Glycogen-Storage Disease

Report of a Case with Generalized Glycogenosis and Review of the Literature

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THE PURPOSE of this presentation is to report in detail the clinical and pathologic findings of a case of generalized glycogen-storage disease involving the heart (type II). Because recent investigations have revealed additional data about the etiology and pathogenesis of this disease and because of the renewed interest in the subject, it seems timely to review its present status with particular reference to cardiac involvement.

Case Report

G. N. was a 6-pound, 6-ounce boy, born October 25, 1956, to a 26-year-old, gravida 7, para 6, white mother by normal spontaneous delivery after a normal gestation. During the first month of life the baby apparently was in good health and usually took its bottle feedings well, but failed to gain sufficient weight. In the second month, the legs swelled intermittently, and frequent bouts of abdominal distention and projectile vomiting occurred, usually 10 to 15 minutes following milk ingestion. The infant was constipated and had one well-formed yellow stool every 2 to 3 days. The mother of the infant was said to have had an enlarged heart. Unfortunately, both parents persistently refused clinical studies for themselves as well as for six living siblings.

On hospitalization at the age of 3 months the infant weighed 9 pounds, 5 ounces and appeared rather ill, hypoactive, dehydrated, and poorly nourished. Enlargement of the tongue was striking. The respirations were rapid. Dullness and absent breath sounds were elicited over the upper left chest and moist rales were present at both bases. The heart was considerably enlarged to the left by percussion, and tachycardia was present. The heart sounds were muffled and a soft (grade II) systolic murmur was heard with greatest intensity near the apex. The abdomen was distended and the liver palpable 2 to 3 cm. below the right costal margin. Bilateral grade-II pitting edema of the legs was noted. Roentgen study of the chest showed extreme globular enlargement of the heart and patchy pneumatic infiltrations in the left upper lobe, with secondary atelectasis in both upper and lower left lobes (fig. 1). Serial electrocardiograms revealed biventricular hypertrophy, sinus tachycardia, sinus arrhythmias, and nonspecific S-T and T-wave changes in all leads. Persistent Q waves were present in leads I, II, aV\textsubscript{L}, and aV\textsubscript{F}, and V\textsubscript{4} to V\textsubscript{6} (fig. 2). Blood electrolytes, peripheral blood picture, and urine were normal.

In the hospital the infant tolerated feedings well, and the pneumonia and cardiac failure responded promptly to antibiotics and digitalis. Because of the striking cardiac enlargement and the heart murmur the presence of a congenital cardiac anomaly was suspected. Two weeks after admission cardiac catheterization revealed normal right atrial and ventricular pressures and oxygen saturations. Following catheterization, the infant developed abdominal distention, respiratory distress, and the clinical findings of right lower lobe pneumonia. After treatment with Digalen, prednisone, and oxygen, he improved gradually and compensation was restored in 3 weeks.

During the seventh month of life (the fourth month in the hospital), marked abdominal distention accompanied by fecal impactions frequently occurred and required enemas and almost daily digital removal.

In view of the clinical, roentgenologic, and electrocardiographic findings the possibility of myocardial storage disease was entertained, and a calf muscle biopsy was performed during the fifth month of hospitalization. Microscopic examination revealed loss of striation of the individual muscle fibers, with swelling and coarse vacuolization of the cytoplasm. Best's carmine stain showed that all these vacuoles were filled with glycogen. After the muscle biopsy several episodes of heart failure and pneumonia occurred, the infant remained almost constantly in critical condition. He died in congestive heart failure at the age of 8\(\frac{1}{2}\) months.

At postmortem examination the weight of the body was 5,070 Gm. and the length was 60 cm. The abdomen was moderately distended. The heart was strikingly enlarged, almost entirely filling the left thorax. It weighed 170 Gm. (four and one-
bronchopneumonia and atelectasis. There were no gross abnormalities of the brain, except that the tissue was unnaturally firm. The neuronal bodies throughout the specimen showed morphologic changes similar to those seen in amaurotic familial idiocy. The cell bodies were swollen and appeared either globular or pear-shaped. The nucleus was pushed to one pole; the Nissl substance of the cytoplasm was finely divided or absent except around the nucleus. In addition, one or more vacuoles were present. This change was marked in all cell groups in the pons and medulla and in the anterior horns of the cervical cord (figs. 8 and 9). It was conspicuous in the pallidum, subthalamic body, and substantia nigra, but less well marked in the putamen, red nucleus, and thalamus. Both periodic acid-Schiff and Best carmine stains gave an intensely positive reaction for glycogen within the cells of these areas. Similar material was found in the perivascular spaces, the muscularis of arteries, and in the entire ependymal lining of the ventricles. There was diffuse scattering of the stained material throughout the entire brain substance. It appeared as a fine granular substance in the white matter. It was also present in the cerebral cortex and was only sparsely seen in the granular and molecular layers of the cerebellum. These changes were absent from the brains of other infants of the same age. The final diagnoses were glycogen-storage disease (Cori-type II); pneumonia and atelectasis; and megaloclon (Hirschsprung’s disease). The immediate cause of death was cardiac failure.

