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Original Article

Renal Involvement in Children with Glycogen Storage Disease

Rokaya El-Sayed*, Samah Mansour*, Randa Sabry, Gamal Taha***, Hesham Safouh*, Mortada El-Shabrawy* and Hanaa El-Karaksy***

*Departments of Pediatrics * and Clinical Pathology**, Cairo University, and Department of Pediatrics, Beni Swaif University****

ABSTRACT

Background: Long term complications of glycogen storage diseases (GSDs) include delayed puberty, hepatic adenomata, and renal disease.

Objectives: In the present study we aimed at detecting renal involvement in children with glycogen storage disease, and determining the most accurate laboratory test to be the gold standard for early detection of this renal dysfunction.

Methods: Twenty seven children known to have GSD were included in this study. Fifteen healthy age- and sex-matched children were also included as controls. Routine urine analysis, urinary β_2 microglobulin and microalbumin were done for all patients and controls. Renal function tests, serum electrolytes, alkaline phosphatase, urinary calcium, blood and urine pH, urinary and plasma aminogram, in addition to calculation of glomerular filtration rate (GFR), bone X rays to detect rachitic manifestations and abdominal ultrasound to measure renal size were done for all patients.

Results: Twenty one patients had one or more renal abnormality. The most common was increased urinary β_2 microglobulin (15/21) followed by abnormal GFR whether low or high (8/21) and microalbuminuria (6/21). Sonographically there was nephrocalcinosis in one case and renal stone in another one. The area under the receiver operating characteristic (AUROC) curve for β_2 microglobulin was 0.86, ($p = 0.01$) and 0.7 for urinary microalbumin/creatinine ratio ($p = 0.15$). The best cut-off level to predict renal abnormality for urinary β_2 microglobulin was 0.22 mg/l with 70% sensitivity and 100% specificity and the best cut-off value for urinary microalbumin/creatinine ratio was 4.5 with 86% sensitivity and 50% specificity.

Conclusion: Renal abnormalities are common in patients with GSD. Urinary β_2 microglobulin can be considered the gold standard for early detection of renal dysfunction in these patients.

INTRODUCTION

The glycogen storage diseases (GSDs) represent clinically diverse consequences of several defects in enzymatic and transport-dependent processes involved in maintaining plasma glucose homeostasis. GSD can present at any age[1]. The prognosis is highly variable[2]. With prolonged survival due to improved therapy, an increasing number of patients are surviving into adulthood; this has led to recognition of late complications such as altered bone mineralization, renal disease, and endocrine abnormalities[3].

Despite advances in therapy, which have resulted in improvement of metabolic abnormalities associated with GSD type Ia, renal disorders continue to be an important cause of morbidity[4].

Nephromegaly caused by glycogen accumulation in the kidneys was included in Von Gierke's original pathologic description

of GSD Ia[5]. Both proximal[6,7] and distal renal tubular dysfunction can occur, resulting in renal tubular acidification defects[8]. Albuminuria is common in adolescents and adults[9], and glomerular hyperfiltration is almost universal[10]. Focal segmental glomerulosclerosis may be a late complication of GSD 1a, and end-stage renal failure has been reported in adults[6].

AIM OF THE WORK

The aim of the present work was to study renal involvement in children with glycogen storage disease, and to determine the most accurate laboratory test that can serve as the gold standard for early detection of this renal involvement.

PATIENTS AND METHODS

This study was conducted on 27 patients suffering from GSD presenting to the Pediatric Hepatology Unit, Cairo University Children's Hospital, Egypt. Fifteen healthy age- and sex-matched children were also included as a control group.

The diagnosis of GSD was based on clinical characteristics (doll-like facies, huge hepatomegaly and stunted growth), ultrasonographic characteristics (huge hepatomegaly with bright echopattern) and histological findings in liver biopsy (distended hepatocytes with pale cytoplasm compressing the sinusoids). Liver biopsy was done after an informed written parent's consent.

