

2002 Workshop - Type I

Type I Glycogen Storage Disease: A Clinical and Research Update by Dr. David Weinstein - BOSTON USA

Prior to 1971, glycogen storage disease type I was considered an almost universally fatal disease marked by extreme failure to thrive and life-threatening hypoglycemia and acidosis. With the wide spread adoption of continuous glucose therapy in the 1970s and cornstarch in the 1980s, the prognosis improved dramatically. Today, patients with type I GSD are healthy adults who are able to participate in almost all activities without limitations. Yet, long-term complications continue to be a problem in many adults.

The focus of the workshop dealt with the following issues:

How should patients with GSD type I be treated
What is known about the long-term complications in GSD type I
What research is being performed

Treatment of GSD:

The goal of treatment is to supply a continuous supply of glucose to maintain plasma glucose concentrations above the threshold for activation of glucose counter-regulatory mechanisms. We strive to keep blood glucose concentrations above 70 mg/dL (3.9 mmol/L) and blood lactate concentrations below 2.2 mmol/L.

In the United States, cornstarch therapy is used as the primary method for delivering glucose. Cornstarch therapy is frequently used around the clock in children as young as 6 months. In contrast, in Europe continuous nocturnal feeds are the primary method for glucose delivery. This controversy is addressed in detail in the European Journal of Pediatrics Supplement (Oct 2002). In our opinion, either method of glucose delivery can be successful as long as the aforementioned goals are met.

The use of uncooked cornstarch was reviewed in detail in Dr. Joseph Wolfsdorf's conference report from 1999. To achieve optimal control, therapy should be individualized. In our experience, less than 10% of adults can make it through the night on one dose of cornstarch. Usually 5-6 doses per day of cornstarch are required (even in adults) to achieve optimal control, and children may need even more doses. It is recommended that cornstarch be weighed on a gram scale to ensure adequate coverage and avoid excessive calories.

Long-term Prognosis and

Complications in GSD I:

Growth:

Adults with type I glycogen storage disease have reached a final height approximately 1 – 1.5 standard deviations (about 2-3cm) below genetic predicted height. The final height in adults treated with cornstarch was –1.2 standard deviations while the height for those treated with continuous feeds according to the European Study on Glycogen Storage Disease (ESGSD) report was –1.53 standard deviations. This difference likely reflects population variations, and the same final height likely would occur with either treatment strategy as long as metabolic control is maximized. Overall, normal heights slightly below genetic potential are anticipated in adults with type I GSD.

Hepatic Adenomas:

Focal hepatic lesions consistent with hepatic adenomas (benign liver masses) continue to occur in 50% of adults with type I glycogen storage disease. The lesions usually appear during puberty, but can appear in younger children. There is no gender predisposition, and the prevalence of adenomas increases with age. There is no apparent difference in prevalence of hepatic adenomas, age of onset, or progression between patients treated with cornstarch and those treated with continuous feeds. Patients with adenomas have been found to have higher mean and peak lactate concentrations suggesting that suboptimal metabolic

control may increase the risk of these lesions. Genetics factors are also important as patients with outstanding metabolic control can still get hepatic lesions. Growth of adenomas has been seen in women taking oral contraception and men taking oral steroids.

Renal Calcification:

Kidney calcification and kidney stones were reported to be a common complication in GSD type 1 in the 1993 survey of adults with GSD. It has subsequently been demonstrated that low concentrations of urinary citrate are almost universal in adults with GSD1a. Citrate is normal chelator (binder) of calcium, and low citrate levels in the urine may predispose to kidney calcification. Treatment with oral citrate has been used for over 3 years with no loss of metabolic control allowing normalization of urine citrate concentrations. Citrate is titrated to achieve a target urinary citrate concentration > 300 mg/g creatinine. Metabolic control does not appear to be significantly associated with renal calcification.

Kidney Disease (Albuminuria)

Low levels of protein excretion (microalbuminuria) have been found in 31% of adults treated with cornstarch and 40-60% of adults treated with continuous feeds. Macroalbuminuria has been reported in 8% of adults treated with cornstarch, and 13% of adults treated with continuous feeds. The populations were different in these reports, and it is not possible to directly compare the effect of treatment strategy on kidney disease. Use of ACE inhibitors results in less albuminuria, and use is indicated if microalbuminuria or hypertension is noted. While data are limited, suboptimal metabolic control appears to be associated with kidney disease.

