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VON GIERKE'S GLYCOGEN DISEASE

Report of Two Cases

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The purpose of this report is to present two cases of von Gierke's glycogen disease, to discuss its clinical characteristics, to review the present concept of the disease, and to digress somewhat on the mechanism of acidosis, particularly in children.

Von Gierke's glycogen disease is apparently limited to infancy and childhood. It is chronic, often with a familial tendency, and is characterized by an excessive accumulation of glycogen in various organs of the body, especially the liver, with subsequent enlargement of the affected organs. The stored glycogen, which cannot be mobilized,[1] seems to have normal chemical and physical properties and can be hydrolyzed by normal liver tissue. The liver may extend to the iliac crest, yet there is neither splenomegaly, ascites, nor jaundice. Appreciable impairment in liver function is not common. The fasting blood sugar is consistently low, usually without symptoms of hypoglycemia. Fasting acetonuria, lipemia, and hypercholesterolemia are not uncommon. Epinephrine may increase acetonuria but does not cause as great a rise in blood sugar levels as would occur normally.

The etiology and pathogenesis of the disease are not clear. It has been postulated that the fetal type of glycogen metabolism may persist into postnatal life,[2] since fetal glycogen does not disappear rapidly by spontaneous glycogenolysis and cannot be readily mobilized by the administration of epinephrine.[3] It has been suggested that the presence of diastatic ferment in the liver is necessary before epinephrine can release glucose from hepatic glycogen stores and that this enzyme is diminished or absent in this disease.[4] The chief organs affected are the liver, heart, kidneys, and brain, apparently in that sequence. Death

usually results from intercurrent infection. Occasionally, however, death may occur from cardiac decompensation, probably because deposition of glycogen within the myocardium impairs its function.

After death the liver glycogen, which ordinarily disappears in a few hours, persists for many days.[5] Chemical analyses have shown a greater than normal amount of glycogen in the organs affected.[3] The liver may contain areas of increased fibrosis.

CASE REPORTS

Case 1—An infant boy, aged 18 months, was first seen in consultation with Dr. Roscoe Leas two months after onset of symptoms. The illness began with four or five loose stools in one afternoon. The baby refused his supper as well as breakfast the following day. He then became drowsy and was admitted to the hospital in a comatose condition. Blood sugar level was 30 mg. per 100 ml. He was revived quickly with intravenous glucose and saline. Six weeks later he again became stuporous and semicomatose; blood sugar levels were extremely low; and intravenous glucose caused a prompt return to consciousness. Blood count showed 4,100,000 erythrocytes with 71 per cent hemoglobin.

The child was bright, well nourished, and seemed normally active. Dental age was approximately normal. There was no goiter. The liver extended into the epigastrium, 3 cm. below the right costal margin in the region of the gallbladder and about 5 cm. below the tip of the xiphoid process (figure).

Urinalysis was normal except for the presence of acetone when blood sugar levels were very low and on the two occasions when the patient was stuporous. An oral galactose tolerance test after 15 Gm. galactose showed no sugar in the urine. Blood sugar level, which was 83 mg. per 100 ml. four hours after a generous breakfast, rose to 96 mg. per 100 ml. five minutes after administration of 3 minims epinephrine 1-1000 solution, and to 104 mg. per 100 ml. five minutes after a subsequent injection of 4 minims epinephrine 1-1000 solution. Blood cholesterol measured 128 and 179 mg. per 100 ml. on two occasions. On a low carbohydrate, high protein diet and 3 capsules lipocaic daily, the child had no attacks during the succeeding eight months.

Case 2—A girl, aged 7, had attacks since the age of 2 years consisting of staring, light-headedness, and pallor. These spells were accentuated by activity, occurred five to twenty times a day, and were often relieved by food.

