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AN INTRODUCTION TO GLYCOGEN STORAGE DISEASE TYPE I

Glycogen Storage Disease (GSD) is a term used to describe a diverse range of conditions involving defects in glycogen metabolism. Glycogen is a branched polysaccharide of glucose and acts as an energy store; mainly in the liver and skeletal muscle.

When the body is in a fasting or stressed state, glucagon and adrenaline stimulate glycogen breakdown (glycogenolysis) releasing glucose for use by the body. Conversely, in a fed state, glucose is converted into glycogen and stored (glycogenesis).[1]

There are many types of GSD involving the liver, muscles and/or other organs. Some examples are listed in Table 1.[2] Not all require a therapeutic diet. For the purposes of this article, we will refer to one type of hepatic GSD that requires intensive dietetic input: GSD Type I. In Figure 1 overleaf, you can see how the defective enzyme for this condition (glycogen-6 phosphatase) fits into overall hepatic glycogen metabolism.

PRESENTATION

GSD Type I typically presents in the first year of life.[3] It is rarely diagnosed in the neonatal period, as small infants feed frequently, but presents when periods of fasting are extended.[2] The exact prevalence is unknown, but is thought to be approximately one in 100,000 births.[2]

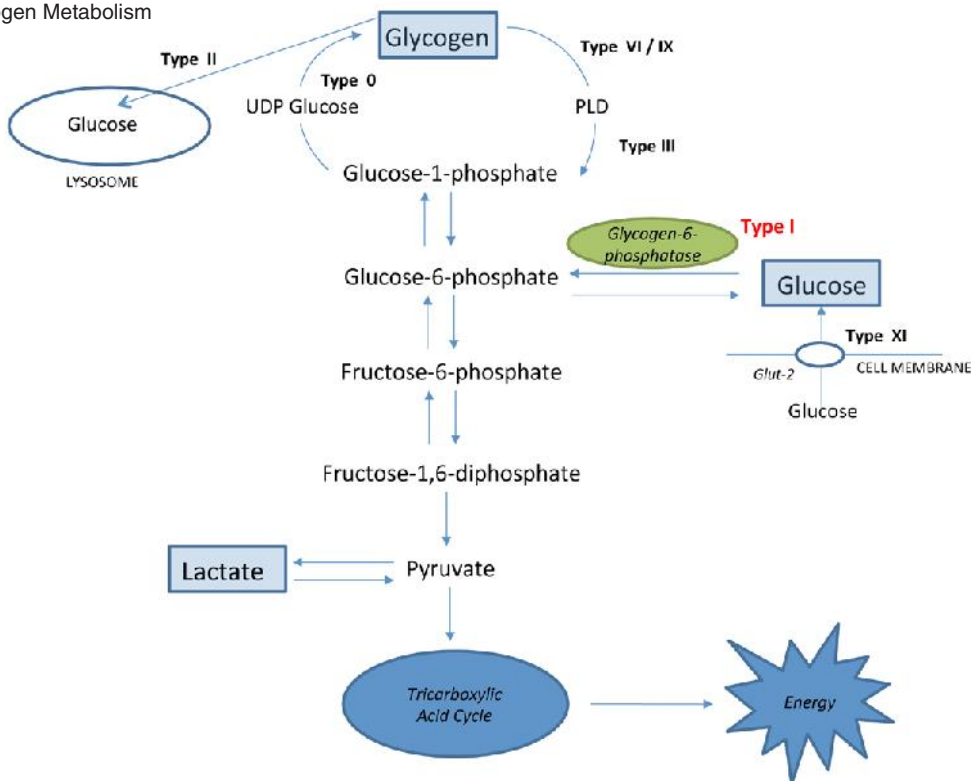
The stereotypical untreated child would present with a large round abdomen (caused by hepatomegaly), fasting hypoglycaemia, significant growth retardation and a 'doll like' face with chubby cheeks.[2,3] However, there can be a vast degree of heterogeneity. A specialist metabolic team can form a diagnosis by looking out for specific clues that differentiate between types; this would then be confirmed by genetic testing.

