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ORIGINAL ARTICLE

Treatment outcomes on growth of children diagnosed with glycogen storage disease presenting to national institute of child health, Karachi, Pakistan.

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ABSTRACT… Objective: To determine the treatment outcomes on growth of children diagnosed with glycogen storage disease (GSD) presenting to National Institute of Child Health (NICH), Karachi, Pakistan. **Study Design:** Descriptive Longitudinal study. **Setting:** Department of Hepatology and Gastroenterology, NICH, Karachi, Pakistan. **Period:** March 2021 to September 2022. **Material & Methods:** Children of either gender aged above 1 year diagnosed with GSD were enrolled. Demographic details and disease details of all children were included and necessary biochemical and laboratory investigations were assessed. Children were treated with uncooked corn starch (corn flour) and dietary restrictions were also advised. Growth outcomes in terms of height, weight and liver size were measured for the period of 6-months and compared with the baseline data. **Results:** In a total of 36 children with GSD, 20 (55.6%) were male. The mean age was 2.81±1.80 years (ranging between 1 to 6 years). At the time of presentation, abdominal distension and hepatomegaly were observed in 36 (100%) children each. Significant improvements were found in terms of height gain among children aged 1-3 years ($p<0.0001$) and 4-6 years ($p=0.0039$) after 6-months of treatment. Although, children between 1-3 years and 4-6 years gained weight after 6 months of treatment but the difference was insignificant ($p>0.05$). Reduction in liver size was observed among children between 1-3 years ($p=0.0073$) and 4-6 years ($p=0.0376$) after 6-months of treatment. **Conclusion:** Treatment with uncooked corn starch (corn flour) and dietary restriction resulted in significant improvement on the growth of children diagnosed with GSD presenting to National Institute of Child Health, Karachi, Pakistan.

Key words: Abdominal Distension, Corn Starch, Glycogen Storage Disease, Growth Failure, Hepatomegaly.

INTRODUCTION

Glycogen storage diseases (GSD) are a group of inherited abnormalities of metabolism due to enzyme deficiencies which are responsible for glycogen synthesis and breakdown.[1,2] The incidence of GSD in Europe, Canada and the United States is estimated to be between 1 in 20,000 to 1 in 40,000.[3,4] Local data reports the glycogen storage disease in children as most commonly reported metabolic disorder with prevalence of 34.4% in Pakistani children.[5] The overall incidence of GSD in the general population is estimated to be around 1 in 100,000 live births.[6-9]

Early diagnosis is very crucial for decreasing organ damage and for enhancing quality of life as well increasing life expectancy. Diagnosis depends upon the clinical, biochemical, radiological and liver biopsy findings.[10,11] Treatment of GSD focuses on preventing further metabolic derangement, complications, achievement of normal psychological and physical growth along with good quality of life. Diet and life style modifications for hypoglycemia with continuous blood glucose monitoring.[10] High fiber diet should be recommended that make 60-70% calories. Fructose and galactose should be avoided. Treatment also depends upon clinical presentation of disease and its severity. Nasogastric infusion of glucose helps to maintain normal blood glucose levels which results in maintaining normal growth rate of children, blood sugar, normal liver and kidney functioning.[8-11]

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The rationale of the study is to provide the appropriate treatment and its effect on children diagnosed with GSD at National Institute of Child Health (NICH), Karachi, Pakistan. Outcome of treatment include normal growth of child, improving parameters of height, weight, and reduction in liver size. Early and appropriate diagnosis of GSD is very important not only for provision of appropriate treatment but also for decreasing the risk of early and late complications. Appropriate treatment is thought to be helpful in increasing growth of child and also increase the life expectancy as well as quality of life. So, our study was aimed to determine the treatment outcomes on growth of children diagnosed with GSD presenting to NICH, Karachi, Pakistan.

MATERIAL & METHODS

The descriptive longitudinal study was conducted in the department of hepatology and gastroenterology, NICH, Karachi, Pakistan from March 2021 to September 2022. Non-probability consecutive sampling technique was used. Children of either gender aged ≥ 1 year diagnosed with GSD during the study period were included. Exclusion criteria were children with other storage disorders. Parents or caregivers of children unwilling to be part of this study were also not included. GSD was described as "a metabolic disorder caused by enzyme deficiencies affecting glycogen synthesis, glycogen breakdown or glycolysis (glucose breakdown), typically within muscles and/or liver cells", and was confirmed on liver biopsy.

