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Glycogen Storage Diseases

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Glycogen is a glucose polymer present in moderate amounts in all animal cells, where it is used as an easily available glycolytic fuel. It accumulates in larger concentration in the liver, where it is stored after a meal as a reserve of glucose to be used during fasting by the whole body.

Glycogen storage diseases include more than 10 different genetic deficiencies affecting specifically one of the enzymes or transporters involved in glycogen metabolism (for review, see ref. 1). They are characterized by a storage of glycogen in abnormal quantity, abnormal location, or with an abnormal structure. In 1954, Gerty Cori (2) recognized the existence of five types of glycogen storage disease and initiated a numerical classification of these disorders, which was later extended by others and is still widely used, at least up to number VII.

Liver and muscle are by far the two tissues in which glycogen metabolism is the most intense and that are, therefore, expected to be the most seriously affected by a deficiency in that metabolism. When the liver is affected, as in glycogen storage diseases types I, III, and VI, the symptomatology is essentially related to the inability of that tissue to convert glycogen to glucose, causing hepatomegaly and hypoglycemia, which is expressed as sweating or convulsion, and is responsible for hypoinsulinism, hyperglucagonemia, hyperlipidemia, and retardation of growth. The main clinical and laboratory features observed in patients with glycogen storage disease types I, III, and VI and their evolution after childhood are shown in Tables 1 and 2.

When the muscle is affected, most typically in types V and VII but also in type III and in a subgroup of type VI, the symptoms are related to the inability of the tissue to provide rapidly a glycolytic fuel for contraction. This symptomatology usually is mild, becoming apparent only in the young adult and during strenuous exercise. Most remarkably, some patients with type V glycogen storage disease (muscle phosphorylase deficiency) had no complaint until they were more than 70 years old, an observation that indicates that subjects deficient in muscle phosphorylase can escape clinical detection. This can explain the male preponderance of about 2:1 observed in all these muscular forms of glycogen storage disease, since males are expected to exercise their muscles more intensively than females and since this difference could be an important factor in the manifestation of the disease.

TABLE 1. *Main clinical and laboratory features in 62 patients with hepatomegalic glycogen storage disease*

	Type Ia	Type Ib	Type III	Type VI
Number of patients	17	7	15	23
Age of clinical onset				
<1 month	4	3		1
1 month–1 year	9	4	13	16
1–2 years	3			4
2–4 years	1		2	2
Hypoglycemia				
Clinical signs	10	5	7	2
Seizures	3	5	6	
Epistaxis	8	1	1	
Enlarged kidneys	8/8			
Xanthoma	2		1	
Adenomas	6	1	4	
Muscular weakness			9	
Low fasting glycemia	13	7	7	1
High fasting lactacidemia	15	6	3	
Hypertriglyceridemia	17	7	13	10
Hypercholesterolemia	15	6	15	16
Hyperuricemia	9	2	2	
Abnormal liver tests	14/14	5	13	18
Elevated creatine kinase			10	
Osteoporosis	12	2	4	4

Courtesy of Prof. M. Odièvre, Hôpital A. Béclère, Clamart, France.

TABLE 2. *Main clinical and laboratory features in 74 patients over 12 years old with hepatomegalic glycogen storage disease*

	Type I	Type III	Type VI
Number of patients	22	32	20
Mean age at time of inquiry (years)	22	19	19
Mean deviation from standard percentile of height			
Before end of puberty	−3.85	−1.3	−1.8
After puberty	−1.6	−0.1	+0.1
End of puberty (years)	18	18	16
Enlarged liver	22/22	24/28	3/20
Normal liver functional tests	11/16	17/32	9/9
Adenomas	11/20	3/7	0
Hypoglycemia (clinical signs)	1/22	1/32	
Hyperlactacidemia	11/15		
Hyperuricemia	14/20	0	0
Hypercholesterolemia	16/21	4/27	2/13
Hypertriglyceridemia	17/20	6/20	0/8
Skeletal muscle involvement		10/28	

Courtesy of Prof. P. Guibaud, Hôpital Debrousse, Lyon, France.