Hypoglycaemia is more prevalent in Type I than other types due to gluconeogenesis (making glucose from non-carbohydrate substrates such as pyruvate, lactate or gluconeogenic amino acids) being disrupted.[3] Blood lactate levels are also high in GSD Type I: glucose-6-phosphate cannot form glucose, so is pushed down an alternate pathway to form lactate, while ketone body production is inhibited. This is

Table 1: Examples of Glycogen Storage Disease Types[1,2]

Type	Eponym	Enzyme deficiency
0		Glycogen Synthase
Ia	Von Gierke	Glucose-6-phosphatase
Ib		Glucose-6-phosphatase translocase
II	Pompe	Acid α-glucosidase
III a/b	Cori, Forbes	Debranching enzyme and subtypes
VI	Hers	Phosphorylase
IX		Phosphorylase kinase and subtypes
XI	Fanconi-Bickel	Glut 2

Figure 1: Basic representation of Glycogen Metabolism



distinctly different from other types of GSD such as Type III, VI and IX - where high levels of ketones are produced.[3]

Life expectancy has improved considerably since initiation of treatment,[4] which continues to evolve as global knowledge and experience widens. Long-term complications of GSD Type I can include hepatic adenomas/carcinomas, renal disease, osteopenia, ovarian cysts, anaemia and hypertension.[4] In GSD Type Ib, there is additional neutropenia and impaired neutrophil function which can cause recurrent infections and inflammatory bowel disease (IBD).[4]

PRINCIPLES OF DIETETIC TREATMENT

A multidisciplinary approach is vital, with specialist dietetic management at its core. Treatment is individualised, but the overriding principals are to:[2]

- maintain normal blood glucose levels;
- correct secondary biochemical abnormalities (not always possible);
- promote normal growth and maintain a healthy body mass index (BMI);
- prevent long-term complications.

Because of the problems releasing a steady source of glucose, an exogenous source needs to be provided. This is initially based on normal basal glucose production rates (Table 2) and adjusted with regular monitoring. Some patients with milder forms of GSD may need only to eat regular meals and snacks and may be able to fast overnight, but with Type I, more intensive dietary input is required.[2] Glucose requirements and fasting times tend to improve with age,[2] but with infants and young children, fasting times can be as short as 90 minutes to two hours. Vitamin and mineral intakes need to be watched closely and supplemented accordingly, as prescribed carbohydrate can displace nutrient rich foods.[2]

Dietetic treatment for GSD Type I varies around the world. A prime example of this is the restriction of fructose and galactose in parts of Europe and the US. This is based on the

Table 2: Glucose requirements used in GSD[5]

Age	Glucose (g/kg/h)	
	Day	Night
Infants	0.5	0.5
Toddlers & children	0.3-0.4	0.3-0.4
Adolescents & adults		0.2-0.25

premise that they increase lactate production via glycolysis.[2] In the UK, we do not restrict as it is felt that slightly elevated lactate levels can be a protective element during hypoglycaemia, providing an alternative fuel for the brain.[2]

OVERNIGHT FEEDING

In the 1970s, continuous overnight enteral feeding was introduced to GSD treatment.[6] This enables a steady, controlled source of glucose to be provided overnight without waking an infant or child frequently for feeding. Managing without an overnight feed can be disruptive or unachievable, especially with very short fasting times.

In infancy, the overnight feed consists of infant formula and is transitioned towards a glucose polymer feed with added micronutrients as the child gets older.[2] A bolus of overnight feed must be given immediately before the feed is started and upon stopping (half the continuous rate), ensuring that the child is covered for the first part of the feed, and for 30 minutes once the feed is stopped.[2]

With the benefits of overnight feeding also come risks. A nasogastric (NG) tube needs to be used until hepatomegaly sufficiently resolves and it is safe to insert a gastrostomy. In GSD Type Ib, NG feeding is needed long term as a gastrostomy poses an infection risk.[2] Community health professionals must be made aware of this as overnight NG feeding is usually not permitted due to risk of tube displacement/aspiration. Even with a gastrostomy, the risk of feed discontinuation can pose the threat of hypoglycaemia.[2] Families are trained to use the feeding equipment and make up feeds correctly. Bed wetting alarms are given to help identify leakages during the night. Some families choose not to have an overnight feed, preferring frequent feeding or UCCS doses.

