INTRODUCTION

Renal and renovascular hypertension accounts for the majority of children with secondary hypertension. In adolescents, essential hypertension becomes increasingly common ***(Batosh and Aronson, 1999)***.

The cause of essential hypertension is likely to be multi factorial; obesity, genetic alterations in calcium and sodium transport, vascular smooth muscle reactivity, the rennin angiotensin system, and insulin resistance have been implicated in this disorder ***(Bernstein, 2008)***.

Normotensive children of hypertensive parents may show abnormal physiologic responses that are similar to those of their parents when subjected to stress or competitive tasks, the offspring of hypertensive adults, as a group, respond with greater increases in heart rate and blood pressure than do children of normotensive parents ***(Bernstein, 2008)***.

Sympathomimetic agents used as nasal decongestants, appetite suppressants and stimulants for attention deficit disorder produce peripheral

vasoconstriction and varying degrees of cardiac stimulation and may cause hypertension in adolescents ***(Bernstein, 2008)***.

In renal failure, a defect in renal sodium excretory function leads to an abnormal pressure natriuresis relationship and activation of renin-angiotensin-aldosterone system, contributing to the development of hypertension and progression of kidney disease ***(Phillips, 2005)***.

Evidence now strongly indicates a role for the Sympathetic Nervous System (SNS) in the patho-genesis of hypertension in renal failure. Hypertension occurs commonly and early in renal disease and is paralled by increases in SNS activity, as indicated by increased muscle sympathetic nerve activity and circulating catecholamines ***(Phillips, 2005)***.

Plasma levels of vanillylmandilic acid (VMA), a catecholamine metabolite more commonly measured in urine, are increased about 15-fold in patients with renal failure compared to those with normal kidney function, clearance of VMA is entirely dependant on renal elimination ***(Hoeldtke, 1989).***

AIM OF THE WORK

The aim of this work is to evaluate the urinary vanillylmandelic acid (VMA) as a marker of pediatric hypertension in patients with chronic renal disease. Its correlation with clinical manifestations of hypertension and renal function tests will be done.

GLOMERULAR DISEASES

Pathogensis:

Glomerular injury may be a result of genetic, immunologic, or coagulation disorders. Immunologic injury is the most common cause of glomerular disease and results in glomerulonephritis which is a generic term for several diseases and a histopathologic term signifying inflammation of the glomerulal capillaries (***Chadban and Atkins, 2005***).

Pathology

The glomerulus may be injured by several mechanisms but has only a limited number of histopthologic responses; accordingly, different disease states may produce similar microscopic changes. Proliferation of glomerular cells occurs in most forms of glomerulornephritis and may be generalized, involving all glomeruli, or focal involving only some glomeruli while sparing others ***(Fogo, 2004)***.

Proliferation commonly involves endothelial and mesangial cells and is frequently associated with an increase in the mesangial matrix (***Chadban and Atkins, 2005***).

Crescent formation in Bowman's capsule is a result of proliferation of parietal epithelial cells. Crescents develop in several forms of glomerulonephritis are thought to be a response to fibrin deposited in Bowman's space ***(Fogo, 2004)***.

Sclerosis refers to the presence of scar tissue within the glomerulus (this term refers to an increase in the mesangial matrix). Tubulointerstitial fibrosis is present in all patients with glomerular disease who develop progressive renal injury. This fibrosis is initiated by injury to the renal tubules, resulting in mononuclear cell infiltrates that release soluble factors that have fibrosis promoting effects (***Chadban and Atkins, 2005***).

Renal diseases are classified into:

I. Conditions particularly associated with hematuria.

II. Conditions particularly associated with proteinuria.

III. Tubular disorders.

IV. Toxic nephropathies-renal failure

(***Davis and Avner, 2008***)

I. Conditions particularly associated with hematuria

Causes of hematuria in children:

a- Glomerular causes:

1) Isolated renal disease:

- IgA nephropathy.
- Alport syndrome.
- Thin glomerular basement membrane nephropathy.
- Post-infectious GN (post streptococcal GN).
- Membranous nephropathy.
- Membranoproliferative GN.
- Focal segmental glomerulorsclerosis.
- Antiglomerulor basement membrane disease.

2) Multi system disease:

- Systemic lupuserythromatosus nephritis.
- Henoch. Schonlein purpura nephritis.
- Wegener granulamatosis.
- Polyrateritis nodosa.
- Good posture syndrome.
- Hemolytic-uremic syndrome.
- Sickle cell glomerulopathy.
- HIV nephropathy.