TABLE 3. *Tissue glycogen content in glycogen storage disease*

Type of disease	Liver glycogen concentration (% of wet weight)	Muscle glycogen concentration (% of wet weight)
Ia	9.8 ± 2.4 (17)	0.73 ± 0.45 (10)
Ib	9.4 ± 2.7 (8)	
	9.0 ± 2.3 (17)*	
II		
Infantile	9.6 ± 2.7 (17)	10.1 ± 3.0 (21)
		8.4 ± 1.9 (21)*
Adult form	3.1 ± 1.9 (4)	2.7 ± 2.0 (4)
		1.2 ± 0.5 (14)*
IIIA	13.6 ± 2.6 (32)	5.6 ± 2.9 (34)
		5.3 ± 1.3 (16)*
IIIB	14.1 ± 2.2 (5)	1.2 ± 0.6 (5)
		0.9 ± 0.3 (5)*
IV	4.6 ± 0.5 (4)	
V		3.3 ± 2.4 (5)
VI		
Without muscle involvement	11.3 ± 3.7 (24)	0.96 ± 0.35 (18)
With muscle involvement		3.0 ± 2.2 (8)
Controls	3.3 ± 1.7 (56)	0.94 ± 0.55 (76)
		1.02 ± 0.32 (36)*

Data from Hers H-G and from *Brown BI (3).

In two other forms of glycogen storage disease, type II and type IV, there is no impairment of the phosphorolytic degradation of glycogen, and the clinical manifestation is related to the overloading of nearly all types of the cells by glycogen, either in an unusual subcellular location (type II) or with an abnormal structure (type IV).

Table 3 shows the mean glycogen concentration in liver and muscle in the various forms of glycogenosis. The overall frequency of the disease has been calculated by Hers et al. (1) from European data, to be around 1 new patient for every 20,000 to 25,000 births. According to the same authors, about 25% of these patients are of type I, 16% of type II, 22% of type III, 2% of type IV, 2% of type V, and 33% of type VI. Type VII is extremely rare in Europe.

TYPE I GLYCOGEN STORAGE DISEASE (GLUCOSE-6-PHOSPHATASE DEFICIENCY)

Historical

Glucose-6-phosphatase catalyzes the hydrolysis of glucose 6-phosphate into glucose and Pi. It is present in liver and kidney and also in some species, including

humans, in the intestinal mucosa. It plays a primary role in animal physiology because it is responsible for the formation of endogenous glucose originating from both gluconeogenesis and glycogenolysis. It is bound to the endoplasmic reticulum, and according to Arion et al. (4,5), three components of the endoplasmic reticulum participate in the process of glucose 6-phosphate hydrolysis: (a) a glucose 6-phosphate specific transporter, called T_1, mediates penetration of its substrate into the microsomal cisternae and is rate limiting for the hydrolysis of glucose 6-phosphate by intact microsomes, (b) a phosphohydrolase localized on the luminal site of the reticulum network, acts on glucose 6-phosphate, mannose 6-phosphate, and pyrophosphate, (c) a second translocase, called T_2, controls the permeability of microsomes to Pi and PPI. Whereas the three components would be required for the hydrolysis of glucose 6-phosphate by intact microsomes, only the second is necessary after disruption of the membrane, but only disrupted microsomes can hydrolyze mannose 6-phosphate.

In 1952, the Coris (6) reported the near complete deficiency of glucose-6-phosphatase in the livers of two patients with hepatorenal glycogen storage disease, and glucose-6-phosphatase deficiency was classified as type I glycogenosis by Gerty Cori (2) in 1954. From 1959 (reviewed in ref. 7), it became progressively apparent that a normal activity of glucose-6-phosphatase could be measured in frozen samples of livers from some of the patients presenting the pathognomonic symptomatology of glucose-6-phosphatase deficiency. This paradox was solved in 1978, when Narisawa et al. (8) reported that a defect in the glucose 6-phosphate transport system was responsible for this Ib type of glycogen storage disease.

