CLINICAL PRESENTATION AND BIOCHEMICAL FINDINGS IN CHILDREN WITH GLYCOGEN STORAGE DISEASE TYPE 1A

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ABSTRACT

Objective: To determine the clinical pattern of presentation and biochemical characteristics of glycogen storage disease (GSD) type 1a in children at a tertiary referral centre.

Study Design: Descriptive / cross sectional study.

Place and Duration of Study: Department of Pediatric, division of Gastroenterology & Hepatology of the Children's hospital, Lahore over a period of 11 years.

Patients and Methods: Confirmed cases of glycogen storage disease (clinical plus biochemical findings consistent with GSD 1a and proven on liver biopsy) were enrolled in this study from neonatal age till 18 years. Data was retrieved from files and electronic record for these cases. Diagnosis was made on the basis of history, clinical findings including hepatomegaly, hypertriglyceridemia, hypercholesterolemia, hypoglycemia and hyperuricemia (if present). Diagnosis was confirmed on liver biopsy. Patients with other storage disorders and benign and malignant tumours were excluded from the study.

Results: Total patients included in the study were 360 with male to female ratio of 1.25:1. Median age at the time of diagnosis was 25.6 months (age range from one month to 18 years). Most common presentation was abdominal distension (83%) followed by failure to thrive (69%) and recurrent wheezing and diarrhoea (44%) each. Seizures were present in only 1/3rd of children. Other presentations included vomiting, respiratory distress, altered sensorium, nephrocalcinosis, epistaxis and hypothyroidism. Few patients around 11% presented with acute hepatitis and later were diagnosed as GSD. Significant hepatomegaly was evident in almost all patients but nephromegaly was present in only 5.5% patients. All children had marked hypertriglyceridemia but cholesterol levels were raised in 1/3rd of children. A large majority of children had deranged ALT more than 2 times of normal and around 38% children had marked anemia. Significant hypoglycemia and metabolic acidosis was documented in around 1/3rd of children. Hyperuricemia was not a constant feature (16%).

Conclusion: This study showed abdominal distension and failure to thrive with hepatomegaly a common presentation with hypertriglyceridemia a constant feature. Huge number of patients in this study showed common metabolic disorder in children with diverse clinical presentation.

Keywords: GSD type 1a, Hypertriglyceridemia, Hepatomegaly.

INTRODUCTION

Glycogen storage diseases (GSDs) are an inherited group of disorder of carbohydrate metabolism resulting in storage of glycogen in different parts of the body especially liver and muscles with varied clinical presentation[1]. GSD type 1 is an autosomal recessive disorder, due to deficiency of an enzyme glucose-6 phosphatase which regulates the glucose production from gluconeogenesis and glycogen breakdown. Advances in research have provided an insight into the genetics of GSD 1 and genes responsible have been isolated[2,3]. The incidence of GSD type 1 is about 1 in 100,000 live births[4].

Abdominal distension with significant hepatomegaly, growth failure and pubertal delay are the characteristic features of GSD 1a along with biochemical abnormalities in the form of hypoglycmia, lactic acidosis, hyperlipidemia and hyperuricemia. Xanthomas and pancreatitis due to excess of lipids may be the presentation in relatively older children[5]. Adolescent and adults often develop liver adenoma that may undergo malignant

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transformation[6]. Proteinuria, hematuria and nephrocalcinosis are the presentations of kidney involvement[7,8].

Liver histology demonstrates prominent storage of glycogen and considerable steatosis with minimal fibrosis. If facilities are available DNA testing for common mutations should be done[9,10].

The goal of treatment should be the maintenance of physiologic glucose levels. Uncooked cornstarch (UCS) is the mainstay of treatment which improves the growth of these children with partial correction of biochemical disturbances[11]. Drugs are required to control metabolic acidosis, hyperuricemia, proteinuria and hypertension. Liver transplantation may be required in some affected patients with poor metabolic control, hepatocellular carcinoma, and/or liver failure[12].

This study is an account of descriptive cross sectional analysis of confirmed GSD type 1a pediatric patients focusing mainly on the clinical profile including diverse presentation, biochemical and histological characteristics.

PATIENTS AND METHODS

Record of children with confirmed GSD's (liver biopsy proven) were analysed from neonatal age till 18 years. This was a descriptive cross sectional study and patients were selected with non probability convenient sampling method, conducted from Jan 2002 to Dec 2013 over a period of 11 years in the department of Gastroenterology & Hepatology at the Children's hospital, Lahore. Diagnosis was made on the basis of history, clinical findings including hepatomegaly, hypertriglyceridemia, hypercholesterolemia, hypoglycemia and hyperuricemia (if present) and recorded on a database. Diagnosis was confirmed on liver biopsy. Patients with other storage disorders, benign and malignant tumours were excluded from the study.

Data was analysed by using Statistical Package of Social Sciences version 19.0 (SPSS, Inc, Chicago, IL, USA) for the collected patients. 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.

RESULTS

Total 360 patients were identified with biopsy findings consistent with GSD 1a. There were 200 males (55.5%) and 160 (44.4%) females with a mean age of 6.3 ± 2.5 years. Median age at the time of diagnosis was 25.6 months (age range was from 1 month to 18 years). Major clinical presentation in this study was abdominal distension and failure to thrive. Pattern of clinical presentations with physical findings are summarized in table-1, and 2. The data for growth for 231 patients (64%) in terms of height showed 72% (less than 3rd centile), 19% (between 3rd-5th centile) and the rest between 5th-10th centile. Consanguinity was

Table-1: Showing pattern of clinical presentation of GSD 1a (n= 360).

