AN AUTOPSY CASE OF TYPE II GLYCOGENOSIS

YASUHIRO NAKAMURA\(^1\), AKIRA TANIMURA\(^1\), CHIKAI YASUOKA\(^2\)
AND HIROHISA KATO\(^2\)

Second Department of Pathology\(^1\) and Department of Pediatrics\(^3\),
Kurume University School of Medicine, Kurume, 830, Japan

Received for publication August 20, 1979

An autopsy case of 10 months old male infant with typical type II glycogenosis was reported.

In addition to routine histopathological and histochemical studies on skeletal muscle biopsy and specimens obtained at autopsy, histochemical analyses of the enzyme activities, electromicroscopic studies on muscle biopsy, and cardiac muscle and liver obtained at autopsy were employed. In our case, His bundle electrogram was performed and histopathologically the shortening and some degenerations were found in the atrioventricular junction, especially in His bundle and central fibrous body.

INTRODUCTION

Type II glycogenosis was reported by Pompe in 1932 at first and in 1963 Hers supported the deficiency of acid α-1, 4-glucosidase in lysosome as the enzymatic abnormality. This disease is an autosomal recessive and characterized by the accumulation of the glycogen in various tissues, especially in the heart and the skeletal muscles. It had been well known that electrocardiographically a short PR interval was one of the significant features of this disease. However, there were not any appropriate explanations about this phenomenon. In addition to the investigations by electromicroscopy, by enzymatic quantitative analysis, and by histochemical studies, comparative histopathology of His bundle with His bundle electrogram was done in this report.

CASE REPORT

A 3500 gm full-term male infant was born on December 17, 1975. His parents were in their mid twenties, and in good health. He had no brothers and sisters.

At birth the baby was in state of asphyxia, and then the resuscitation was immediately performed for five minutes. He had been getting a poor suck reflexes and poor spontaneous activity from the birth time.

At seven months of age, he was referred to our hospital because of the failure to thrive and to fix the neck. Physical examination revealed a weakened muscular tone, poor deep tendon reflexes and poor spontaneous activity. The facial expression was drowsy and the tongue was large. The heart was enlarged on palpation. Cardiac rate was 120 beats per minute and the blood pressure was in normal range. A grade 2/6 Levine ejection systolic murmur was best heard at the third left intercostal space, especially along the sternal border. Peripheral pulses were normal. The liver edge was elastic hard and enlarged 3 cm below the right costal margin.

A routine chest roentgenogram show-
ed cardiac enlargement with 64% of CTR and a pulmonary congestion.

The electrocardiogram revealed a biventricular hypertrophy and a short PR interval (PR=0.09 second). Inverted T waves were shown in leads V1 and V6.

The echocardiogram revealed the hypertrophy of the ventricular wall and the narrowing of the left ventricular cavity.

Laboratory data were as follows: Blood electrolytes, peripheral blood pictures and urinalysis were all within normal limits. Serum protein and lipid analysis were normal. Fasting blood sugar was 86 mg/dl and the tolerance test with use of maltose was normal. Blood lactate was 11.5 mg/dl and pyruvate 0.97 mg/dl. Serum transaminases and lactic dehydrogenase were moderately elevated: the glutamic oxaloacetic transaminase of 289 Karmen units, the glutamic pyruvicoxaloacetic transaminase of 73 Karmen units and the lactic dehydrogenase of 1220 units with normal percentage of isozymes. Other liver function tests were within normal limits with normal serum bilirubin value. Serum creatine phosphokinase was elevated to 120 units.

The clinical impression was generalized glycogenosis. Cardiac catheterization and angiography were performed before the patient was digitalized. There were no remarkable abnormalities.

The diagnosis was confirmed by chemical analysis of the gastrocnemius muscle obtained at biopsy. Light microscopic examination revealed marked enlargement of muscle fibers due to cytoplasmic vacuolization. The vacuoles contained PAS positive and diastase digested substance, suggesting glycogen. Comparative biochemical investigation of the biopsy specimen from this case and at the same time, of gastrocnemius muscles obtained from normal individuals was done about α-1, 4-glucosidase activity and glycogen content. The glycogen content was 13.47 g/wet 100 g (Control 1.64 g/wet 100 g), and α-1, 4-glucosidase was absent in this case.

After hospitalization, the cardiac failure was developed and administration of digitalis, diuretics was done without marked benefit. The clinical course was progressively downhill, with the advent of cardiac failure, and the patient died at the age of 10 months.