General Description

Physical examination reveals short stature, a protuberant abdomen (related to enormous hepatomegaly), and a tendency to adiposity. Xanthoma may be observed over the elbows, knees, buttock, and hips. Fasting blood glucose concentration usually is in the range of 2 to 3 mM, and sometimes much lower. Hypoglycemic convulsion is, with acidosis, the usual cause of death, but profound hypoglycemia may occur without clinical symptoms. This is explained currently by the high (5–10 mM) concentration of blood lactate, which is a substitute for glucose as an energy source for the brain (9). Serum lipids are greatly increased, and this is mainly due to hypertriglyceridemia, which gives to the serum a milky appearance. Cholesterol and phospholipids are increased only moderately. Hyperuricemia frequently is observed, even during childhood, and increases with age, leading to clinical gout. The glucagonemia is about twice the normal value but can be normalized by an oral glucose load. Osteoporosis is a frequent finding. Prolongation of the bleeding time in the absence of thrombocytopenia or coagulation factor deficiency, and expressing itself by frequent and severe nosebleeds, often has been reported. There is also a high incidence of adenomatous nodules in the liver, developing mainly during the second decade, and a few of them undergo malignant degeneration.

In addition to the symptomatology described, type Ib patients exhibit a predisposition for infections (including recurrent otitis, pneumonia, multiple abscesses, pyoderma, and urinary tract infection), which is related to neutropenia.

Biochemical Defect

In type Ia, glucose-6-phosphatase is completely or nearly completely inactive, at least if a correction is introduced in the assay for the activity of nonspecific phosphatases. In type Ib, glucose-6-phosphatase is active after freezing and thawing of the liver sample or in the presence of detergent but inactive in a fresh liver preparation. This situation indicates a deficiency of the glucose 6-phosphate translocase, T_1 (10). A deficiency in the glucose 6-phosphate transport system in the microsomes of one patient has been demonstrated by Igarashi et al. (11).

Physiopathology

In the absence of glucose-6-phosphatase, the lactic acid formed by extrahepatic tissues cannot be converted to glucose by the liver, as it would normally be, and is eliminated by urinary excretion. Furthermore, all the precursors that normally would be converted to glucose in the liver, including glycogen, galactose, fructose, glycerol, gluconeogenic amino acids, and glucose itself, are now converted to lactic acid, of which a part is converted to fatty acids. Since renal threshold for lactate is 5 to 6 mM, the lactacidemia is necessarily elevated.

The low insulin/glucagon ratio results in an abundant release of free fatty acids and of glycerol from the adipose tissue and a high level of these compounds in the blood. A great part of these free fatty acids is taken up by the liver and esterified as triglycerides, which will be either exported as VLDL or stored in lipidic vacuoles. The excess of VLDL formation explains the elevated plasma levels of triglycerides, phospholipids, and cholesterol.

Hyperuricemia is in part explained by a decreased clearance secondary to competitive inhibition of renal tubular urate secretion by lactate. Another factor is an increase in purine synthesis, which presumably is secondary to an increased rate of purine catabolism, in which a decrease in Pi concentration plays a major role. Pi is indeed a potent inhibitor of liver AMP deaminase, which catalyzes the limiting step in the conversion of adenine nucleotides to uric acid.

Functional Tests

Glucagon and epinephrine cause no or little hyperglycemia but, typically, a marked increase in blood lactate. The administration of galactose causes an increase in blood glucose concentration in normal subjects but not in patients deficient in glucose-6-phosphatase (12), and a flat curve is pathognomonic of the disease. The lactacidemia

always increases during the test. A more complex functional test of the *in vivo* activity of glucose-6-phosphatase is based on the faster turnover rate of [^{3}H] glucose than of [^{14}C] glucose (13) observed in normal subjects but not in patients with type I glycogen storage disease. Recently, the use of [^{13}C] glucose has allowed demonstration of the complete absence of glucose recycling in these patients (14).

