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Biochemistry

OVERVIEW OF CLASSIFICATION OF GLYCOGEN STORAGE DISORDER

Dr Meghatai Bhise Assistant Professor, Department of biochemistry, Lokmanya Tilak Municipal Medical College and Sion Hospital, Mumbai

Dr Megha Ganesh Bangar* Assistant Professor, Department of biochemistry, Grant government medical college & Sir JJ group of hospitals, Mumbai. *Corresponding Author

ABSTRACT The glycogen storage diseases (GSDs) are a group of inherited metabolic disorders that result from a defect in one or several enzymes required in glycogen synthesis or glycogen degradation. Classified into various types depending on enzyme deficient and organ involvement. With advance biotechnology techniques and better knowledge biochemical defects with evolving biochemical test it become quite easy 1to screen, classify, diagnosis and treat patient for glycogen storage diseases. It help patients for living longer and better quality of life.

KEYWORDS : Glycogen storage disorder (GSD), Glycogen, enzyme

INTRODUCTION

1857 Claude Bernard first isolate glycogen in liver and stated its chemical and physiological properties. In 1928 Snapper and van Crefeld' described an infant with hepatomegaly, hypoglycaemia, and acetonemia.

The overall GSD incidence is estimated 1 case per 20000-43000 live births The glycogen storage diseases (GSDs) are a group of inherited metabolic disorders that result from a defect in one or several enzymes required in glycogen synthesis or glycogen degradation[1] primarily affects the liver, skeletal muscle, heart, central nervous system and the kidneys. The presence of an excessive amount of glycogen may physically interfere with the function of the tissue but many of the clinical features of the various types of glycogen storage diseases are due directly or indirectly to the impairment of carbohydrate metabolism.

Classification of glycogen storage disorder

Glycogen storage disorder 0
Autosmal recessive inheritance, first described in 1963
Enzyme deficient – glycogen synthase
Gene locus – 17q12.2

Glycogen storage disorder 0a-
NEnzyme deficient - Liver glycogen synthase[2]
Mutation in gene GYS2

Glycogen storage disorder 0b-
Enzyme deficient - Muscle glycogen synthase , Mutation in gene GYS1
Clinical presentation- early morning drowsiness, fatigue fasting hypoglycaemia, ketosis. Short stature and osteopenia, lethargy, pallor, nausea, vomiting
Lab Diagnosis - Elevation of blood lactate, decreased hepatic glycogen on a liver biopsy

Glycogen storage disorder I (Von Gierke Disease)
Autosomal Recessive
Enzyme deficient - Glucose 6 Phosphatase
Incidence – 1 in 50,000- 100,000 births
Mutation in gene for glucose 6- phosphatase located on chromosome 17_q21
Organ affected – liver and kidney

Clinical Presentation – Growth retardation, doll-like face, protruding abdomen, hepatomegaly no splenomegaly, anorexia, vomiting, and weight loss as well as convulsions and coma

Lab dignosis -Hypoglycaemia, lactic acidosis, hyperlipidemia, hyperuricemia, and slight elevation of transaminase levels
Both glycogenolysis and gluconeogenesis are affected.
There are 4 subtypes depending on the abnormality in G6Pase system. catalytic subunit of the system is located inside the endoplasmic reticulum,

Glycogen storage disease type Ia
Enzyme deficient - Glucose 6 phosphate α
Mutation of gene for G6PC

Glycogen storage disease type Ib
Mutation of gene for SLC37A4
Glucose-6-phosphate translocase deficiency
Enzyme deficient – Endoplasmic reticulum glucose 6 phosphate transporter

Glycogen storage disorder Ic and Id
Mutation of gene SLC17A3.
Liver microsomal transport of phosphate and glucose is deficient

Glycogen storage disease type II (Pompe disease, Acid maltase deficiency α-1, 4-glucosidase deficiency)
Incidence - 1 in 40,000 births
Prototype of lysosomal storage disease.
Mutilation in gene chromosome 17q25.2-q25.3
Enzyme deficient- Lysosomal α1→4 and α1→6 glucosidase
Organ affected- All organ
Four forms of GSD type II that are classic, infantile, juvenile, and adult forms
Clinical findings – hepatomegaly, hypoglycemia accumulation of glycogen in lysosomes of liver, heart and muscle death before 1year
Lab dignosis - increased creatinine kinase, aldolase,, and lactate dehydrogenase.

