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The Kidney Involvement In Inborn Errors Of Metabolism

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Abstract— **Inborn errors of metabolism are characterized by a significant heterogeneity in pathophysiological mechanisms and clinical manifestations. A variety of kidney disorders, inherited or acquired, can consist clinical signs of metabolic disorders. The most frequent of them include Fanconi syndrome, renal tubular acidosis, nephrolithiasis, renal cysts and acute kidney injury. On the other hand, many types of inborn errors of metabolism (carbohydrate disorders, lysosomal disorders, organic acidemias, mitochondrial disorders, purine and pyrimidine disorders) can be associated with specific renal disorders. Investigation for renal manifestations should be a necessary part of the routine follow-up of these children, while the recognition of specific patterns of renal involvement must raise suspicion for an underlying inborn error of metabolism.**

Index Terms— **kidney, renal manifestations, Fanconi, nephrolithiasis, tubular acidosis, inborn errors of metabolism.**

I. Introduction

Inborn errors of metabolism consist a heterogeneous group of disorders involving multiple organ systems. They may be individually rare, but collectively they are quite common and can appear at any age group. Moreover, although they tend to be considered as childhood disorders, actually signs can arise at any age. Under this view every pediatrician should be familiar with clinical signs from all organ systems that may be indicative of a metabolic defect [1].

The aim of this educational review is to briefly discuss most common renal manifestations associated with specific inborn errors of metabolism and provide clues about appropriate diagnostic approach.

II. Renal Manifestations in Inborn Errors of Metabolism

Kidney diseases (either congenital or acquired) can be the only symptom leading to the diagnosis of an underlying metabolic defect. They can also consist additional findings revealed incidentally during diagnostic work-up or they can appear later in the course of the disorder complicating the prognosis. Moreover, specific renal manifestations are common between different metabolic disorders.

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In general, metabolic disorders most frequently associated with renal manifestations are lysosomal storage disorders, organic acid disorders, fatty acid oxidation disorders, peroxisomal disorders, disorders of purine and pyrimidine metabolism and carbohydrate disorders. The underlying pathophysiological mechanism of kidney injury in these cases includes accumulation of intermediate metabolism products or disturbed energy production and consequent multiorgan impairment, although the exact cause may not be always elucidated [2].

In a microscopic level histological findings are more often located in cells of proximal and distal tubules, in podocytes, in interstitial macrophages, as well as in glomerular capillary endothelium and include accumulation of storage material and cytoplasmic vacuoles/spheroids [2].

A. *Fanconi syndrome*

Fanconi syndrome is characterized by inadequate reabsorption in the proximal renal tubules of the kidney leading to various electrolyte disorders and growth failure. Inborn errors of metabolism including Fanconi syndrome in their clinical features (either as a primary or as a secondary finding) and their basic traits are summarized in Table 1. Cystinosis, a lysosomal storage disease, is the most common cause [2-5]. However, renal phenotype in these patients may be variable in extent in some cases and may consist a selective proximal tubulopathy rather than real Fanconi syndrome.

B. *Tubular acidosis*

Renal tubular acidosis is characterized by an inability to appropriately acidify the urine along with a normal serum anion gap and it is separated into 3 main types: I (distal), II (proximal) and IV. Type III consists a combined type of proximal and distal renal tubular acidosis [6]. Types II and III can consist clinical features of specific inborn errors of metabolism. (Table 2)

Tubular acidosis type II is encountered in patients with methylmalonic aciduria (organic aciduria), as well as in patients with pyruvate carboxylase deficiency (mitochondrial metabolism disorder). With regards to combined tubular acidosis, it can be a clinical feature in carnitine-palmitoyltransferase deficiency (a disorder of fatty acid oxidation). It should be noted that although adult form of carnitine-palmitoyltransferase deficiency type II consists an exclusively myopathic form, kidney damage can arise from

