ORIGINAL ARTICLE

HEPATIC GLYCOGENOSIS IN CHILDREN: SPECTRUM OF PRESENTATION AND DIAGNOSTIC MODALITIES

Hazrat Bilal, Huma Arshad Cheema, Zafar Fayyaz, Anjum Saeed, Syeda Sara Batool Hamdani

Department of Paediatric Gastroenterology & Hepatology, The Children's Hospital & The Institute of Child Health Lahore-Pakistan

Background: Objectives of the study were to determine the clinical spectrum of presentation and various modalities helpful in the diagnosis of liver glycogenosis short of genetic analysis. **Methods:** All patients under 18 years of age presenting to Paediatric Gastroenterology unit of Children's Hospital, Lahore with suspicion of hepatic glycogen storage disease (GSD) were enrolled over a period of 18 months. Demographic profile and various factors under observation were recorded. Collected data was analysed using SPSS version 22. **Results:** Among 89 enrolled patients F:M ratio was (1.28:1). The most common GSD was type I (71, 79.7%) followed by III (13, 14.6%), II (3, 3.3%), IV (1, 1.1%) and IX (1, 1.1%). The Abdominal distension was the most common presentation in 89.5% followed by hepatomegaly in 86.5%, diarrhoea in 41.6%, doll's like appearance in 31.5% and vomiting, acidotic breathing with convulsions in about 20% of children in GSD I. Hepatomegaly (100%), failure to thrive (85%), developmental delay (69%) and splenomegaly (92.3%) were leading presentation in GSD III. Elevated triglycerides (77.5%) followed by transaminesemia (56%), hypercholesterolemia (63%), hyperuricemia (32%) and hypoglycaemia (14%) were significant biochemical findings in GSD I. Consistently raised liver enzymes (92%) and creatinine phosphokinase (100%) in addition to hypertriglyceridemia (69%) were seen in GSD III. The presence of enlarged hepatocytes with clearing of cells favour GSD1 showed in 79% of children while fibrosis and steatosis usually seen in GSD-III (14.6%). **Conclusion:** Hepatic glycogen storage diseases are serious health issues and should be excluded in any patient who present with hepatomegaly, short stature and hyperlipidaemia to decrease the disease mortality and morbidity.

Keywords: Glycogen storage disease; Children; Presentation

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INTRODUCTION

Glycogen storage diseases (GSD) are a group of inborn error of carbohydrate metabolism where defective enzyme or glucose transport leads to various manifestations in different organs.[1] The hepatic glycogenosis are GSD 0, 1, III, IV, VI and IX and among them type 1 GSD is the most common form. Some types like GSD III and IX may affect both muscles and liver. GSD is one the commonest disorder in Pakistani children with an international incidence around 1:20000 to 43000 live birth.[2]

The hepatic glycogenosis generally presents clinically with abdominal distension, fasting intolerance, hepatomegaly, dolls facies, short stature and failure to thrive. Patient with GSD I can have recurrent diarrhoea, respiratory infections and renal impairment.[3] Glycogen storage diseases III involves both liver and muscle and can develop hepatic fibrosis, cirrhosis and hepatocellular carcinoma.[4,5] The clinical presentation of GSD IV is liver failure and cholestasis in early infancy with gross hepatosplenomegaly. Type XI presents with hypoglycaemia, hepatosplenomegaly, short stature and motor delay. [6]

The common laboratory findings of GSDs are hypoglycaemia, hyperlipidaemia and hyperuricemia in addition to metabolic acidosis while in crises. Aminotransferases and creatinine kinase are usually elevated along with ketotic hypoglycaemia in type III and type IX.[6,7] The characteristic histologic findings on liver biopsy are distension of hepatocytes with glycogen, clearing of cytoplasm and steatosis in type I whereas periportal fibrosis and minimal steatosis are present in type III and sometime type IX.[8,9] The definitive diagnosis of GSDs is made on enzyme analysis which obviates the need for invasive biopsy. Mutational analysis, a non-invasive and easy method, can be performed if facilities and resources are available.[10–12] We aimed in this study to see clinical spectrum of presentation of different types of GSD, various modalities helpful in the diagnosis of liver glycogenosis short of genetic analysis and enzyme essays.

