Glycogen storage disease type III

A case report

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Summary

A 5-year-old Black boy presented with massive hepatomegaly and muscle weakness. Liver biopsy revealed the presence of glycogen pools in the cytoplasm and nuclei of hepatocytes. Erythrocyte glycogen levels, identified as limit dextrin, were grossly increased. The galactose tolerance test as well as the two-stage glucagon stimulation test suggested a decrease in activity of both amylo-1,6-glucosidase and glucose-6-phosphatase enzymes. This was confirmed by direct assays performed on liver tissue and erythrocytes. The decrease in glucose-6-phosphatase activity was attributed to a secondary effect of limit dextrin.

The incidence of all forms of glycogen storage disease, of which at least 10 types are recognized, is about 1 in 40 000. Type III (Cori’s disease) is one of the commoner disorders and differentiates from type I (von Gierke’s disease) may be difficult. Cori’s disease usually carries a better prognosis, and a correct clinical and biochemical diagnosis is therefore important. Type I is a serious disease and death commonly occurs within the first 2 years of life. It has been stated that if the patient survives the first 4 years without mental retardation the muscular weakness and wasting improve while liver size often decreases quite strikingly at puberty. Biochemical differentiation between these two types may be simple in cases with an isolated enzyme defect but may pose problems when a combined enzyme defect is present. In this report we describe a 5-year-old boy in whom the primary amylo-1,6-glucosidase defect was associated with a secondary decrease in glucose-6-phosphatase activity.

Case report

A 5-year-old boy was admitted to the paediatric ward with a history of progressive enlargement of the abdomen and muscle weakness since birth. A family history of similar symptoms during childhood in adult relatives of the patient was obtained. Clinical examination of the child revealed massive hepatomegaly, muscle weakness and multiple buccal papillomas (Fig. 1). Intellectual development and growth rate were normal and no kidney enlargement was demonstrated on radiological investigation. Routine biochemical tests revealed grossly elevated serum aspartate and alanine aminotransferase activities; the bilirubin concentration was normal. Fasting blood glucose levels were found to vary between 1.8 and 2.9 mmol/l. Acid-base status and serum lactate, triglyceride, urate and ketone body concentrations were normal on several occasions when measured under basal conditions.
Special investigations

Light microscopic examination of a needle biopsy specimen from the liver fixed in Lillie's formalin-alcohol-acetic acid mixture showed the presence of large amounts of glycogen in the hepatocyte cytoplasm (Fig. 2). The glycogen stained with Best's carmine and the periodic acid-Schiff method; an amylase digestion control stain was negative. Electron microscopy confirmed the presence of cytoplasmic glycogen and considerable intranuclear glycogen deposits (Fig. 3). Early micronodular cirrhosis of the liver with fine collagenous trabeculae running between the nodules was also noted, but there was no active necrosis, regeneration or inflammation.

Examination of the rectus femoris muscle showed only a moderate increase of glycogen, mainly perinuclear in situation. Chemical quantitation of glycogen in the liver and erythrocytes confirmed increased concentrations of both (14.69 g/100 g wet weight and 453 µg/mg Hb respectively). The structure of the erythrocyte glycogen was evaluated by determining the absorption spectrum of its iodine complex and measuring the percentage hydrolysies by β-amylase. The results were compatible with those described for limit dextrin. Metabolic studies performed on the patient included a galactose tolerance and a glucagon stimulation test (Fig. 4). In the first, 1 g galactose/kg body weight was administered intravenously. An increase in both glucose and lactate concentrations in the serum resulted. The glucagon stimulation test was performed after a 14-hour period of fasting as well as 2 hours postprandially by the administration of 0.5 mg glucagon intramuscularly. Serum glucose or lactate concentrations did not respond after the period of fasting but both increased when the test was performed 2 hours after the ingestion of a carbohydrate-rich meal. The activity of the enzyme amylo-1,6-glucosidase was determined in erythrocytes, using the incorporation of 14C-glucose into glycogen. Although a relatively wide variation was found in normal controls, activity was virtually absent in the patient. Glucose-6-phosphatase activity measured in liver tissue was markedly decreased (2.2 µmol of glucose liberated by 100 mg of liver tissue per hour, with 8.8-13.8 µmol as reference values). The enzyme assays were performed immediately after the biopsy procedure in order to avoid artefactual changes.

Discussion

Hepatomegaly is a feature of both Cori's disease and von Gierke's disease. The finding of muscle weakness in our patient seems to favour the first diagnosis, as von Gierke's disease is primarily a hepatorenal disorder. Muscle weakness may, however, be difficult to evaluate in a sick infant. The biochemical finding of elevated blood aminotransferase activities is well documented in type III glycogenoses. Normal levels of serum lactate, triglyceride and especially urate may be of significance. A striking increase in these constituents is a general feature of von Gierke's disease. Hypoglycaemia occurs in both types but is usually more severe in type I and may be responsible for mental retardation, convulsions and stunting of growth.
Histological investigations confirmed the clinical observation of muscle involvement and the presence of glycogen in hepatocyte nuclei limited the diagnosis to types I and III, as this finding is documented only in these glycogen storage diseases. The increase in erythrocyte glycogen and the resemblance in structure to phosphorylase limit dextrin support the evidence for a primary debranching enzyme defect, which was confirmed by direct enzyme assays. The coexistence of a glucose-6-phosphatase deficiency is suggested by the increase in serum lactate concentration after intravenous administration of galactose. The simultaneous increase of glucose concentration in this test, however, makes the complete absence of this enzyme unlikely. Results of the two-stage glucagon test can also be interpreted as being due to a double enzyme defect.

Examples of multiple enzyme defects, including the simultaneous occurrence of debrancher deficiency along with a reduction in glucose-6-phosphatase activity, have been reported. The validity of some of the results are questionable because of improper handling of specimens and inadequate assays. For a double genetic defect in the patient, both parents need to be heterozygotes for both defects, a situation considered to be extremely rare. A more likely explanation is that the primary enzyme defect, a deficiency of the debranching enzyme which causes a massive accumulation of abnormal glycogen in both the cytoplasm and nuclei of cells, may result in disorganization of cellular metabolism. This may induce a secondary decrease in glucose-6-phosphatase activity which is incomplete.

REFERENCES