Anemia (Low Red Cell Concentrations)

Substantial advances have occurred over the past 2 years in understanding the pathogenesis of anemia in type I GSD. Overall, approximately 50% of patients have anemia. Often the anemia is mild and is associated with metabolic control. Occasionally, however, a more severe anemia can occur which is associated with profound iron resistance. While patients will look iron deficient, oral iron therapy fails to improve the anemia or iron studies. Intravenous iron therapy similarly results in suboptimal response. Investigations into the cause of this severe anemia revealed that it was associated with large hepatic adenomas. More direct evidence that adenomas were involved was gained when a patient had a large (14 x 15cm) adenoma resected. Within weeks of surgery, the patient's iron studies and blood counts returned to normal even though no blood or iron had been given, and the studies have remained normal to date (2 years). Staining of the adenoma demonstrated sparse iron deposition in the adenoma and surrounding normal liver tissue. The adenoma was found to be secreting a hormone inappropriately (called hepcidin) which blocks intestinal absorption of iron and impairs the body's ability to use iron in the bone marrow. Work is presently occurring attempting to identify ways to treat the anemia. In addition, since this hormone is excreted in the urine, it may offer a way to screen for and follow hepatic adenomas and/or cancer.

Research Updates:

New Technology:

Continuous non-invasive glucose monitoring is being tested although there are presently concerns about detection of hypoglycemia since the monitor is not very accurate below 70 mg/dL (3.9 mmol/L). While the technology cannot be recommended at present, it may prove beneficial in the future. A portable lactate meter is also being tested to allow home monitoring of lactate on blood obtained through a finger prick. Validation studies are presently being performed.

Gene Therapy Research

An update on the status of gene therapy or enzyme replacement was given. A more detailed update is given in the recent supplement in the European Journal of Pediatrics devoted to GSD. Progress has been made using traditional gene therapy using viruses to deliver the normal glucose-6-phosphatase gene. While some biochemical correction in the canine model of GSD I has been reported by the Duke University group, clinical improvement has yet to be demonstrated. Toxicity from the viral delivery system remains a concern although a less toxic virus is now being used.

Enzyme replacement has also been achieved through infusion of normal liver cells into a 47 year old with type I GSD. The patient had biochemical improvement and was able to go 7 hours without hypoglycemia, but the lactate concentrations and other biochemical markers remain abnormal. Immunosuppression remains a requirement with this technique.

Other newer techniques were also discussed but the methods are very preliminary.

SUMMARY FOR PATIENTS WITH GSD IA:

Children and adults with type 1a GSD are doing very well, but meticulous attention is required to achieve optimal biochemical control. When treatments are individualized and fine tuned, near normal glucose and lactate concentrations are usually attainable. Improved metabolic control may decrease the frequency of long-term complications. In addition, improved understanding of the pathogenesis of the long-term complications is allowing for treatments to be created.

ADDENDUM FOR PATIENTS WITH GSD IB:

New recommendations were recently released in the October 2002 supplement to the European Journal of Pediatrics. Particular attention was devoted to G-CSF use in type IB GSD. G-CSF has been used since 1989 for treatment of neutropenia, and usage has been associated with improvement in inflammatory bowel disease and fewer infections. The typical dose is between 3 –5 mcg/kg although doses range between 0.5 – 10 mcg/kg. Treatment with G-CSF offers the previously mentioned benefits, but complications have been noted. Almost 100% of patients develop spleen enlargement, and hypersplenism occurred in 38% of patients in a recent US series. Osteoporosis also remains a concern on G-CSF although no fractures have been reported in patients.

The following were released recently as consensus guidelines for G-CSF use:

Indications:

- Persistent neutropenia
- Single life-threatening infection
- Serious inflammatory bowel disease
- Severe diarrhea

Screening for Patients on G-CSF:

- Bone marrow prior to use and annually (a controversial recommendation)
- Ultrasounds every 6 months
- Bone density prior to use and annually

These guidelines must be adjusted based upon the clinical situation and age of the individual with type 1B GSD.

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