MATERIAL AND METHODS

The study was planned prospective analysis, recruiting children from neonatal age till 18 years of age over a period of 18 months from March 2016 to

September 2017 with the suspicion of glycogen storage diseases. The study was conducted at the division of Gastroenterology & Hepatology, Department of Paediatrics, The Children Hospital, Lahore. Diagnosis was made on the basis of history, clinical findings including abdominal distention, hepatomegaly, hypertriglyceridemia, hypercholesterolemia and elevated transaminases. We also included any child with hypoglycaemia, hepatomegaly and metabolic acidosis to rule out gluconeogenetic defect. All children who fulfilled the clinical and biochemical criteria for liver glycogenosis were offered liver biopsy. Liver tissue was sent to histopathology department of Children's hospital and evaluated by the expert histopathology team who were already informed about the aims of study. Diagnosis was confirmed on liver biopsy after having weekly discussion meetings between gastroenterology and histopathology teams. Patients with other storage disorders and benign and malignant tumours were excluded from the study.

After taking informed consent from parents, demographic data was entered on database including age, sex, family history and consanguinity. Detailed history of clinical presentations including abdominal distension, fits, vomiting, diarrhoea, respiratory distress, and developmental delay were taken. Detailed clinical examination of each patient was carried out for doll's like facies, hepatomegaly, splenomegaly, height, weight. Biochemical parameters like blood sugar, Alanine aminotransferase (ALT), Creatinine phosphokinase (CPK), triglycerides, cholesterol level, uric acid were performed at indoor and outdoor settings.

Hypoglycaemia was defined as blood sugar below 54 mg/dl, hyperlipidaemia was taken when triglyceride and cholesterol both were more than 200 mg/dl, hyperuricemia was defined as uric acid level more than 5 mg/dl, ALT considered raised when level more than 60 IU/L in males and 38 IU/L in females. CPK was considered to be raised when level was more than 170 U/L.

Results were compiled and analysed by SPSS version 22.0. Continuous quantitative variables will be summarized as mean±standard deviation (or median and range as appropriate). For categorical variables (ordinal and nominal) frequency and percentages will be presented as table and graphs where applicable. *p*-value less than 0.05 was considered significant wherever applicable.

RESULTS

Eighty-nine children were diagnosed as glycogen storage disease, 50 (56.2%) were male and 39 (43.8%) were female. The most common GSD was type I (71,79.7%) followed by III (13,14.6%), II (3,3.3%), IV (1,1.1%) and IX (1,1.1%) as shown in table-1. The mean age±SD was 2.09±1.65 and 4.1±1.2 years in GSD I and III respectively. Abdominal distension was the most common presentation in 89.5% followed by hepatomegaly in 86.5%, diarrhoea in 41.6%, doll's like appearance in 31.5% and vomiting, acidotic breathing with convulsions in about 20% of children in GSD I. Rare presentation in GSD I included acute viral hepatitis (1.12%), renal stone (1.12%) and pancreatitis (2.24%). Hepatomegaly (100%), failure to thrive (85%), developmental delay (69%) and splenomegaly (92.3%) were leading presentation in GSD III in addition to hepatic nodule in one child (1.12%). Consanguinity was present in 94.4% of children. The summary of clinical pattern of presentation of different types of GSD is shown in table-2. Elevated triglycerides (77.5%) followed by transaminesemia (56%), hypercholesterolemia (63%), hyperuricemia (32%) and hypoglycaemia (14%) were significant biochemical findings in GSD I. Consistently raised liver enzymes (92%) and creatinine phosphokinase (100%) in addition to hypertriglyceridemia (69%) were seen in GSD III. These laboratory findings are shown in table-2.

