INTRODUCTION

Vesicouretric reflux "VUR" or the retrograde flow of urine from the bladder into the ureter is an anatomic and or functional disorder with potentially serious consequences such as renal scarring, hypertension, and renal failure ***(Fanos and Cataldi, 2004).***

Although many children with VUR have no symptoms of UTI yet the prevalence of VUR in normal children has been estimated at 0.4–1.8% ***(Skoog et al., 2010).***

Among infants prenatally identified by ultrasound to have hydronephrosis and who were screened for VUR, the prevalence was 16.2% (range: 7–35%).The incidence of VUR is much higher among children with urinary tract infection "UTI" reaching 30–50%, depending on age ***(Skoog et al., 2010).***

Renal scarring occurs in approximately 10% of patients in the prenatal hydronephrosis group. Scarring in the kidney may adversely affect renal growth and function, with bilateral scarring increasing the risk of renal insufficiency. Renal nephropathy (RN) may be the most common cause of childhood hypertension. 10–20% of children with RN develop hypertension or end-stage renal disease ***(Estrada et al., 2009).***

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical

presentation, and anatomy. The main goal in the management of patients with VUR is the preservation of kidney function by minimizing the risk of pyelonephritis ***(Estrada et al., 2009).***

The standard imaging tests include renal and bladder ultrasonography, voiding cystourethrography (VCUG), and nuclear renal scanning. The standard criterion for the diagnosis of VUR is detection on VCUG, especially at the initial work-up. VCUG provides precise anatomic detail and allows grading of VUR ***(Darge and Riedmiller, 2004)***.

Dimercaptosuccinic acid (DMSA) is the best nuclear agent for visualizing the cortical tissue and differential function between both kidneys. DMSA scanning is used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans during follow-up ***(Westwood et al., 2005).***

DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis ***(Lee et al., 2009).***

The objective of conservative therapy is prevention of febrile UTI. Conservative therapy is based on the understanding that VUR can resolve spontaneously, mostly in young patients with low-grade reflux. Intermittent antibiotic prophylaxis or continuous antibiotic prophylaxis (CAP), and bladder rehabilitation in patients with LUTD. Circumcision during early infancy may be considered part of the conservative

approach regular follow-up with imaging studies (eg, renal ultrasonography, VCUG, nuclear cystography, or DMSA scanning ***(Wheeler et al., 2004).***

Surgical treatment

There are different surgical modalities described in the management of VUR these include endoscopic injection of bulking agents or ureteral reimplantation. With the availability of biodegradable substances, endoscopic subureteral injection of bulking agents has become popular & various results around techniques, long outcome & its value alternative to long-term antibiotic prophylaxis and surgical intervention in the treatment of VUR in children.

Still many authors believe that open surgical techniques whether by intravesical and extravesical techniques is the standard for the surgical correction of VUR method has specific advantages and complications.

The introduction of laparoscopy both conventional and robot-assisted laparoscopic approaches is a new modality that needs to be considered in management of VUR & can yield outcomes comparable to their open counterparts in terms of successful resolution of reflux. Further studies are needed to define the costs and benefits of both approaches ***(Marchini et al., 2011).***

AIM OF THE WORK

The aim of this work is to discuss vesicoureteric reflux in children and to highlight recent methods of diagnosis, evaluation and different management technique with outcome. Trying to outline a protocol of management in tertiary referral hospital.

DEMOGRAPHIC, EPIDEMIOLOGY, PREVELANCE, AND ETIOLOGY

Although VUR is common, its overall prevalence is difficult to quantify because many sufferers are asymptomatic, and invasive investigation leading to diagnosis is carried out only when clinically indicated.

