

2003 Workshop - Type I & III

REPORT ON THE TYPE I AND TYPE III WORKSHOP
FROM 2003 AGSD (UK) CONFERENCE HELD ON 11TH OCTOBER 2003

Workshop given by:

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There were five families with Type I and four families with Type III present.

PRESENTATION BY DR. BALI

Extra Glucose stored as Glycogen

Liver - Maintains glucose homeostasis, if glucose too low the liver releases stored glycogen as glucose for use by brain muscles and RBC's

Muscle - Fuel source for short term high energy consumption in muscle cells themselves.

Glycogen Storage Disease Type III

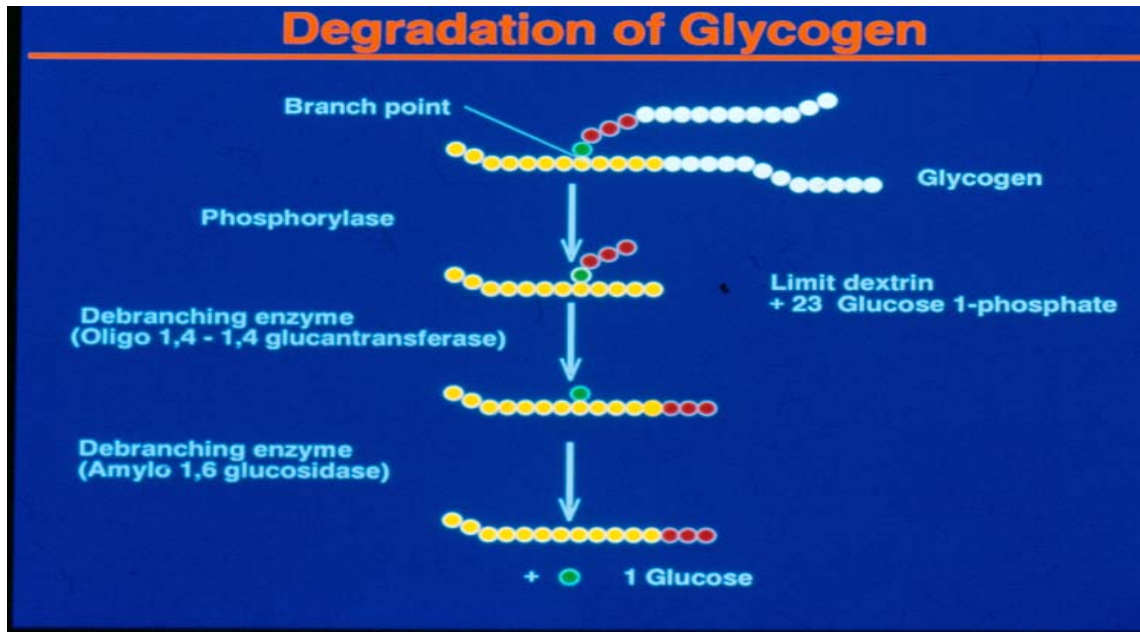
Type III is known as Cori or Forbes Disease and was discovered in 1920. It affects one in one hundred thousand live births.

The enzyme affected is called the Glycogen Debrancher Enzyme (GDE). It is inherited as an autosomal recessive disorder.

GDE is a bi-functional enzyme (gene, AGL) having two independent catalytic activities.. Both catalytic activities are required for a fully functional GDE enzyme.

GDE together with phosphorolase helps in the complete degradation of glycogen.

GDE deficiency causes incomplete glycogenolysis resulting in glycogen accumulation with abnormally short outer chains in organs, mostly liver and muscle.



Complications in GSD III

Hepatomegaly
 Growth Retardation
 Hypoglycemia
 Hepatic Adenomas
 Myopathy
 Cardiomyopathy
 Hyperlipidemia
 Elevated Liver Transaminases
 Overt Liver Cyrrhosis

Subtypes of GSD III

Subtype	Tissue affected by GDE defect or defective activity	% of patients
IIIA	Liver and Muscle(Debrancher deficiency)	75-80
IIIB	Liver only (Phosphorylase Deficiency)	10-20
IIIC	Isolated glucosidase deficiency	Rare
IIID	Isolated transferase deficiency	5

In general about 85% of patients have IIIA and 15% have IIIB.