Treatment

The prognosis of type I glycogen storage disease has been dramatically improved since the introduction by Greene et al. in 1976 (15) of nocturnal nasogastric infusion of a high-glucose formula associated to frequent meals during daytime. By avoiding hypoglycemia, this treatment causes a remarkable decrease of blood lactate, urate, and triglyceride and also of the bleeding time values. There also is an accelerated rate of growth, which may reach 1 cm per month during the first year of treatment.

Another important improvement, introduced by Chen et al. (16) in 1984, is the use of uncooked starch (a 50% suspension in tap water) in the regimen. Because of its slow degradation by α-amylase, this nutrient, at a dose of 2 g/kg body weight, allows the maintenance of a normal blood glucose level for as long as 6 hours.

The treatment of type Ib glycogen storage disease is essentially the same as described previously, but no improvement of the recurrent infections is to be expected.

TYPE II GLYCOGEN STORAGE DISEASE

Historical

In 1932, Pompe (17) described the case of a 7-month-old girl who died suddenly after a short illness, with unexplained hypertrophy of the heart and a large excess of glycogen in nearly all tissues. The disease is currently known as Pompe disease, generalized glycogen storage disease, or cardiomegalia glycogenica and was classified by Gerty Cori (2) as type II glycogenosis. The striking cardiomegaly, which was considered characteristic by many authors, is not always present, and on this basis, two clinical forms were reported. In 1963, Hers (18) demonstrated the deficiency of lysosomal acid α-glucosidase in muscle, liver, and heart of patients belonging to the two types of disease. Subsequently, patients with a relatively mild myopathy and aged up to 60 years were found to lack acid α-glucosidase. Despite the great variation in the clinical manifestations, type II glycogen storage disease is defined as the situation in which acid α-glucosidase is deficient.

Clinical Manifestations

Functional impairment is seen mostly in heart, skeletal muscle, and nervous system. In the infantile form (Pompe disease), the symptoms usually become manifest

were observed regularly in the muscle and also occasionally in liver, although not in brain and heart.

The Enzymic Defect

In Pompe disease, the capacity of acid α-glucosidase to hydrolyze maltose is close to zero in liver and muscle (18). Juvenile and adult cases often show some residual acid α-glucosidase activity, but there are exceptions to this rule.

Physiopathology

Acid α-glucosidase deficiency was the first inborn lysosomal disease to be clearly defined and has been used as a model to establish the pathogenesis of a large number of storage diseases (20). The deficiency of the lysosomal glucosidase is believed to be responsible for the intravacuolar accumulation of glycogen, which has penetrated into the lysosomal system through the process of autophagy. The presence of a normal amount of cytosolic glycogen in the liver and its normal availability for phosphorolytic degradation explain why the patients never become hypoglycemic and respond normally to hyperglycemic stimulation by glucagon. The glycogen in excess is, at least initially, in the vacuolar system.

Treatment

There is no treatment at present for type II glycogen storage disease. Attempts at replacement therapy with purified human placental α-glucosidase were unsuccessful (21).

TYPE III GLYCOGEN STORAGE DISEASE (AMYLO-1,6-GLYCOSIDASE DEFICIENCY)

Historical

The abnormal structure of the glycogen present in excess in both the liver and muscles of one patient was recognized in 1952 by Illingworth and Cori (22). Because this glycogen had very short outer chains, as in a phosphorylase limit dextrin, a deficiency in amylo-1, 6-glucosidase was suspected and actually was demonstrated in 1956 (23). The disease is also called "limit dextrinosis."