(***Davis and Avner, 2008***)

b- Extra glommerular causes of hematurea: as crystalluria, hemoglobinopathy (***Davis and Avner, 2008***).

c- Anatomic abnormalities associated with hematuria:

- *Autosomal recessive polycystic kidney disease (ARPKD):*

Also known as infantile polycystic disease and presented with bilateral flank masses, renal insufficiency, hypertension and hepatasplenomegally related to hepatic fibrosis (***Dell et al., 2004)***.

- *Autosomal dominant polycystic kidney disease (ADPKD):*

This systematic disorder is the most common hereditary kidney disease affecting many organ systems as liver, pancreas, spleen and ovaries. Intracranial aneurysms may be a cause of mortality in adults but are rarely reported in children (***Dell et al., 2004)***.

Presentations with gross hematuria are common within 1-2 days after the onset of an apparent viral upper respiratory tract infection in many forms of gomerulonephritis, such as IgA nephropathy, and

typically resolve within 5 days. This relatively short period contrasts to a latency period of 7-21 days occurring between the onsets of a streptococcal pharngitis or impetiginous skin infection and the development of poststreptococcal glomerulonephritis. Gross hematuria in these circumstances may last as 4-6wk. Gross hematuria may also be seen in children with glomerular basement membrane (GBM) disorders such as hereditary nephritis (Alport syndrome) and thin GBM disease. These glomerular diseases may also present as microscopic hematuria and/or proteinuria without gross hematuria (***Davis and Avner, 2008***).

Approximately 10% of children with gross hematuria have either an acute or chronic form of glomerulonephritis that may be associated with a systemic illness. The gross hematuria, which is usually characterized by brown or cola-colored urine, may be painless or associated with vague flank or abdominal pain (***Davis and Avner, 2008***).

Patients with hermaturia may present with a number of symptoms suggestive of specific disorders. Tea or cola colored urine, facial/body edema, hypertension, and oliguria suggest the acute nephritic

syndrome. Rash and joint complaints suggest Henoch-schönlein purpra (HSP) nephritis or SLE nephritis. Frequency, dysuria, and unexplained fever suggest a urinary tract infection, whereas renal colic suggests nephrolithiasis. A flank mass may signal hydro-nephrosis, cystic disease, renal vein thrombosis, or tumour. Hematuria with headache, visual changes, epistaxis, or heart failure suggests significant hyper-tension (***Davis and Avner, 2008***).

II. Conditions particularly associated with proteinuria

Individuals found to have fixed proteinuria on a first morning urine sample on 3 consecutive days (>+1 on dipstick, or protein/creatinine ratio >0.2) are thought to have renal disease and this fixed proteinuria may be caused by glomerular or tubular disorders (***Wilmer et al., 2003***).

Causes of glomerular proteinuria:

- Focal segmental glomerulosclerosis.
- Mesangial proliferative glomerulonephritis.
- Membranous nephropathy.
- Membranoproliferative glomerulonephritis.
- Amyloidosis.

- IgA nephropathy.
- Acute postinfectious glomerulonephritis.
- Lupus nephritis.

Causes of tubular proteinuria:

- Wilson disease.
- Cystinosis.
- Renal dysplasia.
- Tubulo interstitial nephritis.
- Polcystic kidney disease.

(***Vogt and Avner, 2008***)

Nephrotic syndrome:

Nephrotic syndrome is primarily a pediatric disorder and is 15 times more common in children than adults (***Vogt and Avner, 2008***).

Pathophysiology:

The underlying abnormality in nephrotic syndrome is an increase in permeability of glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The characteristic features of nephrotic syndrome are:

- Heavy proteinuria (40mg/m^2/hr in children).

- Hypoalbuminemia (<2.5g/dL).
- Edema.
- Hyperlipidemia.

(***Vogt and Avner, 2008***)

Cangenital Nephrotic Syndrome:

The most common cause of congenital nephrotic syndrome in infants within the first 3mo of life is Finish-type congenital nephrotic syndrome, which is an autosomal recessive disorder. The clinical features of this syndrome are massive proteinuria (detected in utero by increased α-fetoprotein), large placenta, edema, prematurity, respiratory distress and separation of cranial sutures (***Holmberg et al., 2004***).