**AUTOPSY FINDINGS**

The postmortem examination was performed 2 hours after death. The baby was that of poorly nourished male, measuring 71 cm in length and 6500 gm in weight.

![Fig. 1. The cut surface of the heart. It is uniformly hypertrophied and shows edematous swelling with pale, turbid light-yellowish brown color.](image)

The heart weighed 145 gm (normal, 40 gm). It was uniformly hypertrophied, and had a rounded contour (Fig. 1). The left ventricular free wall averaged 16 mm in thickness, and 11 mm thick in right ventricle. The interventricular septum was also exceedingly hypertrophied, measuring up to 21 mm in
thickness. The cut surface of the myocardium showed edematous swelling with pale, turbid light-yellowish brown color. There were no malformations, abnormalities of the great vessels, coronary arteries and valves. In the microscopical sections the myocardium diffusely involved and had a characteristic appearance of a lace-work pattern that muscle fibers were markedly vacuolated (Fig. 2).

![Fig. 2. The myocardium has a characteristic appearance of a lace-work pattern that muscle fiber is markedly vacuolated. (H.E. ×100).](image)

The glycogen contained in vacuoles were well demonstrated in sections fixed in the absolute alcohol and stained with the method of Periodic Acid Schiff reaction and Best’s carmine, for glycogen. Diastase digestion completely digested out the stainable material, establishing the specificity of the staining reaction. The epicardium and endocardium showed no remarkable changes.

The liver was also enlarged and weighed 340 gm (normal, 250 gm). The capsule of free surface was smooth and light yellowish brown in color. On cut section its surface appeared yellowish brown, of solid consistency and turbid in which no lobular architecture was discerned. Histological sections stained with hematoxylin and eosin showed moderately vacuolated hepatic cells. Best’s carmine stain revealed the presence of glycogen in such vacuoles and Sudan stain demonstrated a fat in the mid-zonal areas of lobules partially.

The right kidney weighed 26 gm, and the left 25 gm, being within normal limits. Histopathologically, the glycogen deposits were demonstrated mainly in the convoluted tubules.

The striate muscles including the muscle of the tongue and diaphragm appeared swollen and turbid. In each muscle fibers appeared marked vacuolization and was stained also by PAS and Best’s carmine stain (Fig. 3).

![Fig. 3. Each of the striated muscle fibers appear marked vacuolization. (H.E. ×100).](image)

The smooth muscles in media of the muscular arteries, bronchi, esophagus and the urinary bladder had a large, clear axial vacuoles in the muscle fibers which had become enlarged.

Thymus weighed under 1 gm, being remarkable atrophy. Both lungs showed atelectasis and congestion. The brain could not be examined.

**ELECTRONMICROSCOPIC STUDY**

Specimens for ultrastructural studies were taken from the gastrocnemius muscle at biopsy, and cardiac muscle
and liver at autopsy. Each specimen was immediately fixed in 2.5% glutaraldehyde pH 7.4 phosphate buffer solution for 2 hours, rinsed in phosphate buffer three times and post fixed in 2% osmium-tetraoxide for 2 hours. The specimens were embedded in Epon: semi-thin sections were stained with toluidine-blue, 500Å thin sections were stained with uranyl acetate and lead citrate. Sections were examined in a HU-12AW type electronmicroscope. Electronmicroscopic examination of the skeletal muscle showed mainly pools of cytoplasmic glycogen granules, but in part membranous fragments were found. Structures resembling lysosomes were infrequent, but the membraneous fragments suggested the broken lysosomes. In the myocardium, lots of cytoplasmic and lysosomal glycogen granules, surrounded by the thin membranous structure, were found.

In addition to glycogen deposition, large mitochondriae and myelin figures were also observed (Fig. 4). In the liver cells, the lysosomal glycogens were more abundant (Fig. 5). Less frequently observed were islets of glycogen existing seemingly within mitochondriae.

**STUDY OF THE CARDIAC COMDUCTION SYSTEM**

For a study of the cardiac conduction system, the His bundle electrogram was performed clinically, and the sub-serial sections of the atrioventricular junction were made at 20μ intervals in this case and two control cases. The His bundle electrogram revealed the shortening of the conduction time at His bundle selectively (Fig. 6).

*Fig. 4.* In the myocardium both the cytoplasmic and the lysosomal glycogen, surrounded by the thin membranous structure, are found. (×5500).