General Description

The enzyme deficiency is generalized to all types of cells, and its clinical manifestation includes the hepatic and muscular symptomatology mentioned above, but

with unequal severity from patient to patient and at different ages (Tables 1 and 2). During infancy and childhood, the disease is difficult to distinguish from type I, and there is little complaint of muscular weakness. The heart may be clinically affected, and cardiac failure has been reported, even in infancy (24). Hepatomegaly tends to disappear after puberty, and some patients reexamined in adults life were clinically normal.

Muscular symptoms appear mostly in adult life and only in some patients. They consist in a slowly progressive weakness with wasting. Among the 23 adult cases with muscular manifestations reviewed (24,25), there was a large preponderance of males over females (16:6). Seven of these patients already had manifestations of the disease during childhood, and 13 still had hepatomegaly.

Genetic Heterogeneity

Van Hoof and Hers (26) measured the activity of amylo-1,6-glucosidase by four methods in the livers and muscles of 45 patients with type III glycogen storage disease. In 34 patients, the enzyme was inactive in both tissues, whatever the method used for its detection. This group was classified as type IIIA. In the other patients, an important residual activity of amylo-1,6-glucosidase could be detected either in liver or in muscle (type IIIB) or only by some of the methods used. In all cases, the stored polysaccharide had the structure of a phosphorylase limit dextrin.

Functional Tests, Diagnosis, and Treatment

Type III can be distinguished from type I by a normal or even exaggerated hyperglycemic response to galactose and also by a lower level of blood lactate and urate. It can be distinguished from type VI by the absence of hyperglycemic response to glucagon under fasting conditions and by its presence 2 hours after a meal. There is no rise in blood lactate during the test.

In most patients, the biochemical analysis can be done on erythrocytes, which contain a large excess of polysaccharide and in which amylo-1,6-glucosidase is inactive. In case of doubt, the enzymic analysis should be repeated on a muscle or liver biopsy, in which the abnormal structure of glycogen also is pathognomonic of the disease. The presence of an excess of polysaccharide in the muscle, as well as of an excess of plasma creatine kinase at rest (Table 1), excludes type I and most cases of type VI. The defect in muscle glycogenolysis also can be evidenced by the forearm ischemic exercise (see Type V), which causes either no or a subnormal rise in blood lactate. Treatment, when required, is similar to that of type I.

TYPE IV GLYCOGEN STORAGE DISEASE (BRANCHING ENZYME DEFICIENCY)

History and General Description

In 1952, Andersen (27) described an infant who was suspected of having glycogen storage disease because of a very large liver and poor hyperglycemic response to

epinephrine. However, the level of blood glucose rose after an intravenous administration of galactose, excluding a deficiency of glucose-6-phosphatase. The spleen was enlarged, but not the kidneys. Subsequently, the patient developed ascites and died at 17 months of age with cirrhosis. At autopsy, Andersen was struck by the poor solubility of the polysaccharide and by its abundance in the reticuloendothelial system. She sent it for further analysis to G.T. Cori, who recognized its amylopectin-like structure and suspected a deficiency of the branching enzyme (2). This deficiency was demonstrated by Brown and Brown in 1966 (28).

The disease, which is also called amylopectinosis or Andersen disease, is very rare. Patients appear normal at birth and for some months thereafter. There is then an insidious onset, with nonspecific gastrointestinal symptoms and progressive hepatosplenomegaly, leading to cirrhosis with portal hypertension. The level of glycemia is normal. Death usually occurs before the third year of life.

The Glycogen Abnormality

The concentration of glycogen in the liver is in the normal range. Ultrastructural studies show cytoplasmic deposits consisting of three components: glycogen particles, fibrils, and finely granular material (1,29). Abnormal glycogen is detected histochemically, ultrastructurally, or chemically but in very variable amounts, not only in the liver but also in numerous other tissues, including skeletal muscle, heart, spleen, rectal mucosa, and nervous tissue. It can be extracted with hot KOH, is poorly soluble, and forms a blue complex with iodine. Chain length analysis reveals its similarity with amylopectin (3.5% branch points, as compared to 6.7 in normal glycogen).