The presence of enlarged hepatocytes with clearing of cells favour GSD1 showed in 79.55% of children, while, fibrosis and steatosis usually seen in GSD-III (14.6%). One patient of each GSD IV and GSD IX were diagnosed on genetic studies. Three patients were diagnosed as GSD II with DCMP (presented with hepatomegaly) diagnosed by enzyme assay. Various forms of GSDs are shown in table-1.

Table-1: Different types of GSD diagnosed on liver biopsies, genetic studies and enzyme assays in Pakistani children (n=89).

Type	No of cases	Percentage
GSD I	71	79.55
GSD III	13	14.60
GSD IV	1	1.12
GSD II	3	3.37
GSD IX	1	1.12

Table-2: Clinical spectrum of presentation of different GSD in Pakistani children (n=89).

Clinical Features n (%)	GSD I n#71	GSD III n#13	*p*-value
Abdominal Distension	65 (91.5%)	7 (53.8%)	0.004
Diarrhoea	30 (42%)	2 (15.3%)	0.118
Failure to thrive (<3centile)	32 (45%)	11 (84.6%)	0.000
Vomiting	19 (21.3%)	-	0.017
Convulsions	14 (19.7%)	-	0.007
Acidotic breathing (pH<7.35)	14 (19.7%)	1 (7.6%)	0.546
Developmental delay	11 (15.4%)	9 (69%)	0.001
Consanguinity	67 (94.3%)	13 (100%)	0.503
Dolls facies	28 (31.5%)	1 (7.6%)	0.045
Hepatomegaly (>4cm)	61 (86%)	13 (100%)	0.334
Splenomegaly	11 (15.4%)	12 (92.3%)	0.003
Pancreatitis	2 (2.24%)	-	0.712
Acute hepatitis	1 (1.12%)		0.845
Hepatic nodule	-	1 (1.12%)	0.845
Renal stone	1 (1.12%)	-	0.845

Table-3: Biochemical parameters of GSD in Pakistani children (n=89).

Lab Results n (%)	GSD I #71	GSD III #13	*p*-value
Hypertriglyceridemia	66 (92.9%)	9 (69.2%)	0.057
Hypercholesterolemia	45 (63.3%)	7 (53.8%)	0.723
ALT (>2XULN)	40 (56.3%)	12 (92.3%)	0.023
CPK (>170 U/L) n (%)	7 (9.85%)	13 (100%)	0.004
Uric acid (>5 mg/dl) n (%)	23 (32%)	4 (30%)	0.592
Hypoglycaemia n (%)	10 (14%)	-	0.003

CPK- Creatinine phosphokinase, ALT- Alanine transaminase, 2XULN- two times upper normal limit, U/L- Unit/Litre

DISCUSSION

Glycogen storage disorders are the most common inherited metabolic disorders of carbohydrate metabolism due to one or more enzyme deficiencies. Exact prevalence is not known in Pakistani children but recently published articles showed it's not an uncommon entity in this part of the world.[13] Amongst the liver glycogenosis, GSD I is the commonest form described in the literature followed by GSD III. This had been the case in our study as well. There is no gender predilection in GSD patients except X-lined consistent with the current study.

Glycogen storage disorders have variable clinical presentations but all forms usually present in infantile period except GSD III can present in older age group. In our study the mean age±SD was 2.09±1.65 and 4.1±1.2 years in GSD I and III respectively which is in contrast to international literature but similar to local description. GSD I being the most common type, it usually presents clinically with abdominal distention, hepatomegaly, failure to thrive, doll's facies, recurrent diarrhoea and chest infection and sometime convulsions. Rarely they can present with complications like pancreatitis, renal calculi and hepatic nodules.[14,15] Our study had almost same clinical description.

Type III GSD being the second commonest form presents in infancy and childhood with abdominal distension, hepatomegaly but with less of hypoglycaemic episodes as compared to GSD I. These findings were consistent with the current study as GSD III was 2nd in frequency and none of the child had hypoglycaemia. The distinguishing features of GSD III from GSD I are age at presentation, motor delay, splenomegaly, elevated transferases and creatinine kinase. The characteristic histological findings are hepatic fibrosis with decreased amount of steatosis on liver biopsy.[16–19] In our cohort of GSD, type III showed almost the same features with raised CPK as a constant feature in addition to clinical features.