Fresh morning urine samples were collected for routine analysis and urinary calcium estimation. Hypercalciuria was defined as a ratio of urinary calcium (mg/dl) to urinary creatinine (mg/dl) in a morning urine sample greater than 0.8 at age 0-6 months, greater than 0.6 at age of 12 months, and greater than 0.22 in children older than 1 year[11].

Urinary β_2 microglobulin and urinary microalbumin were assayed for all patients and controls by immunonephelometric method, Dade Behring BN prospecnephelometer (Dade Behring/Marburg/Germany). Urine samples with pH < 6.0 were adjusted to pH 7-9 soon after sample collection (by addition of 1N NaOH) for stabilization of β_2 microglobulin in urine. Urinary microalbumin/creatinine ratio and urinary β_2 microglobulin/creatinine ratio were calculated.

Glomerular filtration rate (GFR) was estimated using the Haycock-Schwartz formula[12]: GFR (ml/min per 1.73 m^2) = [k × body height (cm)]/ plasma creatinine (mg/dl). The values of k are 0.45 for an infant and 0.55 for a child[13]. The normal GFR for the pediatric patients is from 89-165 ml/min/1.73m^2.

Urinary and plasma amino acids were detected by thin-layer Chromatography (TLC). The chemicals needed for TLC were supplied by Sigma (St. Louis Missouri 63178).

Blood was tested for renal functions: serum creatinine, blood urea nitrogen (BUN), serum electrolytes including Na, K, Ca and phosphorous. Arterial blood gases and plasma lactate were also determined in patients' samples. Renal functions were assayed on Synchron Cx5 clinical system (Beckman Instruments, Inc. Brea, California, USA). Electrolyte levels and

arterial blood gases were assayed on blood gas analyzer (Nova Biomedical, Stat profile 9, Waltham, MA, U.S.A.). All tests were performed using standard laboratory methods.

Renal ultrasonography was performed for patients and control groups using Fukuda Denshi FF Sonic, Model UF-4100 scanner with 5.5 MHz transducer, with the child lying both supine and prone. The maximal renal length was measured and plotted against sonographic renal charts (renal length vs. age) according to the standard reference of Rosenbaum et al.[14]. Nephromegaly was diagnosed when the maximal renal length was above the maximum range.

X-ray on both lower limbs to detect any rachitic or bone density changes was done for all patients.

Statistical Methods:

All patients' data were analyzed using SPSS 10 for Windows XP. Qualitative variables were compared using Chi-square test or Fischer's exact test when appropriate. Quantitative data of two groups were compared by student t-test or by Mann-Whitney U test for non-parametric variables. Comparison of more than two groups was done by using Kruskall-Wallis test. p value was considered significant if less than 0.05. Regression analysis was done to confirm association between quantitative variables. ROC curve was drawn to detect diagnostic reliability of the different parameters used for diagnosis of renal impairment.

RESULTS

Twenty seven patients known to have GSD were enrolled in this study. They were 16 males and 11 females. Their mean age was 7.4 ± 4.66 years.

A significantly high incidence of renal abnormalities (laboratory and sonographic) was detected in our patients, with 21 patients having single or multiple renal abnormalities. Table (1) shows the renal abnormalities which were detected in our patients.

In those 21 patients with renal abnormalities, 12 patients had a single abnormality (6 patients had increased urinary β_2 microglobulin, 3 had low GFR, 2 had glomerular hyperfiltration, and one case had microalbuminuria). Six patients had two abnormalities; all of them had increased urinary β_2 microglobulin in addition to microalbuminuria in 2 cases, hypercalciuria in one case, renal stone in one case, low GFR in one case, and glomerular hyperfiltration in another one. Three patients had more than two abnormalities; all of them had increased urinary β_2 microglobulin, microalbuminuria and glucosuria. One of these patients had nephrocalcinosis and aminoaciduria. Another patient had glomerular hyperfiltration, and aminoaciduria (Table 2).

