Renal Involvement in Various Pediatric Liver Diseases: Review of Literature and Report on Tyrosinemia Cases

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By

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Abstract

Background: Hereditary tyrosinemia type 1 (HT1) is an increasingly recognized inborn error of metabolism among Egyptian children.

Aim: To define the presenting clinical, biochemical and imaging features, the outcome of NTBC therapy and liver transplantation in a cohort of Egyptian children diagnosed with HT1.

Methods: The study was carried out at the Pediatric Hepatology Unit at Cairo University, Children's Hospital. HT1 was diagnosed by quantification of succinylacetone (SA) in dry blood spots.

Results: Twenty-two cases were diagnosed with HT1 over a period of 3 years from August 2006 to July 2009. Infants presenting with focal hepatic lesions and hepatomegaly (n=13) were significantly younger at diagnosis than those presenting with rickets (n=5) (median age 3 vs. 10 months; p= 0.05). Alpha fetoprotein was highly elevated in all cases. Seven children died within few weeks of diagnosis before therapy was initiated. Ten patients were treated with NTBC. The response to NTBC treatment was apparent by a steep drop in serum AFP and undetectable SA in urine within 2 months. Three children underwent living donor liver transplantation after treatment with NTBC for 10, 18 and 22 months respectively. Despite adequate response to therapy there is limitation in use of NTBC because of financial issues. The explanted livers were all cirrhotic with no dysplasia or malignant transformation.

In conclusion: Focal hepatic lesions are the commonest presentation of HT1 patients and they present at an earlier age than rickets. NTBC is effective but very expensive. Liver transplantation is still considered in HT1 patients.

Keywords: tyrosinemia, hereditary tyrosinemia type 1, hepatorenal tyrosinemia, NTBC, liver transplantation, Egypt, infants, children.

CONTENTS

List of Abbreviation

ADPKD	Autosomal dominant polycystic kidney disease
ARPKD	Autosomal recessive polycystic kidney disease
AFP	Alpha-fetoprotein
AGT	Alanine:glyoxylate aminotransferase
ALA	Aminolevulinic acid
ALT	Alanine transaminase
AP	Alkaline phosphatase
ASD	Atreial septal defect
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CHF	Congenital hepatic fibrosis
CMV	Cytomegalo virus
CNIs	Calcineurin inhibitors
CNS	Central nervous system
DBS	Dried blood spot
DPM	Ductal plate malformation
DTRs	Depressed deep tendon reflexes
eNOS	Endothelial NO synthase
ERG	Electroretinogram
FAA	Fumarylacetoacetate
FAH	Fumarylacetoacetate hydrolase
FAO	Fatty acid oxidation
FBS	Fanconi-becile syndrome
FHF	Fulminant hepatic failure
G6Pase	Glucose-6-phosphatase
G6PT	Glucose-6-phosphate translocase, or transporter
GA-II	Glutaric aciduria type II
Gal-1-P	Galactose-1-phosphate
GALE	Galactose 4 epimerase
GALT	Galactose 1-phosphate uridyltransferase
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
GLUT2	Glucose transporter 2
GO	Glycolate reductase
GR	Glyoxylate reductase
GSD	Glycogen storage disease
GSD-I	Type I glycogen storage disease
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus

HFI	Hereditary Fructose Intolerance
HPR	Hydroxypyruvate reductase
HRS	Hepatorenal syndrome
HT1	Hereditary tyrosinemia type 1
ICU	Intensive care unit
K-F	Kayser-Fleischer
LC-MS/M/MS	Liquid chromatography tandem mass spectrometry
LKM	Liver-kidney microsomal
MPGN	Membranoproliferative glomerulonephritis
NO	Nitrous oxide
NSAID	Non steroidal anti inflammatory drugs
NTBC	Nitro-4-trifluoro-methylbenzyol-1,3cyclohexanedione
OLT	Orthotopic liver transplantation
p value	Probability value
PAS	Periodic acid-Schiff
PBD	Peroxisome biogenesis
PBG	Porphobillinogen synthase
PCR	Polymerase chain reaction
PH	Primary hyperoxaluria
PH1	Primary hyperoxaluria type 1
PH2	Primary hyperoxaluria type 2
p-HPPD	Parahydroxyphenylpyruvic acid dioxygenase
PT	prothrombin time
PTT	Partial thromboplastin time
PVR	Prepherial vascular risistance
RTA	Renal tubular acidosis
SA	Succinylacetone
SNS	Stimulated sympathetic nervous system
SPSS	Statistical Package for the Social Sciences
TNF	Tumor necrotic factor
TTN	Transient tyrosinemia of the newborn
TTN	Transient tyrosinemia of the newborn
UTIs	Urinary tract infections
VC	Vasoconstrictors
VD	Vasodilators
VLCFA	Very long chain fatty acid
VSD	Ventrecilar septal defect
WBC	White blood cell
ZWS	Zellweger syndrome