Studies carried out from the 1950s to the 1970s on healthy children suggest that up to 1.8% of newborns suffer from VUR ***(Sargent, 2000).***

More recently, it is has been shown that approximately one-third of children with urinary tract infection (UTI) will suffer from this condition ***(Smellie et al., 1998).***

VUR has a well-recognised genetic component, although the mode of inheritance remains unclear. If a child suffers from VUR, there is a 34% chance that infant siblings will also have this condition. In addition, VUR has been shown to be present in 20–66% of the offspring of affected parents ***(Boris and Puri, 2003).***

VUR demonstrates important gender differences, with girls being more likely to suffer than boys. However, girls tend to present later than boys (2–7 years versus 0–2 years) with lower-grade reflux, often of a functional aetiology. Anatomical factors are more important in the aetiology of male disease ***(Rickwood, 2002).***

In another study investigating the incidence of VUR in children with specific reference to age, gender, and race found that younger children are more likely to suffer from VUR than older children, that girls are twice as likely to be affected as boys, and that white children are three times more likely to have VUR than black children ***(Chand et al., 2003).***

There is a genetic predisposition to VUR, with some studies suggesting an autosomal dominant inheritance with variable penetrance, although no specific genetic loci has been defined ***(Jacobson et al., 1999).***

This finding is dramatically illustrated by the high incidence of reflux in siblings and offspring of patients who have VUR ***(Jerkins et al., 1982)***, which has led to the recommendation of screening children who have a first-degree relative with VUR ***(Scott et al., 1997).***

ANATOMY AND EMBRYOLOGY OF VESICOURETERIC JUNCTION AND TRIGONE

Two events proceed simultaneously to govern the ultimate position and integrity of the uretrovesical junction (UVJ). At one point, the embryonic ureter buds from the mesonephric or wolffian duct to define the metanephric duct or early fetal ureter. The wolffian duct (early vas deferens) and early ureter can be thought of as forming the two upper arms of a Y with the distal mesonephric duct as the stem of the Y. While budding is occurring, the distal mesonephric duct is being drawn and incorporated into the region of the urogenital sinus (UGS), which later becomes the bladder. Incorporation continues until the entire stem is absorbed, leaving the two arms of the Y to enter the bladder separately one as the ureter and the other as the vas and ejaculatory duct in the male prostatic urethra (or the vestigial Gartner duct in the female vagina). The two arms of the Y also rotate relative to each other once they contact the urogenital sinus (UGS)/bladder wall resulting in the ureteric opening (UO). Being proximal to the ejaculatory duct orifice. If the ureteral bud reaches the UGS too soon (believed to be due to early budding), over-rotation draws it high and lateral in the bladder wall, leading to inadequate incorporation, insufficient intramural length in the bladder wall, and reflux ***(Mackie et al., 1975).***

If the ureteral bud reaches the UGS too late (due to budding late), insufficient rotation occurs, resultingin an ectopic ureter that is drawn distally and medially, often obstructing in the bladder neck region or elsewhere. Furthermore, early or late budding is also thought to mistarget the contact between bud epithelium and the metanephros, leading to renal malformations, dysplasia, hypoplasia, or even agenesis.

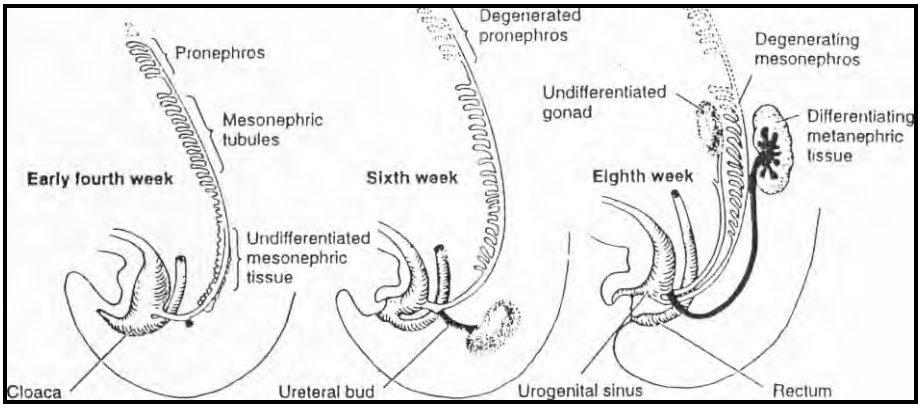

Fig. (1): Schematic representation of the development of the nephric system ***(Tanagho, 2000).***