Glycogen storage disease type III (Cori disease, Forbes disease, amylo-1,6-glucosidase deficiency, glycogendebrancher deficiency)
The enzyme gene was isolated on chromosomes 1p21
It has 2 independent catalytic activities that are oligo-1,4-1,4-glucantransferase and amylo-1,6-glucosidase. Incidence - 1 in 100,000 births
Enzyme deficient- Glycogen disbranching enzyme
Clinical presentation - Hepatomegaly, hypoglycemia, short stature, dyslipidemia, slight mental retardation
Lab diagnosis- increased serum AST, ALT, LDH, and ALP level, Creatine kinase level is increased in GSD IIIb
Two subtypes

Glycogen storage disease type IIIa
Organ affected - liver and muscle, 80% of total type III GSD

Glycogen storage disease type IIIb (Limit dextrinosis,)
Organ affected – only liver 15% of total type III GSD
Clinical Presentation - Highly branched dextrin accumulates

Glycogen storage disease type IV (Andersen disease, brancher deficiency, amylopectinosis, glycogen branching enzyme deficiency)
Gene located on chromosome 3p12, Mutation in GBE1 gene
Autososmal ressisive, first described by Andersen in 1956 as familial cirrhosis of liver with storage of abnormal glycogen

Enzyme deficient – Glycogen branching enzymes
Organ affected- Liver and spleen
Clinical presentation - Hepatosplenomegly accumulations of glycogen and amylopectin in liver cytosol cirrhosis, and death due to liver failure between 3 and 5 years of age failure to thrive,

Glycogen storage disease type V (McArdle disease, myophosphorylase deficiency, muscle glycogen phosphorylase deficiency)
The enzyme gene is localized on chromosome 11q13 gene mutation - PYGM
Enzyme deficient - Muscle phosphorylase
Incidence - 1 in 100,000
Organ affected – muscle
Clinical presentation - Accumulation of glycogen in striate muscles exercise intolerance Transient myoglobinuria due to rhabdomyolysis36 muscle cramps , myoglobinuria patient exhibt second wind phenomenon

Glycogen storage disorder VI (Hers disease; Liver glycogen phosphorylase deficiency)
First reported by Henry-Gery Hers in 1959.
Which is encoded by the PYGL gene located on chromosome 14q22[5]
Enzyme deficient - Liver glycogen phosphorylase.
Incidence - 1 in 65,000- 85,000 births
Organ affected – liver
Clinical presentation – Mild hypoglycaemia; hepatomegaly
Lab diagnosis – increase aminotransferases levels, hypertriglyceridemia and hypercholesterolemia,

Glycogen storage disease type VII (Tarui disease, muscle phosphofructokinase deficiency, GSD of muscle)
Autosomal Recessive disorder
The gene is on chromosome 12q13.3
Enzyme deficient - Muscle and erythrocyte phosphofructokinase
Organ affected- Muscle
Clinical presentation - Haemolytic anaemia, Muscle cramps and myoglobinuria after exercise

Glycogen storage disease VIII hepatic phosphorylase kinase deficiency
Gene located on chromosomes 16q12-q13 mutation in PHKA1
X- Linked recessive inheritance
Enzyme deficient -Liver phosphorylase kinase
Organ affected-liver
Clinical features – Massive Hepatomegaly, Mild hypoglycaemia

Glycogen storage disorder IX (liver phosphorylase kinase deficiency)
Autosomal recessive inheritance first described in 1966 by Dr Hug
Mutation in PHKA1, PHKA2, PHKB, PHKG2 gene
Enzyme deficient - Liver and muscle phosphorylase kinase
Enzyme deficient- cAMP dependent protein kinase A
Clinical Presentation - Hepatomegaly, mild hypoglycaemia, elevated serum triglyceride, cholesterol, ALT level.

GSD IXa- phosphorylase kinase (α2 subunit) deficiency liver and erythrocyte
GSD IXb- phosphorylase kinase (β subunit) deficiency in liver and muscle
GSD IXc - phosphorylase kinase (γ subunit) deficiency in liver
GSD IXd- phosphorylase kinase (α1 subunit) deficiency in muscle

Glycogen storage disorder X (Human muscle phosphoglycerate mutase deficiency, Dimauro disease)
Enzyme deficient - Phosphoglycerate mutase deficiency
Clinical presentation - Primarily affects skeletal muscle, exercise intolerance, muscle cramp, renal insufficiency myoglobinuria

GSD Type XI (Fanconi-Bickel syndrome)
Autosomal recessive inheritance, first described in 1949
Gene localized to 3q26.1-q26.3 mutation in SLCA2 gene
Defects- in a transport protein, the GLUT2 glucose transporter[6,7]
Clinical presentation – Glucose and Galactose tolerance, fasting hypoglycaemia, tubular disfunction.