Review of the Literature

The history of diseases with abnormal storage of glycogen dates back to 1928, when Snapper and van Crefeld described an infant with hepatomegaly, hypoglycemia, and acetonemia. One year later von Gierke reported his anatomic-pathologic investigations of the accumulation of glycogen in liver and kidney cortex and introduced the term hepatonephromegalia glycogenica for this disease. During the following years single cases were reported in which the glycogen storage in the liver was associated with cirrhosis. Others exhibited the clinical picture of amyotonia congenita and of myxedema. The first to describe glycogen storage in the heart muscle was Pompe in 1932, as a result of histochemical studies in a case of idiopathic hypertrophy of the heart. Although he found glycogen in the liver, kidney, thyroid, spleen, and striated muscle, he called this dis-
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Figure 2
Electrocardiogram showing Q waves in leads I, II, aV_L, aV_R, V_4 to V_6, and nonspecific S-T and T changes in all leads.

ease "cardiomegalia glycogenica." It soon became apparent that all these cases were variants of a disturbance in carbohydrate metabolism manifested by storage or excessive amounts of glycogen in the tissues.\textsuperscript{10-13} Initially, it was suggested that the cause of the defect resulting in glycogen storage was most probably a deficiency of enzymes involved in the breakdown of glycogen.\textsuperscript{10,12,14} This theory was verified in 1952 by Cori and Cori, who reported a case of liver glycogenosis with deficiency of glucose 6-phosphatase.\textsuperscript{15,16} With improvement in biochemical methods, various classifications of this syndrome were presented, which apparently depended upon the clinical, pathologic, or biochemical orientation of the author.\textsuperscript{7,17-22} In addition to deficiency of various enzymes, the chemical structure of the glycogen molecule itself was shown to be important in the pathogenesis.

According to the recent classification of Cori and Andersen\textsuperscript{16,23,24} four different types may be distinguished (types I, II, III, and IV).

Type I represents the original von Gierke disease with accumulation of normal glycogen molecules in the liver and kidney cortex. Clinically, the infants manifest growth retardation as displayed by a small body size with "doll-like" features, a protruding abdomen with a strikingly enlarged liver, but without splenomegaly. The kidneys are, at times, greatly enlarged. Anorexia, vomiting, and weight loss as well as convulsions and coma
Gross appearance of heart and lungs. The heart was sectioned along the interventricular septum to show both left and right ventricular walls. Atelectasis of the left lung as a result of the compressive effect of the heart is clearly discernible.

Figure 3

In a high-power view the hollow myocardial fiber cylinders of the myocardium are seen to contain red-staining glycogen droplets. Best's carmine stain.

Figure 5

have been observed. Laboratory studies show hypoglycemia, hyperlipemia, hypercholesteremia, increased blood glycogen levels, acidosis, and acetonuria. These subjects manifest a diminished response to epinephrine, impaired glucose tolerance, hypersensitivity to insulin, decreased or absent neutral serum phosphatase, inadequate response to glucagon and rise in α- and β-globulin in the serum with aminoaciduria.25 Chemical analysis of the liver at necropsy reveals an almost complete absence of one enzyme, glucose 6-phosphatase. Death usually occurs from intercurrent infections.

Type II shows generalized glycogenosis with considerable accumulation of normally structured glycogen in all tissues that normally contain glycogen. The heart is usually extensively involved, as in the cases of Pompe.8 St. Agnese et al.26,27 reviewed the findings in 14 cases of cardiac glycogen storage, and
Rossi, in seven. Since one of the five cases of Illingworth showed an abnormal glycogen molecule, it would not fall in type II. Two cases of cardiac glycogen storage in siblings were described by Childs et al. Several cases with neuromuscular glycogen storage showed markedly enlarged hearts and abnormal electrocardiograms. Recently, one case of cardiac storage with hepatic, renal, and bladder involvement was added by Mazzitello and Briggs. The glycogen displaces the muscle bundles of the myocardium with the result that heart failure is a common cause of death. This type was therefore often referred to as cardiomegaly glycogenica.

It should again be emphasized, however, that this is a generalized glycogenosis, and the stored glycogen may be found in all tissues where it is usually present. The tongue, for instance, was found to store glycogen up to 15 per cent of its total weight, a finding that occasionally led to an incorrect diagnosis of myxedema. The liver may contain up to 10 per cent and the kidney cortex is often markedly involved. The underlying mechanism of glycogen storage of this type has not been determined. According to present knowledge, the glycogen has a normal structure and an enzyme deficiency has not been detected; glucose 6-phosphatase is within normal limits.