FUNCTIONAL ANATOMY OF THE ANTIREFLUX MECHANISM

The phenomenon of vesicoureteral reflux represents a balance of several factors. Abnormality in any of these factors alone or in combination will allow or cause the retrograde flow of urine from the bladder up the ureter and ultimately to the renal pelvis and tubules. These factors include the functional integrity of the ureter, the anatomic composition of the ureterovesical junction (UVJ), and the functional dynamics of the bladder

First, for purposes of reflux prevention, the ureter represents a dynamic conduit, which adequately propels the urine presented to it in a bolus fashion, antegrade, by neuromuscular propagation of peristaltic activity. In so doing, reflux is actively opposed. Moreover, if reflux were to occur, depending on its degree and timing, antegrade flow might be expected to keep refluxing urine from reaching the renal pelvis.

The second component is the anatomic design of the UVJ. At the heart of this unique mechanism lies an intramural portion of ureter that travels within the detrusor muscle as it traverses the bladder wall ***(Elbadawi, 1972).***

At the extravesical bladder hiatus, the three muscle layers of the ureter separate. The outer ureteral muscle merges with the outer detrusor muscle to form Waldeyer sheath.

The latter contributes to formation of the deep trigone.

The intramural ureter remains passively compressed by the bladder wall during bladder filling, preventing urine from entering the ureter. Adequate intramural length and fixation of the ureter between its extravesical and intravesical points is required to create this antirefluxing compression valve. Paquin's early dissections of the UVJ in children revealed an approximately 5 : 1 ratio of tunnel length to ureteral diameter in nonrefluxing junctions compared with a 1.4 : 1 ratio in refluxing UVJs ***(Paquin, 1959)***.

Intravesically, the inner muscle of the ureter merges with detrusor muscle to contribute to the superficial trigone. Some of these inner ureteral fibers pass medially to contribute to the intraureteric ridge (Mercier bar).

The cellular and molecular details that characterize normal and refluxing UVJs are still unknown. However, it is likely that in addition to architectural deficiencies of tunnel length, abnormalities in UV smooth muscle and extracellular matrix composition and neural function may contribute to reflux ***(Oswald et al., 2004).***

Opening of the UVJ is achieved by active contraction of the longitudinal muscles within the tunnel. This draws the extravesical and intravesical points of the intramural ureter closer together, shortening and widening the tunnel, and allows

passage of the urine bolus into the bladder. Indeed, when viewed cystoscopically, a lateral displacement of the UO accompanies the classic jet of urine into the bladder. Although such lateral displacement is functionally normal and necessary to permit urine to pass, permanent lateral displacement by virtue of a constitutively short tunnel characterizes the cystoscopic position of the refluxing UO.

Closure of the UVJ results both from compression of the intramural ureter and a return to its full tunnel length as the ureteral muscle relaxes. Thus active and passive mechanisms dynamically reconfigure the tunnel as needed to allow antegrade passage of urine while preventing retrograde flow.

Finally, the existence of local efferent and afferent neuromuscular coordination between the UVJ and the periureteric bladder wall is suggested by neurophysiologic studies that induce elevation or decrease in intraluminal UVJ pressure during bladder filling ***(Shafik, 1996).***