Approval from Institutional Ethical Committee was acquired (Ref: IERB-48/2021, dated: 02-02-2022) while written and informed consents were obtained from the parents/caregivers of all children. Demographic details of each child were obtained either from parent or from child or from medical record including name and age of child. Height of each child was measured by using measuring tape and standard weighing machine was used to measure weight of the children. Disease details of each child were also obtained from clinical, biochemical and radiological parameters. Clinical characteristics like abdominal distension, hepatomegaly, growth failure, and laboratory characteristics like hypertriglyceridemia, transeminasemia, hypercholesterolemia and hyperuricemia were noted. Radiological characteristics like hepatomegaly, nephromegaly, increased echogenicity, medullay nephrocalcinosis and stones were noted. Hepatomegaly was labeled as increased echogenicity and as fatty infiltration of the liver producing a diffuse increase in echogenicity (a bright liver). Nephromegaly was labeled as maximal renal length above the 95th percentile on ultrasound (confirmed on the basis of medical record). Medullay nephrocalcinosis was labeled as calcification in the medullary portions of the kidney in the distribution of the renal pyramids (confirmed on the basis of medical record). Stones were labeled as presence of features like echogenic foci (confirmed on the basis of medical record). Growth failure was defined as presence of short stature i.e. (height SDs <-2 for particular age and sex). Doll's facies was labeled as facial appearance with a round facial form, full cheeks, a short nose, and a relatively small chin. Hypertriglyceridemia was defined as presence of triglycerides level of >200 mg/dl. Normal transaminasemia levels were defined as aspartate transaminase [AST] <40 IU/L or alanine transaminase [ALT] <35 IU/L. Hypercholesterolemia was described as total cholesterol level >200 mg/dL. Hyperuricemia was labeled as uric acid > 5 mg/dl. Metabolic acidosis was labeled as pH <7.35 and bicarbonate <24 mEq/L. Neutropenia was labeled as the absolute neutrophil count (ANC) of <1500/mm^3. Hypoglycemia was labeled as random blood sugar below 55 mg/dl.

Children were treated with uncooked corn starch (corn flour) and dietary restrictions. For dietary restrictions, fructose, galactose, sucrose and sorbitol were restricted. Patients were advised to come for follow up after a period of 6-months following initiation of the treatment. Growth outcomes in terms of height, weight and liver size were measured for the period of 6-months and compared with the baseline data. All the data was recorded on a specific proforma.

After collection of data, data analysis was

performed using "Statistical Package for Social Science (SPSS)" version 25.0. Mean and standard deviation were calculated for quantitative variables. Frequency and percentages were shown qualitative data. Independent sample t-test was applied to compare height, weight and liver size during study intervals considering p value ≤ 0.05 as significant.

RESULTS

In a total of 36 children with GSD, 20 (55.6%) were male. The mean age was 2.81±1.80 years (ranging between 1 to 6 years) while 25 (69.4%) children were aged between 1-3 years. The mean weight and height were calculated to be 10.7±4.8 kg and 78.2±6.0 cm respectively. Table-I is showing characteristics of all children diagnosed with GSD.

Characteristics		Number (%)
Gender	Boys	20 (55.6%)
	Girls	16 (44.4%)
Age (years)	1-3	25 (69.4%)
	4-6	11 (30.6%)
Consanguinity	Yes	32 (88.9%)
	No	4 (11.1%)

Table-I. Characteristics of children with glycogen storage disease (n=36)

At the time of presentation, abdominal distension, hepatomegaly, increased appetite, failure to thrive, doll's facies, diarrhea, vomiting, and morning fits were noted in 36 (100%), 36 (100%), 34 (94.4%), 23 (63.9%), 11 (30.6%), 9 (25.0%), 6 (16.7%) and 6 (16.7%) children respectively. The mean hemoglobin, total leukocyte and platelet counts were 10.2±1.6 g/dl, 11770±4050/mm^3 and 353555±150138 uL respectively. Frequency of various biochemical abnormalities are shown in Table-II.

