Generalized Glycogenosis Type II (Pompe's Disease)

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Nihill, M. R., Wilson, D. S., and Hugh-Jones, K. (1970). *Archives of Disease in Childhood*, 45, 122. **Generalized glycogenosis type II (Pompe's disease).** The characteristic clinical features of 2 cases of Pompe's disease are presented, namely, signs of a cardiomyopathy with skeletal hypotonia and a characteristic ECG with a short PR interval and high voltage QRS complexes. Glycogen storage disease is confirmed by staining tissue such as lymphocytes, liver, or skeletal muscle with PAS, and the same tissues may be examined for glycolytic enzyme activity in order to characterize the type of glycogen storage disease present.

The clinical features of generalized glycogenosis affecting mainly the heart (Cori, Type II—Cori, 1954) were first described by Pompe in 1932 (Pompe, 1932; Putschar, 1932; Bischoff, 1932). Hers (1963) found that the accumulation of intracellular glycogen in all tissues of the body in Type II glycogenosis was due to an inherited deficiency of lysosomal α 1-4, glucosidase (acid maltase). Ehlers reviewed the 54 cases described up to 1962 (Ehlers *et al.*, 1962), and since then more than 24 other cases have been reported in the English literature (Caddell and Whittemore, 1962; Huijing, Van Creveld, and Losekoot, 1963; Crome, Cumings, and Duckett, 1963; Kahana *et al.*, 1964; Ruttenberg *et al.*, 1964; Lewis and Sutherland, 1964; Rosenstein, 1964; Hohn *et al.*, 1965; Perez-Treviño *et al.*, 1965; Dinscoy *et al.*, 1965; Hernandez *et al.*, 1966; Cardiff, 1966; Hug *et al.*, 1966; Smith, Amick, and Sidbury, 1966; Spach *et al.*, 1966).

We report 2 cases, and discuss recent histochemical techniques which make it possible to diagnose this form of glycogen storage disease during life.

Case Reports

Case 1. This patient was the first-born female child of unrelated, healthy parents, delivered after a full-term, normal pregnancy, weighing 3.2 kg. A paternal cousin has galactosaemia and another cousin has a heart murmur thought to be due to a small ventricular septal defect. There is no other history of heart disease or glycogen storage disease. She thrived well on breast milk until 5½ months when she developed a chest infection. Over the next few weeks, she became

increasingly breathless and started refusing feed by 7½ months, she had become lethargic and floppy and could no longer sit without support. She gradually lost weight and was finally admitted to hospital in heart failure, aged 8 months.

On examination, she was an alert, pale, floppy baby lying in the frog position. Nutrition and muscle mass were normal. There was marked hypotonia such that she was unable to sit without support; reflexes were diminished and sweating was excessive. Her tongue was enlarged and protuberant which made feeding difficult. She was dyspnoeic at rest, with subcostal recession and a prominent sternum. Her liver was enlarged 3 cm below the right costal margin, but there was no cyanosis or oedema. Pulse rate was 160 per minute and regular and the femoral pulses were easily felt. The apex beat was palpable just outside the anterior axillary line and tapping in quality. There was a third sound at the apex and a grade 2-3 mid-systolic murmur heard over the praecordium and loudest in the pulmonary area. There were fine crepitations with diminished breath sounds of bronchial quality over the left lower lobe.

Investigations. Hb, white cell count, blood urea, and serum electrolytes were normal. Serum bilirubin and alkaline phosphatase were normal. SGOT was 6 IU and SGPT was 8 IU. Fasting blood glucose was 84 mg./100 ml. and an oral glucose tolerance test was normal. There were no reducing substances in the urine and the urinary amino acid chromatogram was normal. A search for viruses was negative. Chest x-ray (Fig. 1) showed a grossly enlarged heart with a collapsed left lower lobe. An ECG (Fig. 2) showed a PR interval of 0.08 sec, wide amplitude QRS with an interval of 0.04-0.06 sec. There was left axis deviation of +20° and left ventricular hypertrophy with T wave inversion in leads I, II, III, aVR, and aVF, with ST depression in I, II, aVF, and aVF.

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FIG. 1.—Chest x-ray, Case 1.

Electromyographic examination at 8 months showed findings typical of a myopathic process within the muscles with no evidence of denervation or motor nerve conduction defect.

