 months of age, ovaries of all estrogenized rats contained no corpora lutea (Groups 1–5). In ovaries of Group 1 rats, large vesicular follicles were occasionally found and interstitial tissue was hypertrophied. In animals which had been treated with larger doses of estrone for longer periods, ovaries were further reduced in weight and the development of follicles and interstitial cells was suppressed. In Groups 4 and 5, ovaries were approximately similar in both structure and weight to those of weanling rats, the largest follicles encountered in them being those at the beginning of antrum formation.

Cytological studies revealed that in the anterior pituitary glands of strongly estrogenized rats, gonadotrophs (PAS-positive, AF-negative basophils) were markedly decreased in number. In most of Group 3 rats and in all of Group 4 and 5 animals, the anterior pituitaries were totally devoid of gonadotrophs. In animals of Group 5 showing persistent vaginal cornification even after ovariectomy, castration cells were not found in the anterior pituitaries.

DISCUSSION

Several workers (Barraclough and Gorski, 1961; Arai, 1963; Gorski and Barraclough, 1963; Gorski, 1963) have demonstrated a decrease in the pituitary gonadotrophic activity in androgen or estrogen-induced persistent-estrous and -diestrous rats and ascribed it to a damage caused in the hypothalamic sexual center by injections of the steroid in early postnatal days. Recently Gorski and Barraclough (1963), Gorski (1963), Kikuyama (1963) and Swanson and van der Werff ten Bosch (1964) reported that in persistent-estrous rats functional alterations in the hypothalamus vary in degree according to doses of sex steroid given during infancy. From the results of the present experiments, it seems likely that disturbance of the hypothalamic mechanism involved in the regulation of gonadotrophin secretion increases with doses of estrogen and lengths of the injection period. In Group 3, the same treatment produced both persistent-estrous rats and persistent-diestrous rats. Moreover, in 2 animals of this group, prolonged estrous with prolonged diestrous stages occurred. As will be reported elsewhere (Arai, 1964), in such strongly estrogenized rats as those of Groups 4 and 5, the anterior pituitary glands are almost free from typical gonadotrophs and ovariectomy does not bring about any marked cytological changes in the glands, while animals subjected to weaker estrogen treatment like those of
riage, the apparent absence of the syndrome in the parents and its presence in children of both sexes, may indicate homozygous recessive autosomal gene state.

SUMMARY

Results of clinical investigations on two sibling patients, a brother and a sister, were presented in detail. From early infancy they showed the following main features: absence of subcutaneous fat, hepatomegaly with fatty infiltration of the liver, and abnormal carbohydrate metabolism and hyperpigmentation.

In the elder sister, a ten-years-old girl, subcutaneous fat tissue was markedly atrophied with insulin-resistant diabetes. Her liver showed a severe fatty degeneration and infiltration associated with cirrhosis. In her brother, a 4-years-old boy, no glycosuria was observed, in spite of the occurrence of similar lipoatrophy accompanied with fatty cirrhosis of the liver. Serum lipids, serum phospholipids, and oral fat loading test showed normal values in these patients. Absorption of carbohydrate was also normal. Plasma level of growth hormone, and thyroid and adrenal function were normal in these cases. An electroencephalographic study revealed hypothalamic lesions in both cases.

It is concluded from these findings that a primary defect in lipoatrophic diabetes exists in the mechanism for subcutaneous storage of fat, leading to disordered carbohydrate metabolism and increased hepatic storage of fat with resulting cirrhosis. Namely the fat degeneration of the liver, the abnormalities of carbohydrate metabolism and the hyperpigmentation of the skin were suspected to occur secondarily. A causative relationship was assumed to exist between the hypothalamic lesions and a failing hypothalamic control of pituitary function. It was thought that lipoatrophic diabetes was a homozygous recessive autosomal gene state.

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REFERENCES