According to sonographic percentile reference for renal size[14], none of our patients had detected nephromegaly. Renal stone was detected in one patient and nephrocalcinosis in another one. Coincidental anatomical abnormality in the form of duplex renal pelvis was detected in one case.

Increased urinary β_2 microglobulin was the most frequently detected renal abnormality in patients with GSD, where it

was detected in 15/21 (71.4 %), meanwhile, microalbuminuria was detected in 6/21 (28%), and abnormal GFR was detected in 8/21 (38%).

We report three cases from the same family who had a clinical picture of Fanconi syndrome in the form of glucosuria, aminoaciduria, and who also had microalbuminuria and increased urinary β_2 microglobulin. Two of them had acidosis, one had glomerular hyperfiltration and one had duplex renal pelvis and rickets, the third one had renal stone.

The age of patients with renal abnormalities and non renal abnormalities did not show any significant difference ($p > 0.05$).

By comparing serum creatinine, Na, K, Ca, phosphorous, alkaline phosphatase (ALP), HCO_3, lactate, or urinary creatinine, in both groups with renal and non renal abnormalities we could not find any significant difference (p value > 0.05). The blood pH in patients with renal abnormality was significantly lower than that in patients without renal abnormality, (p value = 0.04). However the urinary pH did not show a significant difference between both groups (p value = 0.08), Table (3).

Comparison of tests of renal affection is shown in Table (4). The urinary β_2 microglobulin/creatinine ratio was significantly increased in the group of GSD with renal abnormalities when compared to those without renal abnormalities and the control group ($p = 0.035$).

Regression analysis showed a significant direct correlation between urinary β_2 microglobulin and urinary microalbumin/creatinine ratio ($r = 0.49$, $p = 0.01$). Meanwhile, GFR did not show any correlation with urinary β_2 microglobulin ($r = 0.19$, $p = 0.4$), or urinary microalbumin/creatinine ratio ($r = -0.02$, $p = 0.9$).

The age of the patients at the present study did not show any significant correlation with urinary β_2 microglobulin, microalbuminuria or GFR ($p = 0.8$, 0.15 and 0.37 respectively).

The area under the receiver operating characteristic (AUROC) curves were 0.86 for urinary β_2 microglobulin ($p = 0.009$) and 0.7 for urinary microalbumin/creatinine ratio ($p = 0.15$), Fig. (1).

Based on the ROC curves the best cutoff level to predict renal tubular dysfunction for urinary β_2 microglobulin was 0.22 mg/l with 70% sensitivity and 100% specificity, and the best cutoff value for urinary microalbumin/creatinine ratio to predict renal glomerular dysfunction was 4.5 with 86% sensitivity and 50% specificity.

Table 1: Renal abnormalities in the studied children with GSD.

Renal abnormalities	*No.*	*%*
Increased urinary β_2 microglobulin	15/27	55.55%
Microalbuminuria	6/27	22.2%
High GFR	4/27	14.8%
Low GFR	4/27	14.8%
Glucosuria	3/27	11.1%
Aminoaciduria	3/27	11.1%
Hypercalciuria	1/27	3.7%
Nephrocalcinosis	1/27	3.7%
Renal stone	1/27	3.7%

Table 2: Combination of renal abnormalities in the studied children with GSD.