Right heart catheterization and Elema Selective

FIG. 3.—Angiocardiogram, Case 1. Right ventricular injection showing right ventricular cavity (RV) distorted by thickened interventricular septum (S). (RA, right atrium; PA, main pulmonary artery).

FIG. 2.—ECG, Case 1. Wide amplitude QRS complexes (half standard in leads aVL, aVF, and chest leads). Short PR interval 0.08 sec., left axis deviation.

FIG. 4.—Angiocardiogram, Case 1, showing filling of left atrium (LA) and upward displacement of left atrial appendage (AP). Dilated left ventricular cavity (LV) which contracted poorly. Left ventricle wall (W) is grossly hypertrophied (AO, aorta).

biplane angiocardiography were carried out under general anaesthesia. There was a systolic gradient of 12 mm. Hg between the right ventricle and the pulmonary artery. Angiocardiography (Fig. 3, 4, 5) showed a distorted right ventricular cavity, and grossly

FIG. 5.—Lateral projection of angiocardiogram, Case 1, showing filling of left atrium (LA), left ventricle (LV) and some dye remaining in the right ventricle (RV). The interventricular septum (S) is much thickened.

thickened ventricular walls and interventricular septum. The clinical features of heart failure, a shortened PR

FIG. 6.—Lymphocyte from peripheral blood, showing large glycogen granules. (PAS. $\times 1200$).

FIG. 7.—Cross-section of deltoid muscle showing vacuolization and granulation of the cytoplasm. (H and E. $\times 55$.)

FIG. 8.—Deltoid muscle showing darkly stained glycogen granules. (PAS. $\times 55$.)

interval with left axis deviation and left ventricular hypertrophy on the electrocardiogram, together with generalized muscular hypotonia, suggested the diagnosis of glycogen storage disease. Staining of peripheral blood lymphocytes with Periodic Acid Schiff (PAS) (Fig. 6), showed excessive glycogen granules in the cytoplasm. A biopsy was therefore taken from the deltoid muscle. One part was fixed in formol picric alcohol at -20°C ., and the other was fresh frozen and cut on a cryostat for enzymatic studies. Control muscle was taken from the sternomastoid of a patient of the same age. Histological section (Fig. 7) showed extremely bizarre muscle fibres with marked vacuolation and granulation in the cytoplasm, which caused enlargement of the individual fibres. Histologically, the granules and some of the material in the vacuoles were strongly positive to PAS and carmine stains (Fig. 8). However,

the staining in the vacuoles and the granules themselves disappeared after prior diastase digestion. This clearly indicates a marked excess of glycogen.

Fresh frozen muscle, peripheral lymphocytes, and red cells were examined for glycogen content and enzyme activity by Dr. H. Patrick at The Hospital for Sick Children, Great Ormond St. (Table). A marked deficiency of $\alpha 1-4$ glucosidase activity was demonstrated together with excessive accumulation of intracellular glycogen. Histochemical demonstration of other enzymes in the muscle tissue by Dr. I. Dawson, including glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, L brancher enzymes, and glucose 6-phosphatase showed normal distribution. There was a slight reduction in the amount of amylophosphatase when compared with the normal control.

TABLE
Glycogen Content and α -Glucosidase Activity in Various Tissues

Tissue	Glycogen Content		$\alpha 1-4$ Glucosidase Activity	
	Control	Patient	Control	Patient
Muscle biopsy	Up to 1.5% wet weight	4.3% wet weight	0.06-0.145*	Nil*
Heart immediately post mortem	Up to 1.5%	3.1%	0.15*	0.015*
Liver (post mortem) ..	Up to 1.5%	12.1%	0.58*	0.03*
Leucocytes			1.1-1.4† (0.6-2.1)‡	0.11†
Red cell	Up to 120 $\mu\text{g./g.Hb}$	66 $\mu\text{g./g.Hb}$		

*Units = μmoles of maltose hydrolysed/min. per g. wet weight

†Units = $\text{m}\mu\text{moles}$ of maltose hydrolysed/min. per mg. protein

‡Figures from Brown and Zellweger (1966).