The child was pale and appeared to be chronically ill. The muscles were poor in tone but seemed to be normal in strength. The liver was enlarged 4 fingers' breadth below the costal margin. Blood sugar level was 44 mg. per 100 ml. two and one half hours postprandial. A single dose oral glucose tolerance test using 50 Gm. glucose gave the following curve:

Hours . . . . . Fasting	½	1	2	3	4
Blood sugar mg./100 ml. . . 51	104	92	62	37	26

After giving 4 minims epinephrine 1-1000 solution the blood sugar level rose from 46 mg. per 100 ml. to 54 mg. per 100 ml. in fifteen minutes. An oral galactose tolerance

test after administration of 15 Gm. galactose showed no sugar in the urine. Bromsulfalein test of liver function revealed 28 per cent retention of dye in thirty minutes. Blood count showed 4,750,000 erythrocytes with 68 per cent hemoglobin. Urine was negative for acetone twice, neither test being after fasting or administration of epinephrine. Diastase levels on peripheral blood were normal. Permission for a liver biopsy was not granted. In two years symptoms were not altered by dietary manipulation, and the size of the liver did not appreciably change by the addition of lipocaic and lecithin. A brother, aged 4, had no enlargement of the liver or hypoglycemic tendency.

COMMENT

It is very probable that these cases are additional instances of von Gierke's disease. Since permission for liver biopsy was not granted, final proof of the diagnosis is lacking. Yet the finding of an enlarged liver in children without ascites, jaundice, or splenic enlargement, the presence of severe hypoglycemia, and the relative lack of response to subcutaneous administration of epinephrine seem more than presumptive evidence to

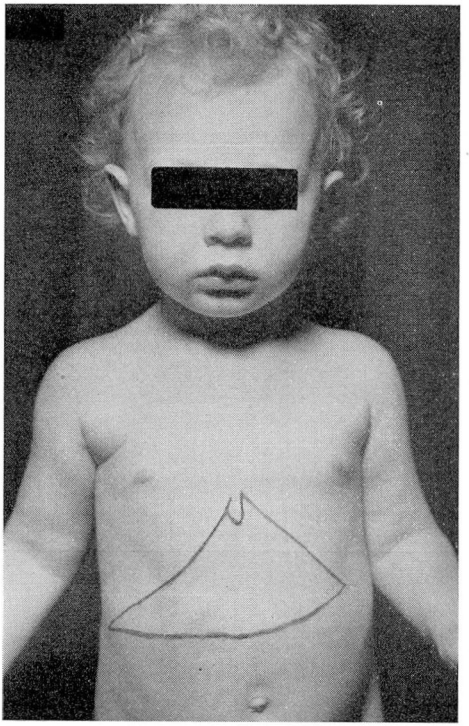

FIG.—Case 1, photograph with black lines showing upper and lower borders of the liver.

support the diagnosis. In one child acetone in the urine during fasting was additional evidence.

Apparently the principal metabolic defect in this disease is the liver's inability to convert glycogen into glucose. Therefore it is not difficult to understand the failure of epinephrine to raise blood sugar levels. This phenomenon is considered to be the most important diagnostic test clinically available. It is also not difficult to understand why acidosis appears readily, especially during fasting.

Shaw and Moriarity[6] demonstrated that children have a greater tendency toward acidosis than adults. They showed that children with epilepsy rapidly develop ketosis and acidosis while fasting. The acidosis was greatest in the third to the eighth day when hypoglycemia was present. Mirsky and Nelson[7] further demonstrated the increased susceptibility of children to acidosis after phlorhizination. After intravenous administration of phlorhizin a loss of 15 to 20 Gm. of sugar in the urine from a normal child and less than that from a diabetic child was followed by hypoglycemia and ketonuria, presumably because of a depletion of liver glycogen. The younger the child, the greater the susceptibility, apparently because of a smaller glycogen reserve. A more pronounced phlorhizin-induced glycosuria is necessary in adults before acidosis becomes manifest.

A different mechanism undoubtedly exists in von Gierke's disease. Here the liver glycogen is abundant, but being fixed, it is no more available for supplying metabolic demands for glucose than if no glycogen stores were present. Theoretically, the stimulus for oxidation of fatty acids and production of ketone bodies is the lack of available glycogen in the liver. If this be the case, it would explain the occurrence of acidosis in this disease.

The disease usually leads to death before the twentieth year. I have been unable to find any record of treatment which alters the usual progress of the disorder. A better understanding of its pathogenesis and treatment will probably come through study of enzymatic activity within the liver.

SUMMARY

In the two reported cases of von Gierke's glycogen disease the diagnosis was supported by the finding of hepatomegaly, severe hypoglycemia, anemia, acetonuria in one, and poor response to administration of epinephrine.

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