Abnormality	**No.**	**%**
No abnormality (n = 6)	6	22.2%
Single abnormality (n = 12)		
Increased urinary β_2 microglobulin	6	22.2%
Low GFR	3	11.1%
High GFR	2	7.4%
Microalbuminuria	1	3.7%
Multiple abnormalities (n = 9)		
Two abnormalities **(n = 6)**		
Increased urinary β_2 microglobulin and microalbuminuria	2	7.4%
Increased urinary β_2 microglobulin and hypercalciuria	1	3.7%
Increased urinary β_2 microglobulin and low GFR	1	3.7%
Increased urinary β_2 microglobulin and high GFR	1	3.7%
Increased urinary β_2 microglobulin and Renal stone	1	3.7%
More than 2 abnormalities **(n = 3)**		
Increased urinary β_2 microglobulin, microalbuminuria, aminoaciduria, glucosuria and nephrocalcinosis	1	3.7%
Increased urinary β_2 microglobulin, microalbuminuria, aminoaciduria, glucosuria and hyperfiltration	1	3.7%
Increased urinary β_2 microglobulin, microalbuminuria, aminoaciduria and glucosuria	1	3.7%

Table 3: Demographic and laboratory findings in the patients groups.

	GSD without renal abnormality (n = 6)	GSD with renal abnormality (n = 21)	p value
Age (years)	10.13 ± 4.15	6.6 ± 4.6	> 0.05
Sex male	4 66.7%	12 57.1%	1.0
female	2 33.3%	9 42.9%	
Serum Creatinine (mg/dl)	0.52 ± 0.13	0.51 ± 0.17	0.9
Serum electrolytes			
Na (mmol/L)	143.00 ± 2.7	140.00 ± 7.36	0.5
K (mmol/L)	4.63 ± 0.87	4.46 ± 0.93	0.75
Ca (mg/dl)	8.92 ± 0.39	8.89 ± 0.71	0.9
P (mg/dl)	4.56 ± 0.92	3.9 ± 1.08	0.2
ALP enzyme (U/L)	410.67 ± 149.61	669.75 ± 393.38	0.1
Blood pH	7.40 ± 0.00	7.36 ± 0.07	0.04*
HCO_3 (mmol/L)	22.66 ± 3.48	19.27 ± 5.25	0.2
Lactate (mmol/L)	1.30 ± 0.8	1.44 ± 1.16	0.85
Urine pH	5.08 ± 0.2	5.50 ± 0.97	0.08
Urine creatinine (mg/dl)	94.5 ± 42.25	61.12 ± 45.77	0.12

* $p < 0.05$ is considered significant.

Table 4: Comparison of Urinary β_2 microglobulin, microalbumin and calcium in the studied groups.

	GSD without renal abnormality (n = 6)	GSD with renal abnormality (n = 21)	Control (n = 15)	p value
Urinary β_2 microglobulin/ Cr ratio	0.37 (0.22-3.1)	0.41 (0.12-367.0)*	0.22 (0.11- 0.4)	0.035*
Urinary microalbumin/ Cr ratio	8.5 (1.0-16.0)	13.0 (2.0-14.0)	8.9 (2.0-24.0)	0.26
Urinary Ca/Cr	0.01 (0.0-0.1)	0.08 (0.0- 0.4)	-	0.054

Data are represented as Median (Min-Max), $p < 0.05$ is significant

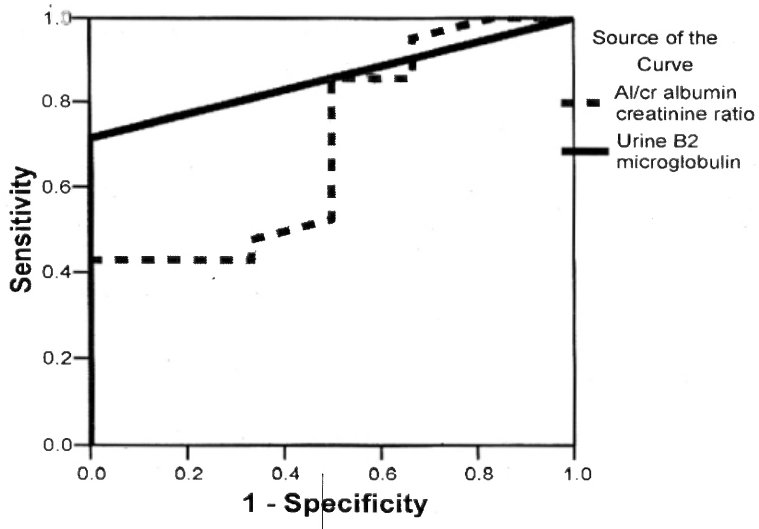

Fig. 1: ROC curve of urinary β_2 microglobulin and urinary microalbumin/Cr ratio.