Hers (1963)

FIG. 9.—The heart of Case 1 with left ventricle opened to show grossly thickened left ventricular wall (LV) and septum (S) with fibroelastosis of the left ventricular septal wall. The right ventricular cavity (RV) is small and compressed by the thickened septum. (AO, aorta; PA, main pulmonary artery; AV, aortic valve; MV, mitral valve.)

Clinical course. Her course in the hospital was marked by increasing hypotonia, difficulty with swallowing, and recurrent respiratory infections. The heart failure was reasonably well controlled with digoxin, mercaptopurin injections on alternate days, and nursing in humidified oxygen. Towards the end of her life, she required tube feeding and became centrally cyanosed without added oxygen, with resistant heart failure; she finally succumbed to a further chest infection, aged 11 months.

After death, needle aspiration specimens were taken from the heart and liver and immediately frozen at -20°C . for estimation of glycogen content and acid maltase activity (Table). At necropsy, the heart (Fig. 9) was grossly enlarged and weighed 190 g. (normal 40 g.). The enlargement was mainly left ventricular (wall = 20 mm.), without valvular disease or anatomical abnormality. There was subendocardial fibrosis of the interventricular septum on the left side only. Reduction in the size of the right ventricular cavity was due to bulging of the septum, which was 20 mm. thick. The right ventricular wall measured 7 mm.

FIG. 10.—Section of myocardium showing lacework pattern caused by accumulation of intracellular glycogen granules. (H. and E. $\times 55$.)

Histological examination revealed heavy glycogen deposits in the cardiac muscle (Fig. 10), producing the typical lace-work pattern, and in skeletal muscle and liver. Excessive glycogen was also found in the kidneys, leucocytes of the spleen, bronchopneumonic exudate, and to a lesser extent in the Purkinje cells of the cerebellum.

Blood from both parents was sent to Dr. David Hsia in Chicago for estimation of acid maltase activity. He found values of 4.07 and 4.76 μmoles of maltose/min. per mg. of protein in the mother's and father's blood respectively, while control blood showed activity of 6.36 μmoles of maltose/min. per mg. protein. Dr. Hsia considered these values to be in the heterozygous range.

Case 2. This patient was originally reported by Crome *et al.* in 1963 with special reference to the neurohistological changes in generalized glycogenosis. He was admitted to the Westminster Children's Hospital in 1961 for cardiovascular assessment and the clinical features and cardiac findings are reported again because of the marked similarity to Case 1.

He was the second male child of healthy, unrelated parents, born after a normal pregnancy at full term, weighing 2.5 kg. Apart from transient neonatal asphyxia, there were no abnormalities noted, and he thrived and was well until he was admitted to hospital at the age of 6 months for removal of a haemangioma on the left eyelid and right side of the neck. He suffered a cardiac arrest while being intubated and after resuscitation, he was found to have an enlarged heart.

On examination, he was a small baby weighing 5.6 kg., with marked hypotonia and a high-pitched weak

cry. The pulse rate was 124 per minute and all pulses were palpable. The apex beat was palpable in the mid-axillary line in the fifth interspace, and there was a soft third sound at the apex, but no murmurs were heard. The liver was palpable 2 cm. below the right costal margin; there was no cyanosis or oedema, and the lung fields were clear.

A chest x-ray (Fig. 11) showed a grossly enlarged heart, and an ECG (Fig. 12) showed a PR interval of 0.08 sec., a wide amplitude QRS with an interval of 0.04–0.06 sec. There was left axis deviation ($+20^\circ$) and marked left ventricular hypertrophy. Deep Q waves are seen in leads II, III, aVF, and V3–6, with T wave inversion in leads I, II, aVL, and V3. A search for viruses was negative.

Progress. After the cardiac arrest, he developed cardiac failure with dyspnoea and a constantly enlarged liver in spite of digitalization and regular diuretics. Further chest infections developed, and the hypotonia became more severe, with difficulty in feeding, and he died at the age of 9 months.

Post-mortem findings. The heart was grossly enlarged, weighing 160 g. (normal 38 g.) with thickened ventricular walls (LV 20 mm., RV 10 mm.) and some endocardial thickening.

FIG. 11. Chest x-ray, Case 2.