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Introduction

On the basis of several clinical and experimental researches, it is possible today to deepen the different mechanisms regarding kidney and liver relationship. There are many alternations which may occur in the kidney secondary to liver disease. The liver may be affected by renal disorders, also both liver and kidney diseases may be associated in certain disorders ***(Wong and Blendis, 2001).***

In all cases the various pathological mechanisms by which the kidney diseases occurred secondary to liver diseases can be divided into:

1. Renal functional impairment:

Renal functional impairment is mainly considered due to hemodynamic dearrangement with a progressive decrease in peripheral vascular resistance (PVR), an increase in cardiac output and rate which are the characters of hyperdynamic circulation leading to outer cortex renal ischemia ***(Gentlini and La Villa, 2008)***.

2. Metabolic renal damage:

Metabolic renal damage is due to abnormal serum levels of bile acids, bilirubin and perhaps toxic hepatic molecules which induce tubular dysfunction. Renal tubular acidosis (RTA) type I which is the most common renal disorder between hepatic patients (30% -50%) is the best example for this group ***(Epstein, 1996)***.

3. Organic renal impairment:

Organic renal impairment is principally based on immunological response to viral antigens and abnormal hepatic products with presence of immunocomplexes and cryoglobulins in the blood and their deposition in the subendothelial and subepithelial glomerular areas. Deposition of

immunocomplexes and cryoglobulins lead to complement activation, mesangial cell proliferation and monocyte-macrophage cell infiltration ***(Gines et al., 1997b)***.

The association of renal and hepatic abnormalities can be found in different congenital malformation syndromes, hereditary metabolic disorders which are capable of alternating liver and kidney function, immunological, toxic and septic diseases ***(Shet et al., 2002*)**. In patients with liver cirrhosis, both glomerular and tubular dysfunctions can be observed; also in the course of liver transplantations an increased rate of renal dysfunction was observed ***(Wong, 2002).***

Aim of the work

Hypothesis 1: Renal involvement is not uncommon among children suffering from a variety of liver diseases. When a hepatologist is confronted with a child suffering from liver disease and shows symptoms or signs of renal involvement, the hepatologist seeks a pediatric nephrologist's opinion. Multidisciplinary approach to this child will be beneficial, but a lack of systematic review hinders this goal.

Aim 1: To review the literature about all types of possible renal involvement in pediatric patients with all types of liver disease. This review might be used as a guideline by the pediatric hepatologist and nephrologist to approach a child with both liver and kidney disease.

Hypothesis 2: Tyrosinemia type 1 (hepatorenal tyrosinemia, OMIM No. 276700) is a rare autosomal genetic disorder caused by mutations in the gene encoding for the enzyme fumarylacetoacetate. The clinical and pathological manifestations involve mainly the liver, kidney and peripheral nerves. Starting 2006, diagnosis of tyrosinemia became available for Egyptian children; since then 22 cases have been diagnosed and some of them received treatment in the form of NTBC. Tyrosinemia cannot be considered a rare metabolic liver disease among the Egyptian population.

Aim 2: Because of the availability of diagnostic and therapeutic tools; tyrosinemia will be selected as an example of a disease that involves both the liver and the kidney to be explored in this thesis.

CHAPTER ONE

Renal Involvement in Pediatric Liver Diseases

I-Renal Involvement in Metabolic Liver Diseases:

1-Glycogen storage disease type 1:

Type I glycogen storage disease (GSD-I) is an autosomal recessive disorder due to the deficiency of glucose-6-phosphatase activity in the liver, kidney and intestine ***(Labrune, 2002)***. This deficiency impairs the ability of the liver to produce free glucose from glycogen and from gluconeogenesis ***(Guven et al., 2006).*** Since these are the two principal metabolic mechanisms by which the liver supplies glucose to the rest of the body during periods of fasting, it causes severe hypoglycemia ***(Kasahara et al., 2009; Bernier et al., 2009).***

There are two different subtypes of type I glycogen storage disease called type Ia and type Ib. GSD Ia is caused by a deficiency of the glucose-6-phosphatase (G6Pase) enzyme in liver, kidney and other organs of the body (***Lee and Leonard, 1995)***. GSD Ib is caused by a deficiency in glucose-6-phosphate translocase, or transporter (G6PT) enzyme that helps in transporting G-6-Pase enzyme from one point to another ***(Brix et al., 1995)***.