Clinical Variability in GSDIII

Liver - Moderate to massive hepatomegaly (size of liver)
 - Liver symptoms improve with age, they usually disappear after puberty
 - Overt liver cirrhosis is rare.

Muscle - Problems usually minimal in children but they may become predominant in adults when they reach their 30's and 40's.
 - Slow progressive muscle weakness (proximal and distil only)
 - Some patients can become wheel chair bound.

Heart - Some with asymptomatic cardiomyopathy.

- Some with symptomatic cardiomyopathy which leads to death.
- Some with only muscle and no apparent heart involvement.

Possible Long Term Effects of GSD III

Liver cirrhosis / failure
 Progressive muscle weakness & wasting
 Polycystic ovaries
 Hepatic Adenomas
 Ventricular hypertrophy

Treatment of GSD III

(This is less demanding than GSD I)
 Frequent meals high in carbohydrate and cornstarch as well as a high protein diet if hypoglycaemia is a problem. (because gluconeogenesis is intact the protein can be shunted for glucose production).
 Physical therapy for progressive myopathy.
 Liver transplant if end stage cirrhosis

Goals of Nutritional Therapy

Prevent hypoglycemia- without overtreatment.
 Correct metabolic derangement without overtreatment.
 Provide optimal nutrition to support growth and development

Diet Guide Lines for GSD III

Carbohydrates (~40-50%)
 Protein (~25%)
 Fat (<30%)
 Vitamins and minerals as needed.

Night.

During the night either a nasogastric tube or cornstarch should be used.
 For the NGT use Formula >25% protein (severe cases may follow same glucose guidelines used for GSD I)
 Cornstarch may be added to Formula at bedtime (1.75-2.5g/kg body weight.)

Alarms needed for tube feeding failure.

Warnings

Clinical severity cannot be predicted by biochemical subtypes (IIIA / IIIB)
 Appears to be no correlation between amount of debrancher protein and clinical severity.
 Muscle biopsy essential for measuring GDE activity and for accurate prediction and initial diagnosis (IIIA vs IIIB)
 Severity of myopathy and cardiomyopathy may not be predictable.

About 50 patients have been seen or followed up at Duke University.

Gene

The GDE gene is localised on chromosome 1p21 and has 35 exons spanning at least 85Kb of DNA.

31 disease causing GSDIII mutations have been discovered so far.
 Exon 3 mutations (Q6X and 17delAG) are found only in GSD IIIB

PRESENTATION BY DR. LEE

Dr Lee has 52 patients at UCHL. 16 have GSD Ia, 4 have GSD Ib, 2 have GSD II, 17 have GSD III, 5 have GSD V, 1 has GSD VII and 7 have GSD IX.

Dr Lee concentrated on three subjects

- (1) Current Dietary Regimens
- (2) Renal Disease
- (3) Starch Therapy

Sub Types of Type I

- Type Ia : Glucose-6 phosphatase Deficiency
- Type Ib: Glucose-6-phosphatase transport protein Deficiency (can be called Type non Ia)

Both enzyme testing and genetic testing can be used to diagnose GSD I

Current Dietary Requirements

Glucose therapy in GSD I

	Glucose Requirement mg/kg/min	Glucose Supply g/kg/hour
Infancy	8 – 9	0.5
Childhood	5 – 7	0.3 – 0.4
Adolescence & Adulthood	2 – 4	0.2 – 0.25

This can be administered by nasogastric tube (ONNGT) or cornstarch (UCCS)

Daily Treatment preferred by UCHL

	Infancy	Childhood	Adolescent
Daytime	Glucose-2 hourly	UCCS	UCCS
Nighttime	ONNGT	ONNGT	? UCC