Type IV is a rarely seen condition among all GSD's and presents with hepatosplenomegaly, jaundice, ascites, deranged liver function tests, hypoalbuminemia, prolonged coagulation and progressive hepatic fibrosis/cirrhosis due to excessive glycogen deposition in the liver.[20,21]In our study only one (1.4%) child had clinical suspicion and later on was confirmed on enzyme analysis. Sometime children are referred because of massive hepatomegaly, respiratory distress, developmental delay and raised lipid profile to rule out GSD I or III.[22,23] Three such patients (3.37%) were referred due to massive hepatomegaly, raised lipid profile and extended workup confirmed pompes disease as cardiomyopathy was documented on ECHO and confirmed on enzyme analysis.

In addition to clinical features, the biochemical findings helpful in the diagnosis of GSD I are hypertriglyceridemia, hypercholesterolemia, hypoglycaemia and metabolic acidosis which is less pronounced in type III.[13] Hyperuricemia is only raised in 20–30% of children in first decade only to rise more in the second decade. In the present study, significant proportion (both GSD I & III) had hypertriglyceridemia, hypercholesterolemia but hypoglycaemia and hyperuricemia were mainly seen in type I.

Initiation of metabolic crises in GSD starts with hypoglycaemia resulting in metabolic acidosis, convulsions and death if not managed well in time. In this study, hypoglycaemia was evident in 14% of GSD I but none of type III with significant p-value of 0.003. Among the liver glycogenosis, elevated creatinine phosphokinase supports the diagnosis of GSD III in addition to clinical suspicion and biochemical evidence. Normal CPK does not rule out GSD III. In this study almost all GSD III had elevated CPK as compared to 10% of GSD I with significant p-value of 0.004. Liver enzymes were raised in about half of GSD I in contrast to GSD III which had constant elevation in > 90% consistent with international literature.

Liver biopsy is still being done in developing countries for the diagnosis of GSD patients in addition to clinical and biochemical features. Mosaicism being a major finding in GSD I with minimal steatosis in contrast to fibrosis plus steatosis which is usually a feature of GSD III. In our study, major group of children had findings of mosaicism with minimal steatosis and nuclear hyperglycogenation consistent with GSD I (79.7%). Around 14% of children had GSD III diagnosis on liver biopsy with significant fibrosis in addition to steatosis. Availability of enzymes assays and genetic studies in developed world has almost obsoleted liver biopsy but in developing countries like Pakistan, main diagnostic tool is still liver biopsy in addition to clinical and biochemical features. Five children could be diagnosed as type II, IV, IX on the basis of enzyme assay and genetic studies.

This was one of the first study done prospectively to analyse the clinical spectrum of presentation of different GSD's and helpful diagnostic modalities short of genetic testing and enzyme assays. Financial constraints and facilities for more sophisticated and less invasive techniques to diagnose these children are still very scarce in this part of the world, so, we are still dependent on clinical, biochemical and histological findings for the diagnosis of these children.

CONCLUSION

Abdominal distention, hepatomegaly along with hypertriglyceridemia were the consistent findings in liver glycogenosis. Failure to thrive, splenomegaly, raised liver enzymes, creatinine phosphokinase and metabolic crises may help in differentiating different GSD's. Liver biopsy may help in diagnosis of GSD's in developing countries like Pakistan where genetic studies and enzymes assays facilities are not available publically.

AUTHORS' CONTRIBUTION

HB: Chief researcher. HAC: Supervision and review of the manuscript. ZF: Data collection. AS: Critical review of the manuscript. SSBH: Data collection.

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Address for Correspondence:

Hazrat Bilal, Department of Paediatric Gastroenterology & Hepatology, The Children's Hospital & The institute of Child Health Lahore-Pakistan

Cell: +92 334 907 7814

Email: hazratbilaldr@gmail.com