Glycogen storage disorder XII (Red cell aldoase deficiency, aldoase deficiency)
Autosomal recessive inheritance
Gene – ALDOA on 16p11.2
Enzyme defects- Aldoase
Haemolytic anaemia, myopathy
Glycolysis, gluconeogenesis, pentose phosphate pathway, fructose and mannose metabolism
Anaemia, splenomegaly, cholecystitis ,Intellectual disabilities

Glycogen storage disorder type XIII
Autosomal recessive inheritance
Mutation in ENO3
Enzyme defects- β enolase
Clinical presentation - Muscle cramps, exercise intolerance
Lab diagnosis – elevated serum creatinine level

Glycogen storage disease type XIV congenital disorder of glycosylation type 1
Autosomal recessive inheritance
Enzyme deficient – phosphoglucomutase
Gene affected – PGM1
Clinical presentation – hypoglycaemia, growth retardation, dilated cardiomyopathy
Glycolysis, gluconeogenesis are affected

Lafora disease
Autosomal recessive inheritance
Enzyme affected – Laforin, malin Gene – EPM2A, NHLRC1
Presence of inclusion bodies (Lafora bodies) in most organ
Clinical presentation Seizures, ataxia, myoclonus, dementia

Summary of glycogen storage disorder

Sr no	Name	Gene	chromosomes	Enzyme deficiency	Clinical feature	Autosomal	Involvement
0	-	GYS2	12p12.2	Glycogen synthesis	Hypoglycaemia, hyperketonemia	Autosomal Recessive	Hepatic
Ia	Von gierke disease	G6PC	17q21.31	Glucose 6 phosphate	Hypoglycaemia, lactic acidosis, ketosis, hyperlipdemia	Autosomal Recessive	Hepatic
Ib	-	SLC37A4	11q23.3	Endoplasmic reticulum glucose 6 phosphate transporter	Hypoglycaemia, lactic acidosis, ketosis, hyperlipdemia, Neutropenia and recurrent infection	Autosomal Recessive	Hepatic
IIa	Pompe disease	GAA		Lysosomal α1→4 and α1→6 glucosidase	Accumulation of glycogen in lysosomes of liver, heart and muscle; death before 2 years	Autosomal Recessive	Neuro-muscular
IIb						X-linked recessive	Neuro-muscular
IIIa	Limit dextrinosis, Forbes or Cori disease	LAMP2	Xq24	Liver and muscle debranching enzymes	Highly branched dextrin accumulates; Fasting hypoglycemia; hepatomegaly	Autosomal recessive	Neuro-muscular
IIIb	Limit dextrinosis	AGL		Liver debranching enzymes		Autosomal recessive	Both
IV	Amylopectinosis Andersen disease	GBE	3p12.3	Branching enzyme	Glycogen with few branches; hepatospleno megaly; mild hypoglycemia; death by age of 5	Autosomal recessive	Both

V	Myophosphorylase deficiency, McArdle syndrome	PYGM	11q13.1	Muscle phosphorylase	Excercise intolerance; accumulation of glycogen in muscles	Autosomal Recessive	Neuro-muscular
VI	Hers disease	PYGL	14q22.1	Liver phosphorylase	Mild hypoglycemia; hepatomegaly; better prognosis than other types	Autosomal recessive	Hepatic
VII	Tarui disease	PFKM	12q13.11	Muscle and erythrocyte phosphofructokinase 1	Glycogen in muscles accumulated; exercise intolerance; hemolytic anemia	Autosomal recessive	Neuro-muscular
VIII				Liver phosphorylase kinase	Hepatomegaly, mild hypoglycaemia		
IXa		PHKA2	Xp22.13	phosphorylase kinase α subunit (liver)	Hepatomegaly, mild hypoglycaemia	X-linked recessive	Hepatic
IXb		PHKB	16q12.1	Phosphorylase kinase, β Subunit		Autosomal recessive	Hepatic
IXc		PHKG2	16p11.2	Phosphorylase kinase gamma Subunit		Autosomal recessive	Hepatic
IXd		PHKA1	Xq13	Phosphorylase kinase α Subunit (muscle)		X-linked recessive	Neuro-muscular
X				cAMP dependent protein kinase A	Hepatomegaly accumulation of glycogen in liver		
XI		SLC2A2	3q26.2			Autosomal recessive	Hepatic
XII	Red cell aldolase deficiency			Aldolase	Muscle cramp, exercise intolerance	Autosomal recessive	
XIII				β enloase	Muscle cramp, exercise intolerance		

SUMMARY

With advance biotechnology techniques and better knowledge biochemical defects with evolving biochemical test it become quite easy to screen diagnosis and treat patient for glycogen storage diseases. It help patients are living longer and with a better quality of life.

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