Presentation	No. of cases	Percentage %
Abdominal distension	300	83.3
Failure to thrive	231	64.2
Recurrent wheezing	160	44.4
Diarrhoea	145	40.3
Vomiting	100	27.8
Seizures (hypoglycaemia)	82	22.8
Altered sensorium	60	16.6
Respiratory distress (acidotic breathing)	58	16.1
Acute hepatitis	40	11
Epistaxis	20	5.5
Acute pancreatitis	03	0.83
Hepatic adenomas	01	0.27

present in about 68% of patients. Nephromeglay and nephrocalcinosis was present in about 5.5% patients. Laboratory findings are tabulated in table-4. Ten patients (2.77%) were also found to have associated hypothyroidism. Percutaneous liver biopsy showed steatosis, minimal fibrosis and nuclear hyperglycogenation. The pattern of findings was mosaicism (90.6%), steatosis (39.2%), minimal fibrosis (16%), nuclear hyperglycogenation (21.4%).

DISCUSSION

GSD's are a spectrum of disordered carbohydrate metabolism present at different age groups. GSD 1a is inherited in an autosomal recessive fashion and the most lethal one if not managed appropriately[1,13]. It has diverse clinical presentations and varied biochemical abnormalities. The most consistent clinical presentation in the literature for GSD 1a is protuberant abdomen and failure to thrive which is similar to the current study documenting as 83% and 64% respectively[6,13]. Other clinical presentations like seizures due to hypoglycaemia, diarrhoea, recurrent wheezing, vomiting and acidotic breathing are well documented in the literature[5,6,14]. Few patients present with epistaxis, acute pancreatitis, hepatic adenomas with underlying GSD 1a as the primary disorder[15]. In this study, there were 11% patients who initially presented with acute hepatitis A and later on were diagnosed as GSD 1a based on persistent hepatomegaly in follow up and liver biopsy result.

Protuberant abdomen with hepatomegaly (100%) due to storage of glycogen was the second to growth failure in this study which is similar to other studies[16]. GSD 1a classically does not have enlarged spleen but we found around 5% of our patient with splenomegaly consistent with literature[17]. Doll's face appearance associated with GSD 1a which has been well described in the literature was present in around 18% of our patients.

The most important metabolic and biochemical derangement encountered in GSD 1a are hypoglycaemia, metabolic acidosis, hypertriglycerdemia and hyperuricemia[18,19]. Hypoglycaemia is usually the starter of cascade leading to metabolic acidosis along with convulsions and progressive derangement in the consciousness level because of rising lactate levels. Hypertriglycerdemia is a constant feature in majority of the children with GSD 1a as described in this study as well[19,20].

Normal ALT or mild transaminesamia is present in GSD 1a but constant increase in transaminase has also been described in the literature[6,21]. Few patients in this study had ALT levels in thousands but those cases were later on diagnosed as acute hepatitis A. Anemia ranging from 25-80% reported in the studies which is similar to our result of 38% in this study[22].

Table-2: Showing physical examination findings (n= 360)

Physical findings	No. of cases	Percentage %
Hepatomegaly	360	100
Growth failure	212/231	91.8
Doll's facies	66	18.3
Splenomegaly	15	4.2

Table-3: Showing laboratory findings (n= 360).

Laboratory findings	No. of cases	Percentage %
Hypertriglyceridemia (N< 200 mg/dl)	360	100
Transeminasemia(N <40IU/L)	279	77.5
Anaemia (< 10gm/dl)	140	38.9
Hypercholesterolemia (<200 mg/dl)	120	33.3
Metabolic acidosis pH <7.35	60	16.6
Hyperuricemia(N < 6 mg/dl)	42	11.7

Percutaneous needle liver biopsy for these patients showed mosaicism a major finding consistent with GSD 1a. The presence of steatosis and nuclear hyperglycogenation is not diagnostic of type 1a which can be present in other types of GSDs. Fibrosis with steatosis is a features of GSD type III[23,24]. Our patients showed mosiacism, steatosis, nuclear hyperglycogenation and minimal fibrosis as 90.6%, 39.2%, 21.4% and 16% respectively.

The limitations of our study include the fact it is a retrospective, single center data and diagnostic constraints and dependence on clinical and histological findings because of non availability of genetic testing and, moreover, the potential effect of missing the data cannot be ruled out. However, with this good number of sample size, the clinical variability of presentation is also important to recognize this disorder early on considering the potential benefit of timely intervention with optimal nutritional therapy and lethal outcome if not managed appropriately. Further, long term prospective studies are required to see the affect of treatment and growth potentials in these patients.

CONCLUSION

This study showed abdominal distension and failure to thrive with hepatomegaly a common presentation with hypertriglyceridemia a constant feature. Huge number of patients in this study showed a common metabolic disorder in children with diverse clinical presentation. Clinical and biochemical features with histopathology input are still widely used for diagnosis of GSD type 1a in developing countries because of financial constraint and availability of genetic studies.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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