Pathogenesis

The several types of glycogen present in the tissues of the patients could be formed by the combined action of glycogen synthase and either amylo-1,6-glucosidase (30) or a residual branching enzyme activity (31). The poor solubility of the abnormal glycogen appears to be at the origin of the cellular injuries, including deposition of an amylopectin-like material in lysosomes, mostly of the reticuloendothelial system. The presence of normal glycogen explains the absence of hypoglycemia.

Diagnosis

Diagnosis rests essentially on the abnormal glycogen structure and on determination of the branching enzyme deficiency in muscle, or cultured fibroblasts.

Treatment

Liver transplantation deserves consideration, since it might relieve the major symptomatology, although many tissues other than the liver are affected.

TYPE V GLYCOGEN STORAGE DISEASE (MUSCLE PHOSPHORYLASE DEFICIENCY)

History and General Description

In 1951, McArdle (32) described the case of a 30-year-old man who suffered from muscular pain and stiffness following exercise. In contrast to normal, blood lactate fell during exercise. McArdle concluded that his patient was unable to convert muscle glycogen into lactate. The deficiency of muscle phosphorylase was established in 1959 by several groups of investigators (33–35) in similar cases.

Typically, cramps occur after exercise. Moderate exercise, such as walking on level ground, can be performed by most patients at their own pace, even for long periods. More vigorous activities also can be accomplished if they are intermittent. The concentration of serum creatine kinase at rest usually is elevated and may reach many times the normal value after exercise. The increase in blood ammonia, inosine, and hypoxanthine, which is normally observed after anoxic exercise, is exaggerated (36), indicating an excessive degradation of the adenine nucleotide pool.

About half of the patients have experienced occasional benign pigmenturia. There are a few reports of renal blockade. These patients were men who had performed vigorous exercise during which they were aware that they were exceeding their usual tolerance. The disease usually is diagnosed in the second or third decade. The absence of symptomatology during childhood is unexplained, and the male preponderance of about 2:1 is common to all forms of muscular glycogen storage disease.

Diagnosis

The absence of venous lactate response to ischemic work is characteristic of all diseases in which there is an impairment in the conversion of glycogen or glucose to lactate in the muscle. This includes the deficiencies in muscle phosphorylase, phosphorylase *b* kinase, amylo-1,6-glucosidase, glucose-phosphate isomerase, phosphofructokinase-1, or other glycolytic enzymes. As initially described by McArdle (32), a sphygmomanometer cuff placed about the upper arm is inflated above the systolic pressure, and the subject squeezes the sphygmomanometer bulb once every second for 1 minute. Affected patients usually are unable to perform the work for more than 40 to 50 seconds. If there is no rise in blood lactate, it is essential to measure the activity of muscle phosphorylase, phosphofructokinase-1, or possibly other enzymes to distinguish between the various disorders listed above.

Physiopathology and Treatment

Contracture and cramp may be observed in normally exercising subjects, and alteration of the muscle membrane is reflected by the appearance of several typically muscular enzymes and of myoglobin in the plasma. Because of its low molecular

weight, myoglobin is excreted rapidly in the urine. In McArdle patients, all these normal manifestations of muscular fatigue occur under much milder exercising conditions because of the inability to utilize glycogen. In general, there is no need for specific therapy.

TYPE VI GLYCOGEN STORAGE DISEASE (LIVER PHOSPHORYLASE OR PHOSPHORYLASE *B* KINASE DEFICIENCY)

History and General Description

In 1959, Hers (37) described three patients, one boy and two girls, with the hepatomegalic type of glycogen storage disease and displaying normal activities of glucose-6-phosphatase and amylo-1,6-glucosidase but a greatly diminished activity of phosphorylase in their livers. The glycogen content was normal in the muscle of these patients. This form of glycogen storage disease has been classified as type VI, or Hers disease, by Stetten and Stetten (38) and often erroneously considered as corresponding only to the primary defect of liver phosphorylase.