Complications in GSD I

- Growth Failure
- Osteoporosis
- Renal Calcification
- Renal Dysfunction
- Hepatic Tumours
- Hyperlipidaemia
- Polycystic Ovaries
- Gout
- Anaemia
- Pulmonary Hypertension
- Pancreatitis
- Inflammatory Bowel Disease (Ib)
- Bacterial Sepsis (Ib)

Issues in Adult management of GSD I

- Frequency of long term complications
- Prevention and treatment of complications
- Liver transplantation
- Pregnancy

Renal disease

Long Term Renal Outcome in GSD I

Patients	60 (Rake et al 2002) (20 -45.4 yrs)	37 (22 male) (Talente et al 1994) (18 – 43 Yrs)	
	56%	65%	Renal stones
	29%	22%	High blood pressure
	53%	61%	Protein leak in urine
	3	1	Haemodialysis or transplant
	96%		small albumen leak

There is a need to try and prevent renal stones and to manage urine leak
It can be seen from these figures that the risk of renal failure is very small.

Renal stones occur in GSD I when there is:

- High blood uric acid
- High urine calcium
- Low urine citric acid

Treatment

- Block the Renin – Angiotension System using ACE inhibitors and AT-11 blockers
- Improve metabolic control
- Perhaps Potassium citrate supplements to prevent calculi

Efficacy of Cornstarch

Cornstarch lasts approximately four hours.

Problems:

- Inadequate length of normoglycaemia
- Appetite suppression
- Risk of nutritional deficiencies
- Obesity

If pancreatin (pancreatic enzyme) is added to uncooked cornstarch it can help to keep the glucose levels up in some patients. Cornstarch is definitely superior to all other forms of starch. Research is being undertaken in developing a cornstarch that will keep the glucose levels up to 40% longer.

Management of GSD I alternative to diet

- Drugs: Potassium Citrate, Sodium Bicarbonate, ACEi
- Liver Transplantation
- Hepatocyte Transplantation
- Gene Transplant Therapy

TOPICS RAISED AFTER THE PRESENTATIONS.

Liver Problems

The Type I liver is softer than the Type III liver. It contains more fat and can change from day to day.

Incidence of the need for liver transplant in GSD patients very low.

Only Type I patients can get adenomas on the liver and these are almost always benign and rarely turn malignant.

A Type Ib patient had a successful liver transplant at eight years.

Great Ormond Street Hospital has carried out three liver transplants altogether.

A Type Ia patient gave birth after a kidney and liver transplant.

As yet liver cell transplantations are not very successful as too few cells can be used and the drugs needed to stop rejection can cause kidney damage.

Gastro oesophageal reflux is caused by a large liver pressing on the valve at the bottom of the gullet. This will diminish with age as the liver gets smaller.

Dietary Requirements

Cons of using a gastrostomy or a nasogastric tube

Gastrostomy

Sensitive skin can react badly
Can cause infection in Type Ib patients
Children can be embarrassed by having one

Nasogastric Tube

The tube can leak. (anti-wetting device can signal this)
Blockages can occur
The tube can be pulled out unintentionally by the patient.

Cornstarch CAN be mixed with anything as long as it is NOT heated in any way.

If the lactic acid is kept slightly above average this allows for a much freer diet
Duke University has done a project to establish that a high protein diet and exercise helps
Type III

Polycystic Ovaries

All Type III females develop cystic ovaries but it does not affect fertility.
One in four develop polycystic ovaries. In such cases it is not beneficial to be overweight.
Cystic ovaries are common in Type I patients too.

Gene Replacement Therapy

Duke University have reared several puppies with GSD I. They are a cross between a
Maltese terrier and a Beagle and are called a Malteagle. Sadly none have lived longer than 27
days.

Duke are also trying to create a mouse model for Type III but it is very difficult.

NB: In the United Kingdom only two patients have died in the last twelve years. One from a
cancerous liver and one from a pump accident.