

## **Appendix H Type 1 Glycogen Storage Disease Information-Sheet**

During the third cycle of user evaluations of the application, all users were supplied with the following information on Type 1 Glycogen Storage Disease, if they asked for additional information on this disorder. It is envisaged, that in the future, information such as this will be available from the “library” component of SIMPRAC. Unfortunately, at the time of the user evaluations, this was not available. The information for this information-sheet was sourced from Chen and Burchell (1995).

### **TYPE 1 GLYCOGEN STORAGE DISEASE (VON GIERKE DISEASE)**

#### **GENERAL DESCRIPTION**

Type 1 GSD is an autosomal recessive disorder that was first described as “Hepato-nephromegalia glycogenica” by von Gierke in 1929. In 1952 Cori and Cori demonstrated that the primary defect responsible for this disorder was an absence of Glucose-6-phosphatase activity. Since that time a number of patient with a similar clinical picture but without a reduction in enzyme activity have been identified. Some of these patients have subsequently been shown to have a defect in microsomal glucose transport. The deficiency of glucose-6-phosphatase, or these microsomal transport systems in liver, kidney and intestinal mucosa, results in excessive accumulation of glycogen in these organs. The stored material in the liver is glycogen and fat. The deficiencies also lead to inadequate hepatic glucose production.

#### **CLINICAL FEATURES:**

Patients may present in the neonatal period with hypoglycaemia and lactic acidosis, but more commonly present at 3 to 4 months of age with hepatomegaly and hypoglycaemic

seizures. These children often have a doll-like facies, with excess adipose tissue in the cheeks, protruberant abdomen with thin arms and legs, and short stature.

Skin xanthoma over the upper and lower limbs may be present in infancy, and correlate with the degree of hyperlipidaemia. The lipid abnormalities are the result of increased very low density lipoproteins (VLDL).

The spleen and heart are of normal size.

Epistaxis and easy bruising, secondary to impaired platelet function, are common. The platelet dysfunction is thought to be a result of chronic hypoglycaemia.

Hypoglycaemia and lactic acidaemia occur after a brief fast. This was the cause of death in many children before the disorder was first recognized. Hyperuricaemia may be present in young child, but gout rarely develops before puberty. Despite the marked hepatomegaly, the liver transaminases are usually normal or only slightly elevated.

In Type 1B GSD the clinical picture is the same, with the additional finding of neutropenia and impaired neutrophil function. This in turn leads to recurrent bacterial infection. Many patients also have chronic inflammatory bowel disease.

#### LONG-TERM COMPLICATIONS:

These tend to occur only in adult patients.

- Gout
- Hepatic adenoma and hepatocellular carcinoma

- Renal disease (focal segmental glomerulosclerosis, nephrocalcinosis)
- Pulmonary hypertension
- Osteoporosis
- Symptoms may be exacerbated by pregnancy

#### PATHOPHYSIOLOGY:

*Hypoglycaemia:* Glucose-6-phosphatase activity requires two components of the microsomal membrane: (1) a glucose-6-phosphate (G6P) specific transport system, that shuttles G6P from the cytoplasm to the lumen of the endoplasmic reticulum (G6P translocase), and (2) an enzyme, glucose-6-phosphate phosphohydrolase, bound to the luminal surface of the membrane. Defects in either of these components leads to a block in the final step of gluconeogenesis. Interestingly, patients are still able to generate glucose from other pathways, although the specific mechanisms remain obscure. Thus, patients have endogenous glucose production rates around half that of control subjects.

*Lactic Acidosis:* Increased levels of G6P are in equilibrium with fructose-6-phosphate, which leads to an increase in fructose-2,6-bisphosphate, that in turn results in increased glycolysis and lactic acid production.

*Hyperuricaemia:* Increased serum urate results from decreased renal clearance and increased production. Accumulation of phosphate esters results in decreased intrahepatic phosphate, thereby reducing the inhibition of AMP deaminase. This in turn causes increased degradation of adenine nucleotides, and increased production of urate.

*Hyperlipidaemia:* Hyperlipidaemia is due to the increased production of acetyl-CoA, NADH and NADPH from glycolysis. These intermediates act as substrate for triglyceride production, which is then associated with increased hepatic production of VLDL. Furthermore, increased cytosolic acetyl-CoA leads to increased malonyl-CoA

and inhibition of Carnitine Palmitoyl Transferase 1. Thus, transfer of fatty acids, and subsequent beta oxidation within mitochondria, is inhibited.

#### MOLECULAR BASIS OF THE DISEASE:

Type 1a: The Glucose-6-phosphatase gene has been mapped to chromosome 17. The gene contains 5 exons and spans approximately 12.5 kb. A large number of mutations have been associated with this disorder.

Type 1b: The Glucose-6-phosphate Transport 1 gene has been mapped to chromosome 11. Several mutations have been associated with this disorder.

Type 1c:

Type 1d: This is due to a defect in the microsomal glucose transporter, GLUT7.

#### DIAGNOSIS:

Liver biopsy and estimation of hepatic glucose-6-phosphatase activity is the gold standard.

The role of genetic studies is currently being explored, and remains uncertain.

#### TREATMENT:

The goal of treatment of Type 1 Glycogen Storage Disease, is to maintain normal blood glucose concentration. Maintenance of normoglycaemia will correct most of the metabolic abnormalities, and reduce the morbidity associated with the disease. In infancy this may involve parenteral glucose administration or nasogastric feeding. In older children and adults, uncooked cornstarch at a dose of 1.75 - 2.5 g/kg body weight every 6 hours is the treatment of choice. Compliance can be a difficult issue.

Intake of fructose and galactose should be restricted as it cannot be converted to free glucose. As the diet is restricted, supplementation with multivitamins and calcium may be required.

Allopurinol may be used to treat hyperuricaemia, aiming to reduce the uric acid concentration below 380  $\mu\text{mol/L}$ .

Diazoxide has been used in children to improve blood glucose and reduce lactic acidosis. Such treatment has been associated with improvements in growth rates.

Despite the lipid abnormalities, endothelial vascular dysfunction and atherosclerosis seem to be rare in these patients. It has been suggested that treatment of severe mixed hyperlipidemia in GSD should possibly involve fibrates that activate lipoprotein lipase and may enhance the clearance of IDL, rather than omega-3 fatty acids, which principally suppress hepatic secretion of VLDL.

Individuals with Type 1b GSD may benefit from the administration of GM-CSF. Such treatment has been associated with correction of neutropenia, and a decrease in the number and severity of bacterial infections.

Liver transplantation has been performed in several patients where other treatment has failed. It results in the correction of hypoglycaemia and the other biochemical abnormalities found in this disease. However, it does not affect the progression of renal disease.