Type III, originally described by Cori in 1952, was diagnosed by analysis of liver and muscle in a 12-year-old child. The glycogen accumulates chiefly in skeletal muscle, heart, liver, kidneys, and to a lesser degree in other tissues. These subjects present a large liver, flaccid muscles, and at times, an enlarged heart. The debrancher enzyme (amylo-1, 6-glucosidase) is absent in skeletal and heart muscle. The glycogen molecule is abnormal, having very short outer branches and approaching the structure of phosphorylase limit dextrin. The abnormality may be the result of the deficiency of the debrancher enzyme. Cori has shown that this type of glycogen storage is a familial disease that is apparently as common as the original von Gierke's disease, but the mortality is much lower.

Type IV also shows storage of abnormal glycogen molecules in the liver, reticuloendothelial system, and probably skeletal muscle. The literature includes only one case that has been studied clinically, pathologically, and biochemically. This infant showed hepatomegaly, splenomegaly, hypoglycemia, and icterus. The postmortem examination revealed glycogen storage in a severely cirrhotic liver and in the spleen, lymph nodes, and intestinal mucosa. It was determined by biochemical analysis that the glycogen molecule has fewer and longer chains than its normal counterpart and resembles the structure of maize amylopectin. The storage of these molecules is associated with cirrhosis of the surrounding tissues. The glycogen is probably so insoluble that it comes out of solution at 37°C, acts as a foreign body, and gives rise to fibrous tissue reactions. The chemical structure suggests a deficiency in the branching enzyme (1, 4→1, 6-transglucosidase). It has been shown that this disease also is familial.

A type V with glycogen storage in striate muscle mainly has been proposed, but there is very little information available and complete studies have not been reported thus far.
Discussion

According to the criteria recently established, our case is classified as type II glycogen-storage disease, accompanied by unusual involvement of the nervous system. Infants with this type tolerate their feedings poorly, fail to gain weight, show progressive anorexia and vomiting, and are subject to attacks of dyspnea, cyanosis, and cardiac failure. They are listless, may exhibit muscular weakness, neurologic abnormalities, and striking enlargement of the tongue. The symptoms usually start between the second and sixth month of life. In our case the feeding problems associated with constipation and projectile vomiting led to hospitalization, but no satisfactory reason for the feeding problems was found. Necropsy findings suggest that the vomiting was probably the result of the megacolon (Hirschsprung's disease) caused by the abnormality of the intramural plexus myentericus (Auerbach), which showed extensive glycogen storage. We are not aware of other reports in which feeding problems and constipation were correlated with glycogen storage in the autonomic ganglia cells of the intestine. The infant subsequently developed pneumonitis and atelectasis of the lungs and frequent bouts of cardiac failure.

Probably the most prominent physical finding was the enormous enlargement of the heart, which nearly filled the left thoracic cavity. A variety of cardiac murmurs has been described, but a systolic murmur appears to be predominant. High voltage with ST-T changes similar to those in our case have been observed in other cases of cardiac glycogen-storage disease.

The carbohydrate metabolism in glycogen-storage disease is usually within the normal limits; there is no acidosis, ketosis, or hypercholesteremia.

The prognosis of type II glycogen-storage disease is very poor. With the typical criteria the disease is practically always fatal during the first 8 months of life. About 20 cases have been reported thus far in the literature. We as yet have no definite information whether milder cases may survive for longer periods.

A skeletal muscle biopsy, as in our case, may establish the diagnosis. It has not been definitely established whether glycogen is always stored in the skeletal muscle of these patients. Eight of the 14 cases of St. Agnese and two of Rossi's seven showed storage in...
the skeletal muscle, but it is not known whether a muscle biopsy was performed in all cases.

A positive muscle biopsy in infants with large globular hearts and cardiac failure without evidence of congenital valvular or septal defects is suggestive of type II glycogen-storage disease. The differential diagnosis includes hypothyroidism, mongolism, amyotonia congenita, idiopathic myocarditis (Fiedler), endocardial fibroelastosis, and fat myocarditis (Kugel-Stollogg).

The pathologic findings include a five- to six-fold increase in the weight of the heart, a lacework appearance of the myocardial fibers with enormous accumulation of glycogen within the fibers replacing the muscular tissue. Glycogen can be found also in the tongue, in the musculature of the diaphragm, neck, trunk, and extremities, in smooth muscle, in the reticuloendothelial system, kidney, liver, bone marrow, thymus, and in the central nervous system and autonomic ganglia.

Summary

A case of glycogen-storage disease (Cori-type II), with accumulation of glycogen in the myocardium, skeletal muscle, smooth muscle, liver, kidney, central nervous system, and autonomic ganglia is presented.

Glycogen storage in the autonomic ganglia of the intestinal tract (Plexus-myentericus-Auerbach), which gave rise clinically to Hirschsprung’s disease, could explain the feeding problems and constipation often observed in these cases.

The classification into four different types of Cori and Andersen appears to be the most satisfactory one at the present time. These types are different disease entities with the same expression of abnormality, the deposition of glycogen; but the pathogenesis and the clinical and pathologic findings are strikingly different.

Glycogen storage of the heart is probably more common than the review of the literature indicates. Many of these cases are missed, mainly types III and IV, because the possibility is not considered and the patient is inadequately studied in life and during necropsy.

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References

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