III. Tubular disorders

Renal tubular acidosis (RTA) is a disease state characterized by abnormal anion gap, metabolic acidosis resulting from either impaired bicarbonate reabsorption or impaired urinary acid (hydrogen ion) excretion, it is classified into:

- Proximal (type Π) RTA.
- Distal (type I) RTA.
- Hyperkalmic (type IV) RTA.
- Rickets associated with renal tubular acidosis

(***Alper, 2002***)

Inherited tubular transport abnormalities:

a- Bartter syndrome:

Bartter syndrome inherited as autosomal recessive disorder with a biochemical features of hypokalemic metabolic alkalosis with hypercalciuria, resemble those seen with chronic loop diuretic use and reflect a defect in sodium, chloride and potassium transport in the ascending loop of Henle (***Hebert, 2003).***

b- Gitelman syndrome:

It is an autosomal recessive disorder characterized by hypokalemic metabolic alkalosis, with distinct feature of hypocalciuria hypomagnesemia resembles those of chronic thiazide diuretic use (***Kleta and Bockenhauer, 2006***).

Tubulointerstitial nephritis (TIN):

Tubulointerstitial nephritis is classified into acute and chronic forms. The classic presentation of acute TIN is the triad of fever, rash and arthralgia in the setting of arising serum creatinine value.

The chronic TIN most commonly occurs as a result of an underlying congenital renal disease or may occur as an idiopathic disease ***(Alon, 2004)***.

IV. ***Toxic nephropathies – Renal failure***:

a) Toxic nephropathy.

b) Renal cortical necrosis.

c) Renal failure.

i. Acute renal failure.

ii. Chronic kidney disease.

(***Vogt and Avner, 2008***)

a) Toxic nephropathy:

Medications, diagnostic agents (iodinated radiographic contrast Media) and chemicals may alter the kidney directly (though reduction of renal blood flow, acute tubular necrosis, intratubular obstruction) or indirectly (through induction of an allergic or hypersensitivity reaction in the vessels or interstitium) (***Chesney and Jones, 2004***).

In addition, marine animals, reptiles and insects produce a number of biologic nephrotoxins that result in acute renal failure (***Chesney and Jones, 2004***).

b) Renal cortical necrosis:

In newborns, cortical necrosis is most commonly associated with hypoxic/ischemic insults as perinatal asphyxia, but, after the neonatal period, cortical necrosis is most commonly seen in children with septic

shock or sever hemolytic-uremic syndrome (***Palapattu et al., 2001***).

c) Renal failure:

i. Acute renal failure:

Acute renal failure (ARF) is a clinical syndrome in which a sudden deterioration in renal function results in the inability of the kidney to maintain fluid and electrolyte homeostasis. ARF occurs in 2-3% of children admitted to pediatric tertiary care centers and in as many as 8% of infants in the neonatal intensive care unit (***Vogt and Avner, 2008***).

ii. Chronic Kidney Disease:

The prevalence of CKD in the pediatric population is approximately 18 per 1 million. The prognosis for the infant, child, or adolescent with CKD has improved dramatically over the past 4 decades because of improvements in medical management (aggressive nutritional support, recombinant erythropoietin, and recombinant growth hormone), dialysis techniques, and renal transplantation (***Vogt and Avner, 2008***).

Definition:

Chronic kidney disease (CKD) is defined as either renal injury (proteinuria) and/or a glomerular

filtration rate <60ml/min/1.73m^2 for >3 months (***Seikaly et al., 2003).***

Etiology:

In children, CKD may be the result of congenital, acquired, inherited, or metabolic renal disease, and the underlying cause correlates closely with the age of the patient at the time when the CKD is first detected (***Elnahas and Bello, 2005***).

In patients less than five years congenital abnormalities, congenital nephrotic syndrome, polycystic kidney disease, renal vein thrombosis, and hemolytic uremic syndrome are more common. In patients more than five years of age, acquired diseases as lupus nephritis, metabolic disorders (cystinosis, hyperoxaluria) and certain inherited disorders (polycystic kidney disease) may present throughout the childhood years (***Vogt and Avner, 2008***).

Pathogenesis:

Progressive injury with ongoing structural/ metabolic genetic diseases usually occurs. However, compensatory hyperfiltration, may cause progressive damage to the surviving glomeruli, that contribute to renal functional decline (***Vogt and Avner, 2008***).