CORN STARCH

The 1980s saw the introduction of uncooked corn starch (UCCS).[7] This slowly releases glucose to help maintain normal levels and lessens the need for very frequent feeding.[2] It is usually introduced in children aged one to two years and above, as it is thought that before this age it is not effectively utilised by the body.[2,3]

The starting dose is usually 1.0-2.0g/kg,[2] once per day and must be built up slowly at home to prevent gastrointestinal side effects. UCCS must be given cold or at room temperature, mixed into a drink such as water, milk or squash, or mixed into yoghurt or custard. In cases where the child refuses the UCCS, it can be administered via feeding tube, but care needs to be taken not to cause blockages.

A modified starch (Glycosade) is used with some GSD patients. More research is needed and is planned in the UK; initial studies have shown that Glycosade may be able to achieve a longer duration of normoglycaemia than UCCS, smoother blood glucose response and improved metabolic control.[8,9,10]

CARBOHYDRATE PORTIONING

While enough carbohydrate needs to be provided to prevent hypoglycaemia and metabolic derangements, providing too much can also result in adverse effects. Excess adiposity and glycogen storage, along with hyperlipidaemia and swings in blood glucose levels can all arise from giving too much carbohydrate.[4]

In some GSD patients, carbohydrate counting can be a very useful tool to ensure that the right amount of carbohydrate is given at meals and snacks. In some children who are not carbohydrate counting, advice surrounding carbohydrate portion sizes is given, taking into consideration prescribed carbohydrate from UCCS and/or the overnight feed. Carbohydrate from complex, starchy foods rather than sweet sugary ones is advised and healthy eating advice is a priority.

Glycogen storage disease in liver

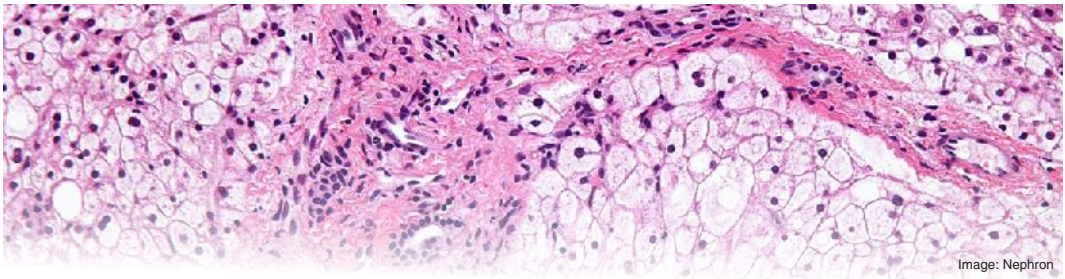


Image: Nephron

MANAGEMENT OF ILLNESS

In times of illness, it is important to ensure a supply of glucose to prevent hypoglycaemia and metabolic instability, at least the glucose requirements for age.[3] Families are taught an emergency regimen which consists of a glucose polymer solution given at regular intervals (usually two-hourly or continuously via a feeding pump), providing sufficient carbohydrate and fluid.[2] If this is not tolerated, hospital admission is necessary to commence IV dextrose.[3]

MONITORING

Children with GSD Type I need close monitoring. Growth is particularly important, as it is a key indicator that the prescribed treatment is effective.[2] Changes to feeding regimens need to be made regularly as children grow. A specialist metabolic team is likely to regularly admit children for 'profiling'. This involves the child being fed their usual diet, and measurements (glucose + lactate for GSD Type I) being taken before each meal, snack, UCCS dose and before, after and during the overnight feed if they have one. Continuous Glucose Monitoring (CGM) may also be used in the home environment.

CHALLENGES

GSD can be a challenging and distressing disorder to manage for families, particularly in children prone to hypoglycaemia. Frequent feeding needs to be regimented, and sometimes missing a feed by a matter of minutes can cause a child to become hypoglycaemic. The multidisciplinary team needs to provide sufficient education and support to ensure that families have the tools to manage.

Picky eating is also common; this is compounded by frequent feeding and can be extremely stressful for families, especially when regular feeds are the basis of treatment. A 'back-up' feed may be necessary to administer via a feeding tube to prevent any food aversions worsening.

CONCLUSION

GSD Type I requires intensive dietary treatment and care from a specialist, multidisciplinary metabolic team. Treatment and knowledge is continuously evolving, and hopefully long-term outcomes will continue to improve.

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