As summarized by Lederer et al. (39), it appears that type VI includes at least three different genetic defects that have in common a low activity of liver phosphorylase: (a) a sex-linked phosphorylase *b* kinase deficiency, described by Huijing and Fernandes (40), in which the muscle enzyme is unaffected, (b) an autosomal phosphorylase *b* kinase deficiency, which affects both liver and muscle (41,42), and (c) deficiency of liver phosphorylase, which may be complete (43,44) or partial (39). Their clinical manifestation is essentially that of a mild form of hepatomegalic glycogenosis, without hyperlactacidemia and hyperuricemia. Strikingly, most of these patients respond normally to the hyperglycemic action of glucagon. The evolution is usually benign (Table 2). As reported by Hers, et al. (1), these patients can, however, develop liver adenomas and malignant tumors (3 deaths in a series of 205 patients) or liver cirrhosis with esophagal varices (2 cases in the same series). Clinical muscle involvement in patient with the autosomal recessive form of phosphorylase *b* kinase deficiency rarely has been reported.

Diagnosis and Treatment

Although the symptomatology is milder than in type I and type III, only biochemical analysis allows a clear diagnosis. Phosphorylase *b* kinase can be measured not only in a liver biopsy but also in erythrocytes (39) or leukocytes (40). Its normal activity allows determination of the diagnosis of liver phosphorylase deficiency when the activity of the latter enzyme is low. Most patients do not require a specific treatment.

TYPE VII GLYCOGEN STORAGE DISEASE (DEFICIENCY OF MUSCLE PHOSPHOFRUCTOKINASE)

History and Clinical Description

In 1965, Tarui et al. (45) described three siblings, a 13-year-old female and 23- and 27-year-old male adults, complaining of easy fatigability and having symptoms similar to but more severe than those of McArdle disease. Muscle glycogen was increased and the concentration of glucose 6-phosphate was about 30-fold the normal. Phosphorylase was normally active, but phosphofructokinase was almost undetectable. Erythrocyte phosphofructokinase was decreased by about 50%. Subsequently, similar cases were reported, with a male preponderance of 2:1 (1). The disease is also known as Tarui disease.

Physiopathology

The factors that differentiate type VII from type V are (a) that the muscle is unable to utilize glucose and (b) that the erythrocytes are affected, causing a hemolytic tendency and increased reticulocyte counts as well as an elevated serum bilirubin. The 50% decrease in activity of the erythrocyte phosphofructokinase is due to the fact that this enzyme is a tetrameric hybrid of which two protomers are of the muscular type. Since erythrocytes have no other source of energy than glycolysis, of which phosphofructokinase catalyzes a limiting step, this partial defect is responsible for the shorter life span of these cells.

For these reasons, phosphofructokinase deficiency is the most severe specifically muscular glycogen storage disease. Blood ammonia, inosine, hypoxanthine, and uric acid increase as a result of an accelerated degradation of purine nucleotides, and a similar myogenic hyperuricemia can be observed, to a minor degree, in types III and V (46).

Diagnosis and Treatment

The diagnosis rests on the biochemical or histochemical determination of the enzymic defect in the muscle. There is no specific treatment.

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DISCUSSION

Dr. Diamond: Could you tell me whether autophagy occurs in all cells, and what contribution it makes to turnover in general? That is, to the turnover of all cytoplasmic enzymes and mitochondria. Is autophagy the main mechanism of degradation?

Dr. Hers: Cell physiologists believe that it is the main catabolic mechanism in all cells. If one looks carefully, one finds some vacuoles overloaded with glycogen in all types of cells, with the exception of the erythrocytes, in type II glycogen storage disease.