Biochemical Abnormalities	Frequency (%)
Hypertriglyceridemia	28 (77.8%)
Hypercholesterolemia	11 (27.5%)
ALT (>2xULN)	33 (91.7%)
CPK (>170U/L)	5 (13.9%)
Hyperuricemia (>5mg/dl)	14 (38.9%)
Hypoglycemia	2 (5.7%)
Neutropenia	8 (24.3%)
Urinary ketones	11 (30.6%)
Metabolic acidosis	14 (36.8%)

Table-II. Frequency of biochemical abnormalities among children with glycogen storage disorders (n=36)

Significant improvements were found in terms of height gain among children aged 1-3 years (70.5±3.6 cm vs. 74.1±2.9 cm, p<0.0001) and 4-6 years (92.2±4.5 vs. 95.4±4.6 cm, p=0.0039) after 6-months of treatment. Although, children between 1-3 years (p=0.1251) and 4-6 years (p=0.1921) gained weight but the difference was not found to be statistically significant after 6-months of treatment. Reduction in liver size was observed among children between 1-3 years (12.0±2.4 cm vs. 10.5±2.2 cm, p=0.0073) and 4-6 years (13.5±2.7 cm vs. 12.1±2.9 cm, p=0.0376) after 6-months of treatment (Table-III). No mortality was noted in this study.

Parameters	Age (years)	Baseline	After 6-month	P-Value*
Height (cm)	1-3	70.5±3.6	74.1±2.9	<0.0001
	4-6	92.2±4.5	95.4±4.6	0.0039
Weight (kg)	1-3	8.2±3.7	9.5±3.4	0.1251
	4-6	14.3±4.2	15.7±4.8	0.1921
Liver Size (cm)	1-3	12.0±2.4	10.5±2.2	0.0073
	4-6	13.5±2.7	12.1±2.9	0.0376

Table-III. Comparison of height, weight and liver size among children having glycogen storage disease (n=36)

DISCUSSION

In this study, most common clinical presentation/ features among children with GSD were abdominal distension and hepatomegaly noted in 100% children each. We noted that failure to thrive was present in 63.9% children. The literature reports similar findings where abdominal distension and hepatomegaly are found in almost 100% GSD cases while growth failure is also reported in majority of GSD cases.[12-14] Although data is scarce but it has been revealed earlier that most of the cases with early onset of clinical features present with hepatomegaly and/or hypoglycemia while raised lactate levels are also commonly observed in these cases.[15,16] Short stature is commonly reported among GSD cases while metabolic abnormalities like hyperlipidemia and hyperuricemia are also common.[17,18] Some other studies have also reported hypoglycemia, metabolic acidosis or convulsions but hypertriglyceridemia is known to be the most common biochemical abnormality observed.[19-21]

In this study, ALT>2xULN was revealed in 91.7% GSD children. Mild transaminesamia or persistently increased levels of transaminase have been found by other researchers in the past as well which needs regular monitoring of these biochemical parameters among children with GSD type1.[22-24]

As children of GSD in this study were treated with uncooked corn starch (corn flour) and advised dietary restrictions for duration of 6 months. The outcome was noted in terms of improvement in height, weight and liver size. Significant improvements were found in terms of height gain among children aged 1-3 years (70.5±3.6 cm vs. 74.1±2.9 cm, p<0.0001) and 4-6 years (92.2±4.5 vs. 95.4±4.6 cm, p=0.0039) after 6-months of treatment. Although, children between 1-3 years (p=0.1251) and 4-6 years (p=0.1921) gained weight but the difference was not found to be statistically significant after 6-months of treatment. Reduction in liver size was observed among children between 1-3 years (12.0±2.4 cm vs. 10.5±2.2 cm, p=0.0073) and 4-6 years (13.5±2.7 cm vs. 12.1±2.9 cm, p=0.0376) after 6-months of treatment. Our findings are consistent with what has been described in the literature as the introduction of uncooked corn-starch into the daily dietary treatment of GSD has been shown to result in improvement and better quality of life.[25,26]

The mainstay of GSD treatment is to aim prevention of hypoglycemia. There are multiple approaches adopted by clinicians to avoid hypoglycemia like continuous provision of dietary supply of glucose or by frequent ingestion of uncooked corn starch during day and night or nocturnal intragastric feeding.[24,25] Good dietary management of GSD have proven to minimize the metabolic derangements among such cases while it also decreases the risk of long-term complications.[26] We did not observe any major hypoglycemia episodes especially during nights among our cases which could also have helped in renal functioning among these cases. Some researchers have shown that impairment in the intestinal glucose absorption might be in-vitro and in-vivo among cases of GSD.[27,28] Among GSD, lactose, fructose and sucrose needs to be avoided except for fruits, vegetables and small amounts of milk products. Enough essential nutrients, vitamins and minerals should be given.

CONCLUSION

Treatment with uncooked corn starch (corn flour) and dietary restriction resulted in significant improvement on the growth of children diagnosed with GSD presenting to NICH, Karachi, Pakistan.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Arit Parakash	Study concept, Data analysis, Proof reading.	
3	Ayesha Merchant	Methodology, Discussion.	