Reduced glycogen breakdown results in increased glycogen storage in liver and kidney, causing enlargement of both ***(Iyer et al., 2007).*** If GSD-I disease has been ineffectively treated there will be disturbed renal function which will be manifested by persistent proteinuria, hypertension, renal stones, altered creatinine clearance or a progressive renal insufficiency ***(Chen and Burchell, 1995)***. Glomerular hyperfiltration is seen in the early stage of the renal dysfunction and can occur even before proteinuria ***(Martens et al., 2009 and Cabrera Abreu et al., 2004)***.

Ultrasonographically demonstrable renal stones and/or nephrocalcinosis are frequently found in GSD-I patients especially in older children ***(Simoes et al., 2001),*** with renal colic, hematuria, and passage of stones are the clinical manifestations ***(Cochat et al., 2009).*** Although hyperuricemia is a feature of the GSD-I, the stone analysis in certain patients showed predominant calcium oxalate monohydrate and a small amount of calcium phosphate without uric acid composition ***(Iida et al., 2003)***.The exact mechanism of renal stones in GSD-I is not clear but chronic acidosis and hyperuricemia may be the contributing factors ***(Weinstein et al., 2006)***.

Fanconi-like syndrome can occur rarely in GSD-1 with the proximal renal tubular defects include (microglobulinuria, generalized amino-aciduria, phosphaturia, renal tubular acidosis and rarely glycosuria) ***(Chen and Van Hov, 1995).*** It is observed that Fanconi-like syndrome typically occurs in young patients who have not received any specific therapy for GSD-I ***(Wolfsdorf et al., 1997)***.

The predominant renal histology in patients with longstanding proteinuria (average 10 years) is focal segmental glomerulosclerosis and interstitial fibrosis in various stages of progression ***(Correia et al., 2008)***. Diffuse membrane proliferative glomernlonephritis, interstitial nephritis and crescentic glomerulonephritis ***(Lee et al., 1995; Mundy et al., 2003)*** have been reported in patients without proteinuria or only moderate proteinuria (<1 g/24 h) ***(Bodamer et al., 2002)***. Increased mesangial matrix and cellularity, thickening, wrinkling, and lamellation of glomerular basement membrane with glycogen deposition are the characteristic alterations in GSD-1 ***(Chou et al., 2002; Koeberl et al., 2007)***.

The risk factors for the development of focal segmental glomerulosclerosis are hyperfiltration, hypertension, hyperlipidemia and hyperuricemia ***(Restaino et al., 1993; Leuzzi et al., 2003)***.

Secondary amyloidosis involving the kidneys has been reported in GSD-Ia in patient who underwent liver and kidney transplantation ***(Brix et al., 1995)***.

2- Fanconi-Bickel syndrome (FBS):

Fanconi-Bickel syndrome is a rare type of glycogen storage disease (GSD) due to homozygous or compound heterozygous mutations within glucose transporter 2 (GLUT2) which is the gene encoding the most important facilitative glucose transporter in hepatocytes, pancreatic cells, enterocytes, and renal tubular cells ***(Sakamoto et al., 2000)***.

Patients usually first present at an age of 3 to 10 months with the typical combination of clinical symptoms in the form of hepatomegaly secondary to glycogen accumulation, glucose and galactose intolerance, fasting hypoglycemia (***Parvari et al., 1997)***, tubular nephropathy, and severely stunted growth**.** The diagnosis of FBS is easily established in cases that show the combination of all these typical clinical signs ***(Santer et al., 2002)***.

At the early stage the patient may have fever, vomiting, failure to thrive, and chronic diarrhea, but later on patients typically develop a very protuberant abdomen, a moon shaped face, with fat deposits on shoulders and abdomen ***(Pascual et al., 2004; Watanabe et al., 2005)*** as shown in figure 1. Growth and puberty are severely retarded with signs of hypophosphatemic rickets like swelling of joints, bowing of the legs, pathological fractures and teeth problems ***(Sahin et al., 2000)***.

The kidneys of most patients are relatively large ***(Akagi et al., 2000; Riva et al., 2004)*** with signs of generalized tubular dysfunction (hyperaminoaciduria, hyperphosphaturia, hypercalciuria, hyperuricosuria,