Table 1:Inborn errors of metabolism associated with Fanconi syndrome

Disorder	Type of disorder	Age of onset	Clinical manifestations from other systems	Inheritance	Treatment
Hereditary fructose intolerance	Carbohydrate disorder	infancy	vomiting, sweating, lethargy, coma after fruits and vegetables introduction	autosomal recessive	diet free from fructose
Galactosemia	Carbohydrate disorder	neonatal to early infancy	liver failure, developmental delay, cataract	autosomal recessive	diet free from lactose and galactose
Lowe syndrome	Intracellular trafficking of clathrin-coated vesicles	birth	hypotonia, deformities , cataract, mental retardation	X-linked	low protein diet, calcium/potassium/carnitine supplementation
Dent disease	Endocytosis in the proximal tubule	childhood	nephrolithiasis, rickets	X-linked	thiazide diuretics, vit D supplementation
Fanconi-Bickel syndrome (glycogen storage disorder)	Carbohydrate disorder	infancy	hepatosplenomegaly, rickets, puberty delay, growth retardation	autosomal recessive	low galactose diet, vit D/calcium supplementation, replacement of water and electrolytes
Cystinosis	Lysosomal storage disorder	3-12 months	severe growth retardation, cornea deposits, diabetes, nervous system problems	autosomal recessive	cysteamine
Disorders of mitochondrial respiratory chain	Mitochondrial disorder	variable	severe myopathy, lactic acidosis, macroglossia	variable	vitamin supplementation, pyruvate, N-acetylcysteine
Tyrosinemia type I	Lysosomal storage disorder	6 months to early childhood	liver failure, cardiomyopathy	autosomal recessive	nitisinone, low protein diet, liver transplantation

Table 2:Renal tubular acidosis and inborn errors of metabolism

Diagnosis	Type of disorder	Age of onset	Clinical manifestations from other systems	Inheritance	Treatment
Renal tubular acidosis type 2					
1.Pyruvate carboxylase deficiency	1. Carbohydrate disorder	1. prenatal period to early infancy	1. hypotonia, ataxia, microcephaly, blindness, respiratory problems, hepatosplenomegaly	1. autosomal recessive	1. supplementation with thiamine/lipoic acid, biotin, citrate, aspartic acid
2.Methylmalonic aciduria	2. Organic acidemia	2. infancy	2. encephalopathy, seizures, failure to thrive, hepatomegaly, pancreatitis	2. autosomal recessive	2. low protein diet, carnitine, cyanocobalamin, liver transplantation
Combination of type I and II renal tubular acidosis (type 3)					
1. Carnitine palmitoyltransferase I deficiency	1. Disorder of fatty acid oxidation	1. early childhood	1. hypoketotic hypoglycemia, muscle weakness, hepatomegaly	1. autosomal recessive	1. avoidance of fasting, low lipid diet, nighttime feeds
2. Carnitine palmitoyltransferase II deficiency	2. Disorder of fatty acid oxidation	2. neonatal-infancy or adulthood (myopathic form)	2. hypoketotic hypoglycemia, cardiomyopathy, seizures, sudden death, myopathy	2. autosomal recessive	2. triheptanoin, L-carnitine, lipid restriction, avoidance of fasting

Table 3: Nephrolithiasis and inborn errors of metabolism

Stone composition	Diagnosis	Type of disorder	Clinical manifestations from other systems	Inheritance	Treatment
Cystine	Cystinuria	Luminal brush border transporters disorder (proximal renal tubule cells)	chronic pain, hematuria, pyelonephritis, asymptomatic	autosomal recessive	hydration, acetazolamide, citrate, salt/protein restriction, penicillamine
Calcium oxalate	Primary hyperoxaluria	Peroxisomal disorder	hematological problems, renal failure	autosomal recessive	liver and kidney transplantation
Xanthine (xanthinuria type I)	Deficiency of xanthine dehydrogenase	Purine & pyrimidine disorder	renal failure	autosomal recessive	high fluid intake, avoiding foods rich in purine
Xanthine (xanthinuria type II)	Deficiency of molybdenum synenzyme	Purine & pyrimidine disorder	renal failure, brain dysfunction, seizures, microcephaly	autosomal recessive	no specific, experimental trials with co-factor derived from E. coli
Uric acid	Lesch-Nyhan syndrome	Purine & pyrimidine disorder	neuropsychiatric symptoms, renal failure	X-linked	allopurinol
Uric acid	Phosphoribosyl pyrophosphate synthetase superactivity	Purine & pyrimidine disorder	sensorineural deafness	X-linked	allopurinol
Uric acid	Glycogen storage disease type I	Carbohydrate disorder	developmental delay, hepatomegaly, neutropenia, hypoglycemia	autosomal recessive	allopurinol, citrate supplementation, thiazides
2-8-hydroxyadenine	Adenine-phosphoryvosyl-transferase deficiency	Purine & pyrimidine disorder	renal failure	autosomal recessive	allopurinol