DISCUSSION

Deficiency of the enzyme glucose-6-phosphatase is the biochemical defect in GSD type 1. Normally this enzyme is present in the liver, intestine and kidneys[15]. Lack of the enzyme in the kidney makes it obvious that glycogen storage will not be restricted to the liver but also the kidney will be involved, possibly resulting in renal damage. Many authors detected a generalized proximal tubular disorder in other types of hepatic glycogenosis, similar to that of GSD I, which was also associated with hyperfiltration, microalbuminuria and glomerular mesangial expansion[4,16-20].

Twenty one of our patients (78%) had one or more renal abnormalities; while only six (22%) showed no laboratory or sonographic evidence of renal abnormalities.

β_2 microglobulinuria was the most frequently detected abnormality; as it was high in 15/21 (71.4%) of our patients. β_2 microglobulin is a polypeptide that is freely filtered and then mostly reabsorbed and degraded in the proximal renal tubule, urinary β_2 microglobulin is a marker of proximal renal tubular dysfunction[30]. At the same time, acidosis was significantly more common in patients with renal abnormalities when compared with those without renal abnormalities. Many authors detected β_2 microglobulinuria, generalized aminoaciduria, phosphaturia and/or renal tubular acidosis in patients with GSD I[4,8,18].

Abnormalities in GFR were detected in 8/21 patients with renal abnormality. Four patients had glomerular hyperfiltration, and 4 had glomerular hypofiltration. The age of patients with high GFR was beyond one year. Similar results were reported by many authors[6,10,21-23]. Lin et al. detected renal hyperfiltration in 2/5 of their patients; their ages were below 18 months on first evaluation[24]. Visser et al. reported that progressive renal disease in GSD I starts

with a silent period of hyperfiltration that is already present in the 1st year of life[25]. In a considerable number of patients, after a period of silent hyperfiltration, renal damage develops with proteinuria, hypertension and renal dysfunction later on[15]. Hyperfiltration - induced proteinuria or pathological glomerular changes are relatively late complications of GSD I and would therefore not be seen in patients as young as ours or as those of Lin et al. whose patients' ages were below 13 years of age.

Microalbuminuria was higher in the group with renal abnormalities when compared to the group without abnormalities; however the difference did not reach statistical significance. Many authors stated that microalbuminuria may develop at the end of the first or second decade of life and is an early detectable manifestation of progression of renal disease[15,19,21]. Visser et al. recommended estimation of urinary albumin regularly in patients suffering from GSD I[25]. Microalbuminuria observed before 5 years of age must be differentiated from urinary excretion of small proteins caused by proximal tubular dysfunction[20].

The overall incidence of microalbuminuria in our patients was 6/27 (22%). In a study done by Weinstein et al.[4], they detected increased urinary microalbumin excretion (> 20 μg/min) in 8/26 (31%) of their patients, and clinical albuminuria (> 300 mg/24 hr) in two patients (8%). The mean age of their patients was older than that of our patients (20.8 ± 5.1 versus 7.4 ± 4.6 years). We detected a higher level of urinary microalbumin/creatinine ratio in the renal group when compared to the non-renal and control groups, although the difference did not reach statistical significance. This might be explained by the young age of our patients. In the London series, the proteinuria in GSD I was greater than other GSDs and directly related to the age ($r = 0.41$, $p < 0.03$)[23]. The age of our patients did not show any significant correlation with the urinary microalbumin/creatinine ratio ($r = -0.29$, $p = 0.15$). Of 14 patients with GSD I, Baker et al. found increased microalbuminuria in 3 teenaged patients and proteinuria of 2 to 8 gm in another 3 patients[10]. In the series reported by Reitsma-Bierens et al. three patients aged 2-22 years had proteinuria[21].