*Fig. 5.* In the hepatic cells, the lysosomal glycogen is more abundant. (×6000).

*Fig. 6.* The His bundle electrogram reveals the shortening of the conduction time at His bundle selectively.
Therefore, the length of His bundle was measured histologically. Some abnormalities were found in this case comparing with two control cases; marked thickening of His bundle caused by the swelling of each myofibrils, shortening of His bundle—be shortened approximately 800μ—and the narrowing of the central fibrous body (Fig. 7). There were no changes of nodal arteries and no significant difference of conduction system between before and after the His bundle of this case.

DISCUSSION

Since glycogen storage disease was first reported by von Gierke in 1929, many different types of glycogenosis have become known. Among these glycogenosis, the cardiac form, first described in 1932 (Pompe, 1932), is variously referred to as glycogen storage disease of the heart, Pompe's disease, generalized glycogenosis, and type 2 of Cori. Currently it was thought to be as a generalized glycogenosis with increased deposition of glycogen in all tissues, primarily in the cardiac muscle.

Clinically an enlarged tongue, cardiac murmurs, cardiomegaly, poor muscle tone, intermittent cyanosis, sluggish activity, rapid or labored respiration, weak cry, poor feeding and slow weight gain have been observed and the disease may be progressive. The cardiac manifestations of the disease are the most important and cardiac failure is the chief cause of death.

Pathologically the disease is characterized by enormous hypertrophy of the heart secondary to massive deposition of glycogen in myofibrils. In addition, extensive deposition of glycogen may occur in other tissues: tongue, liver, kidney and skeletal muscle. In our case, the deposition of glycogen was observed in cardiac muscles, striated muscles, smooth muscles, liver and kidneys. A lacework appearance is characteristic microscopical feature of cardiac muscle on Pompe's disease. Best's carmine stain or Periodic Acid Schiff stain with diastase digestion is histochemically suggestive of the presence of glycogen.

The pathogenesis on glycogen deposits has been variously discussed. Since Hers reported (Hers, 1963) the deficiency of acid alpha-1, 4-glucosidase in liver, heart and skeletal muscle of five children with this disease and subsequently in the liver of the rat, the enzymatic activity was demonstrated within the lysosomal fraction. Baudhuin (Baudhuin et al., 1964) described vacuoles filled with glycogen in electron-micrographs of liver at first and subsequent studies revealed the glycogen accumulation in the cells could be divided into two types, lysosomal and extralysosomal cytoplasmic glycogen. The lysosomal glycogen is characterized by granules in groups surrounded by a membranous structure and is predominant in the hepatic cells. The cytoplasmic glycogen is rather diffusely scattered in cytoplasm and is abundant in striated muscles. The former appears
to be found solely in Pompe's disease. Pompe's disease has been thought to be purely a result of lysosomal deficiency of alpha-1, 4-glucosidase and the deposits of glycogen occurs principally with membrane limited sacs. But some authors suggest that an extralysosomal factor plays a significant role in the pathogenesis of Pompe's disease (Hug et al., 1967).

In addition to various cardiac manifestations including cardiomegaly and cardiac murmurs, some electrocardiographic changes are well known to be a feature of this disease. From Ehlers (Ehlers et al., 1962), the characteristic electrocardiographic changes of this disease are short P-R interval, high voltage of QRS and T, and left ventricular hypertrophy. In our case, special attention was paid on a short P-R interval and His bundle electrogram. His bundle electrogram was shown that the conduction time of His bundle was selectively shortened in our case. Histopathologically sub-serial sections of the atrioventricular junction revealed three abnormalities of His bundle: hypertrophy and shortening of His bundle, and the narrowing of the central fibrous body. It was thought that the increased concentration of glycogen in the myocardium and the conduction system might shorten the conduction time in this disease (Caddell, 1962). But this concept would not be able to explain the selective shortening of P-R interval and the findings of His bundle electrogram in our case. Histologically there was no noteworthy difference in distribution of the glycogen throughout the conduction system.

The following possibilities are thought to be the cause of shortened P-R interval in our case; the shortening of conduction time in the atrioventricular junction, especially in His bundle, due to thickening and degeneration of His bundle and shortening of the central fibrous body.

To our knowledge, this would be the first case of Pompe's disease in which a His bundle electrogram was performed and the comparative histopathological study was done.

REFERENCES