C. Nephrolithiasis

Nephrolithiasis consists a relatively common finding in general population and although it may be due to a variety of causes, several inborn errors of metabolism can also account for some of these cases [9]. Patients with nephrolithiasis associated with inborn metabolic diseases have some characteristics in common: onset of the disease during childhood, bilateral/multiple and recurrent stones, presence of extra-renal involvement. The appropriate analysis of stone composition on an available stone is based on highly specific crystal identification and biochemical analyses and can provide useful evidence for the diagnosis of an underlying metabolic defect. (Table 3)

Inherited metabolic defects mainly associated with nephrolithiasis include inborn errors of amino acid metabolism (cystinuria), disorders of purine and pyrimidine metabolism (Lesch-Nyhan syndrome, xanthine dehydrogenase deficiency, phosphoribosyl pyrophosphate synthetase superactivity, adenine-phosphoryvosyl-transferase deficiency), hyperoxaluria and glycogen storage disease type I [9-12]. In most of these disorders nephrolithiasis consists an early symptom. On the contrary, in glycogen storage disease type I it occurs later during the evolution of the defect [11,12].

D. Additional renal manifestations

A variety of additional kidney disorders, congenital or acquired and varying from mild to severe, have also been reported in children with inborn errors of metabolism, including organic acidurias, fatty acid oxidation disorders, peroxisomal disorders, amino acid disorders and glycogen storage diseases. (Table 4) In general, it is estimated that at least 10% of patients who progress to renal-replacement therapy have an inherited kidney disease. These conditions include both structural and functional disorders, among which are counted diseases resulting from inborn errors of metabolism [13].

It should be mentioned that several of the entities described in Table 4 either include a broad spectrum of differential diagnosis (tubulointerstitial nephritis) or consist life-threatening situations requiring emergent medical intervention (hemolytic-uremic syndrome), thus leading to a late diagnosis of the definite underlying disorder. However, inborn errors of metabolism could provide the

pathophysiological background for many cases of kidney problems of "idiopathic" origin.

Finally, acute kidney damage could arise from uncontrolled myoglobinuria due to metabolic defects characterized by extensive muscular damage [13-17]. (Table 4)

III. Diagnostic approach

All the above entities are characterized by the presence of non-specific signs and symptoms: dehydration, electrolyte disorders, failure to thrive, myoglobinuria, abnormal urine color, renal cysts. A thorough analysis of an arterial blood gas test can offer valuable information and guide further investigation. More specifically, hypochloremic metabolic acidosis with increased anion gap classically points inborn metabolic disorders [18,19]. The laboratory investigation for such disorders may be financially unaffordable for many centers and should be primarily focused on treatable diseases. On the other hand, the deeper knowledge of the associations between clinical renal manifestations and underlying errors of metabolism permits a more cost-effective approach preventing from unnecessary investigations. defect, even beyond infancy [20,21]. Although diagnosis of rare inborn errors of metabolism may be difficult, specific findings from the kidneys can appropriately and cost-effectively guide diagnostic procedure, narrowing the spectrum of possible metabolic defects. Moreover, investigation for kidney disorders should be a necessary part of the routine follow-up of these patients.

On the other hand, acute kidney injury may consist a complication of poor control of a metabolic disorder. Current treatment approach is mainly based on dietary interventions, which exert a palliative effect on kidney disorders, as well as on kidney transplantation. More studies are awaited to further investigate the effect of new therapeutic practices (e.g. enzyme replacement therapy) on renal manifestations in this population.

Table 4: Other renal disorders associated with inborn errors of metabolism

Renal manifestations	**Disorder**
Renal cysts	• Peroxisomal disorders (Zellweger syndrome) • Fatty acids oxidation disorders (e.g. (multiple deficiency acyl-CoA dehydrogenase, carnitine-palmito-transferase II deficiency)
Hemolytic- Uremic syndrome	Cobalamin metabolism disorder
Nephrotic syndrome, tubulointerstitial nephritis, glomerulonephritis	• Organic acidurias (e.g. methylmalonic) • Glucogen storage disease type I
Acute renal failure with myoglobinuria	• Disorders of glycolysis • Fatty acids oxidation disorders (e.g. carnitine-palmito-transferase II deficiency)

References

[1]. Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia,1969-1996. Pediatrics. 2000;105:e10.