Renal enlargement was described by Von Gierke in the first pathological description of hepatorenal glycogenosis and is regarded as a common feature of GSD I[10,15,18,23,26]. None of our patients had detectable nephromegaly on ultrasonographic examination.

Renal stones or nephrocalcinosis were common findings in patients with GSD I, although these have mostly been reported in adults[1]. We detected renal stone in only one patient and nephrocalcinosis in another one. Fick and Beek reported a child with GSD Ia who had bilateral enlarged echogenic kidneys and medullary calcium deposition at the age of 6 months[27]. Restaino et al. also reported five GSD I patients with renal calculi at ages ranging from 3-11 years[8]. During the initial evaluation of their 5 patients, Lin et al. detected nephromegaly and increased echogenicity[24]. Three of them had nephrocalcinosis or renal stones, and all were younger than 18 months, with one as young as 3 months. The combination of low

urinary citrate and increased urinary calcium excretion likely explains the high incidence of nephrocalcinosis and nephrolithiasis in subjects with GSD Ia[4]. We detected hypercalciuria in patients with renal abnormalities compared to those without abnormalities, although the difference did not reach statistical significance ($p = 0.054$).

Fanconi-like syndrome was detected in 3 patients, in the form of glucosuria with normal blood glucose level (euglycemia), aminoaciduria and subclinical acidosis. One of these patients had clinical and radiological evidence of rickets, another one had nephrocalcinosis. These three patients were stunted in growth with weight and height below 5th percentile. They were from the same family and they had a picture of Fanconi-Bickel syndrome which is a rare type of GSD. It is an autosomal recessive disorder of carbohydrate metabolism characterized by hepatorenal glycogen accumulation, Fanconi nephropathy, and impaired utilization of glucose and galactose. Clinical signs as originally described by Fanconi and Bickel are hepatomegaly secondary to glycogen accumulation, fasting hypoglycemia, a characteristic tubular nephropathy, rickets, and markedly stunted growth[28]. Saltik-Temizel et al. concluded that Fanconi-Bickel syndrome should be borne in mind in patients presenting with hepatomegaly and tubular dysfunction[29].

Early institution of therapy may explain why proximal renal tubular acidosis is not seen frequently in GSD I and many authors suggested that it is secondary to the poor metabolic control of GSD I[1,19,30].

Urinary β_2 microglobulin (mg/dl) in this study showed better sensitivity and specificity than its ratio per creatinine in prediction of renal involvement in our patients. This could be explained by the presence of increased renal tubular secretion of creatinine in cases with reduction of GFR. This increase may result in artificially low U Pr/Cr values[31,32]. Since medical laboratories do not require 24 hours urine collection for β_2 microglobulin measurement, unlike for microalbumin, and propose random urine as a suitable specimen for measuring this parameter using its absolute reference value, we propose urinary β_2 microglobulin as the most suitable test - with its high statistical significance (p value = 0.009) - for predicting renal involvement. The area under ROC of urinary β_2 microglobulin was 0.86; at which we could define one single cut-off level of 0.22 mg/dl that gave 70% sensitivity and 100% specificity. The area under ROC for albumin/creatinine ratio was 0.7, with 86% sensitivity and 50% specificity at cut-off level of 4.5, (p value = 0.15).

In conclusion, renal abnormalities in the form of high urinary β_2 microglobulin, microalbuminuria, abnormalities in GFR, whether high or low, are commonly detected in GSD. Fanconi-like syndrome, nephrocalcinosis and renal stones are less frequently encountered.

Urinary β_2 microglobulin, can be considered the gold standard for early detection of renal involvement in patients with GSD. Routine testing of urinary β_2 microglobulin is recommended in these patients before institution and during follow-up of metabolic control.

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