Discussion

Genetics. Pompe's disease is inherited as an

autosomal recessive with equal sex distribution (Spach *et al.*, 1966). Studies of heterozygotes have been few (Nitowsky and Grunfeld, 1967),

FIG. 12.—ECG, Case 2. Shortened PR interval 0.08 sec. with similar morphology to Case 1 (standardization 1 mV–1 cm.)

but Hsia (personal communication, 1968) considers the values for the enzyme activity obtained in the parents of our patients to be in the heterozygous range.

Pathogenesis. In Pompe's disease, absence of α 4-6 glucosidase from the intracellular lysosomes causes accumulation of structurally normal glycogen in lysosomal sacs where it is unavailable for normal degradation by glycolytic enzymes (Kahana *et al.*, 1964). Some of the glycogen is seen to be dispersed throughout the cytoplasm on electron microscopy (Cardiff, 1966), and it has been postulated that other glycolytic enzymes may be absent in Pompe's disease (Brown and Zellweger, 1966). However, all clinical parameters of glycogen metabolism are normal, including the glucose tolerance test and responses to adrenalin and glucagon; hypoglycaemia does not occur in these patients.

Glycogen accumulates in all tissues of the body, particularly cardiac and skeletal muscle, and liver; it also accumulates in neurones of the central nervous system, spinal cord, and autonomic ganglia (Crome *et al.*, 1963), which may cause symptoms of mental retardation, hypotonia, and constipation.

In this disease, cardiac and skeletal muscle contain between 3-10% glycogen, with an average content of 7.5% of wet weight. The heart is usually grossly enlarged, being 2 to 8 times normal weight (average 4 times normal in 58 cases), the left ventricle being twice the size of the right. Almost all cases developed heart failure, though in two cases described by Zellweger *et al.* (1965) aged 4 and 15 years, the heart was clinically unaffected.

Differential diagnosis. The differential diagnosis of the heart failure lies between endocardial-fibroelastosis, myocarditis, anomalous coronary artery, or sclerosis of the coronary arteries. The one distinguishing feature in Pompe's disease is the ECG, which, according to Caddell and Whittemore (1962), has a characteristically short PR interval, of less than 0.09 sec. in 86% of cases, a wide amplitude QRS in 98%, left ventricular hypertrophy in 65.7%, and left axis deviation in 40% (the latter is usually found in older patients).

Heart failure is due to cardiomyopathy (Goodwin, 1967), caused by excessive accumulation of glycogen in the muscle fibres. Some cases develop fibroelastosis if they survive long enough. Hohn *et al.* (1965) estimated that over half the cases had evidence of outflow tract obstruction, as shown in Case 1, and in the case of Ehlers *et al.* (1962), and

that this obstruction was probably the cause of the systolic murmur which had been heard in 47% of cases.

The chest x-ray shows gross cardiac enlargement—mainly left ventricular, very similar to cases of uncomplicated fibroelastosis, and the x-rays of the present cases are typical examples.

Muscle weakness was noted in 60% of reported cases and is due to a primary myopathy, as shown in the electromyogram, though anterior horn cell infiltration (Crome *et al.*, 1963), heart failure, and chest infection will accentuate this weakness. Macroglossia was also reported in 32% of cases and can suggest the appearance of cretinism or Down's syndrome (Clement and Godman, 1950).

Special investigations. Confirmation of the diagnosis is most easily made by examination of the peripheral blood lymphocytes for glycogen content by periodic acid-Schiff staining, which normally does not show any glycogen granules in the cytoplasm. The lymphocytes may also be examined for acid maltase activity (Huijing *et al.*, 1963). Liver and muscle biopsy specimens may be obtained by needle aspiration and give consistent results (Hug *et al.*, 1966).

Cardiac catheterization and angiocardigraphy serve to rule out anatomical cardiac defects and abnormal coronary arteries, and may show the greatly hypertrophied myocardium.

From the cases reported (Crome *et al.*, 1963; Smith *et al.*, 1966; Zellweger *et al.*, 1965) and also the current case, excessive glycogen deposits within the muscle produce an abnormal electromyographic pattern which is characteristic of a myopathy. It seems that motor nerve conduction velocity is unimpaired.

Treatment. No treatment has so far been successful in this disease. Resection of the hypertrophied septum was attempted by Ehlers *et al.* (1962), but the patient died after the operation. Recently Hug and Schubert (1967) administered acid maltase extracted from *Aspergillus niger*—but the patient failed to show any marked improvement.

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