[2] Olson C, Silva JL, D'Agati FG. Hepstinstall's Pathology of the kidney. 7th ed. Jennette, Philadelphia, United States; 2015

[3] Wang LC, Lee WT, Tsai WY, Tsau YK, Shen YZ. (2000) Mitochondrial cytopathy combined with Fanconi's syndrome. Pediatr Neurol. 2000;22:403-406.

[4] Bockenhauer D, Bokenkamp A, van't Hoff W, LevtchenkoE, Kist-van Holthe, et al. Renal phenotype in LoweSyndrome: a selective proximal tubular dysfunction. Clin J Am Soc Nephrol. 2008; 3:1430-1436.

[5] Nesterova G, Gahl WA. (2013) Cystinosis: the evolution of a treatable disease. Pediatr Nephrol. 2013; 28:51-59.

[6] Magen D, Berger L, Coady MJ, Ilivitzki A, Militianu D, et al. A loss-of-function mutation in NaPi-II a and renal Fanconi's syndrome. N Engl J Med. 2010; 362:1102-9.

[7] Santos F, Ordóñez FA, Claramunt-Taberner D, Gil-Peña H. (2015) Clinical and aboratory approaches in the diagnosis of renal tubular acidosis. Pediatr Nephrol. 2015;30:2099-2107.

[8] Karet FE. Inherited renal tubular acidosis. Adv Nephrol Necker Hosp 30: 147-162

[9] Battle D, Ghanekar H, Jain S, Mitra A.Hereditary distal renal tubular acidosis: new understandings. Annu Rev Med. 2001;52:471-484.

[10] Jaeger P. Genetic versus environmental factors in renal stone diseases. Curr Opin Nephrol Hypertens. 1996; 5:342-346.

[11] Pak NY. Medical management of nephrolithiasi —a new, simplified approach for genetic practice. Am J Med Sci. 1997; 313:215-219.

[12] Cochat P, Pichault V, Bacchetta J, Dubourg L, Sabot JF, et al. (2010) Nephrolithiasis related to inborn metabolic diseases. Pediatr Nephrol 25:415-424

[13] Chen YT. Type I glycogen storage disease: kidney involvement, pathogenesis and its treatment. Pediatr Nephrol. 1991;5:71-76.

[14] Capelli I, Battaglino G, Baraldi O, Ravaioli M, Cuna V, et al. Kidney Transplantation and inborn errors of metabolism. G Ital Nefrol. 2015;32, pii: gin/32.S64.6.

[15] Huemer M, Scholl-Bürgi S, Hadaya K, Kern I, Beer R, Seppi K, et al. Three new cases of late-onset cblC defect and review of the literature illustrating when to consider inborn errors of metabolism beyond infancy. Orphanet J Rare Dis. 2014, doi: 10.1186/s13023-014-0161-1.

[16] Wilson GN, de Chadarévian JP, Kaplan P, Loehr JP, Frerman FE, et al. Glutaric aciduria type II: review of the phenotype and report of an unusual glomerulopathy. Am J Med Genet. 1989; 32:395-401.

[17] Paul EA, Guttenberg M, Kaplan P, Watkins D, Rosenblatt DS, et al. (2013) Atypical glomerulopathy associated with the cblE inborn error of vitamin B_{12} metabolism. Pediatr Nephrol. 2013; 28:1135-39.

[18] Blau N, Duran M, Blaskovics ME. Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases. 2nd ed. Springer, Berlin–Heidelberg-New York; 2003

[19] Hoffmann GF, Zschocke J, Nyhan WL. Inherited metabolic diseases. A clinical approach. 1st ed. Springer-Verlag, Berlin-Heidelberg; 2010

[20] Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. Pediatrics. 1998; 102:E69.

[21] Evangeliou A, Lionis C, Michailidou H, Spilioti M, Kanitsakis A, et al. Inherited metabolic disorders in Crete and the involvement of primary health care physicians in early diagnosis. J Inherit Metab Dis. 2001; 24: 877-80.