Dr. Lentze: I have a question about raw starch as treatment for hypoglycemia in these children. There is a mechanism in our gastrointestinal tract to persorb raw starch molecules as a whole, and it was shown in the 1960s that you can find and identify raw starch molecules or particles all over the body (1–5). Since raw starch is now fed regularly to children with glycogen storage disorders, it becomes an important issue.

Dr. Hers: To the best of my knowledge, this problem has not yet been taken into consideration in type I glycogenosis.

Dr. Shafrir: Hyperlipidemia in the glucose-6-phosphatase deficiency syndrome is a remarkable occurrence because it appears in the face of hypoinsulinemia. This is a unique situation, which shows that an increased load of substrate can induce the hepatic lipogenic enzymes in the absence of insulin. Is hyperuricemia only the result of competition between lactate and uric acid for excretion in the kidney, or is it also due to the increased flow of glucose 6-phosphate through the pentose shunt pathway and increased production of ribose, which is incorporated into the nucleotides and then degraded to uric acid?

Dr. Hers: This is not only due to competition with lactate but also to degradation of adenine nucleotides and the formation of uric acid. The explanation for this excessive formation of uric acid is a greatly increased activity of AMP-deaminase, which catalyzes the limiting step of uric acid formation. The most important property of this enzyme is that it is normally 95% inhibited, namely, by inorganic phosphate. If you release the inhibition of this enzyme by decreasing the concentration of phosphate, you may increase tremendously the velocity of AMP degradation to uric acid. There is some evidence that in type I glycogenosis there is hypophosphatemia and a decreased concentration of phosphate in the liver because phosphate normally is formed by glucose-6-phosphatase and also because phosphate esters accumulate in the liver.

Dr. Hopwood: Dr. Hers, I would like you to comment about the latest concepts in lysosomal membrane transport and whether you have a prediction about the presence of a specific glucose transporter to remove the end products of glycogen degradation from the lysosome. There have been several recent articles describing the active transport of N-acetylglucosamine and sialic acid out of the lysosome. Do you expect specific transporters of glucose to be found in the lysosome membrane?

Dr. Hers: I am not aware of this work.

Dr. Rossi: Do you know why patients with the type I have the kidney complaint?

Dr. Hers: Because the kidney has this property to share some of the metabolic systems of the liver. Glucose-6-phosphatase is found only in liver and kidney, at least in most animals, and in some species, including humans, also in intestine. Von Gierke described the first case of what we believe was a type I (although there was no enzyme analysis at that time) because of huge kidneys and huge liver overloaded with glycogen. Although the kidney is involved in type I, the kidney disease is not very serious. A recent report (6) described some renal defect in patients who were getting older, but it is not one of the major symptoms.

Dr. Rossi: What were the consequences of enzyme therapy in these diseases?

Dr. Hers: As early as 1963, we administered exogenous enzyme to these patients. This approach is very naive because it is very difficult to give, for instance, glucose-6-phosphatase, and hope that it will reach the liver in the right place and do what we expect it to do. If you inject a foreign protein in the circulation, it would be taken up by the tissue by endocytosis and then could finally reach the lysosomes, that is, the place where we really need it. On this basis, we injected first some impure glycosidase into a child with type II glycogenosis, and later we purified the human enzyme from placenta and injected it into patients. The result was very disappointing. This idea was used later by other people in other lysosomal diseases but, up to now, without success.

Dr. Hopwood: I have commented earlier about transport across lysosomal membranes. I agree with Dr. Hers about enzyme replacement therapy. It has been tried by many people but has not worked because the lysosomal enzymes that were administered generally were of the low uptake form. This means that they are not efficiently taken up by cells and remain in circulation, and when they eventually are taken up, they may be degraded within the lysosome before they have a chance to act. This is one of the basic problems of enzyme replacement therapy, and the other is to produce sufficient enzyme of the high uptake form to allow transport to the lysosome where it should function efficiently.

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