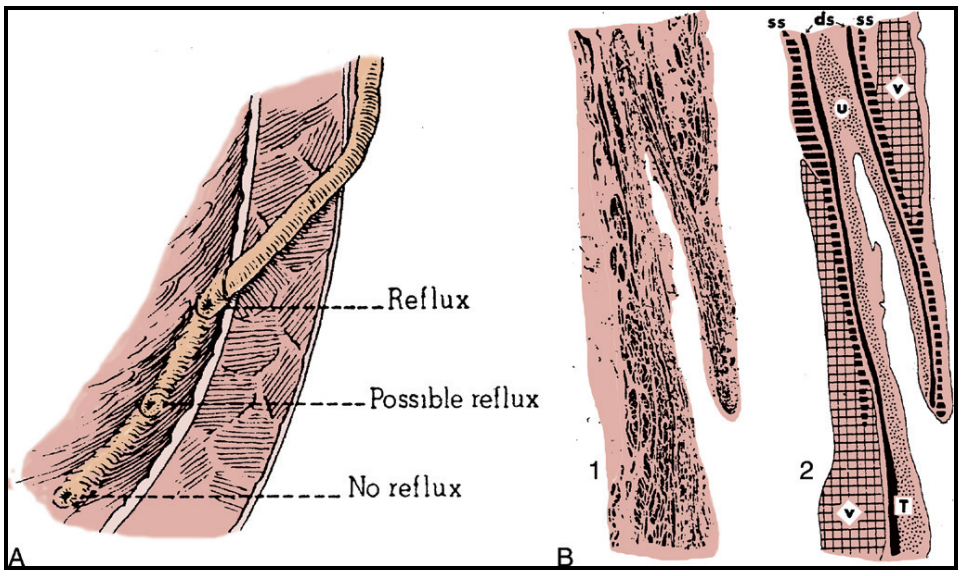

Fig. (2): A, A refluxing ureterovesical junction has the same anatomic features as a nonrefluxing orifice, except for inadequate length of the intravesicalsubmucosal ureter. Some orifices with marginal submucosal tunnels may reflux intermittently. B, Ureterovesical junction in longitudinal section.1, Photomicrograph; 2, diagrammatic representation. The ureteral muscularis (u) is surrounded by superficial (ss) and deep (ds) periureteral sheaths that extend in the roof of the submucosal segment and continue beyond the orifice into the trigonal muscle (t). The relationship of the superficial sheath to the vesicalmuscularis (v) is clearly seen. Transverse fascicles in the superior lip of the ureteral orifice belong to the superficial and deep sheaths. No true space separates ureter from bladder ***(Glenn, 1972).***

PHYSIOLOGY OF THE VESICOURETERIC REFLUX

The urine bolus is transported by ureteric peristaltic from the renal pelvis and reach the UVJ level. The ureter can only shorten its length at this terminal transvesical trajectory because of its anatomical structure. The ureter contracts longitudinally so is able to slide freely within its detrusor wall tunnel and actively retracts the ureteric wall over the urinary bolus so discharging it into the bladder lumen.

When the ureteric orifice is widely opened and no passive antireflux mechanism, the ureteric constriction which discharge the urine into the bladder lumine is still present in the juxtavesical region, preventing retrograde upstream urinary leakage. Further distal immigration of ureteric "contraction wave" into the superfascial trigone reestablishes the passive antireflux mechanism through an active lengthening of the sub mucosal ureteric length ***(Roshani et al., 2000).***

PATHOPHYSIOLOGY AND REFLUX NEPHROPATHY

VUR is defined as the nonphysiologic retrograde flow of urine from the bladder up the ureter into the kidney and is the result of an insufficient vesicoureteral junction.

The severity of VUR is measured using the grading system according to the International Reflux Study Committee ***(Bogaert and Slabbaert, 2012).***

Primary or congenital VUR is caused by a congenital maldevelopment of the vesicoureteral junction, which is too short and has a possible lack of a fixed attachment between the ureter and the detrusor ***(Radmayr et al., 2005).*** Based on observations of incidence of VUR among siblings and twins, it is now known that primary or congenital VUR is autosomal dominantly inherited and is polygenic with variable penetrance and expressivity ***(Chertin and Puri, 2003; Briggs et al., 2010).***

The recommendations for screening in siblings are from both the American Urological Association (AUA**)** ***(Peters et al., 2010)*** and the European Association of Urology (EAU) ***(Tekgul et al., 2011).*** The parents of a child with VUR should be informed about the higher incidence among siblings.

It is recommended that a renal ultrasound be performed in siblings that are not toilet trained. If the renal ultrasound shows any abnormality, VCUG is recommended.

If no ultrasound screening is performed, special attention for UTI and early treatment should be initiated, followed by a complete investigation for VUR.

Secondary reflux develops under the influence of anatomic or functional infravesical obstructions due to inflammatory or neuropathic disorders of the bladder. Although most children with VUR will have excellent long-term prognosis, a small group has a significant risk. This risk can be minimized in areas with good medical health care where prompt diagnosis and treatment of acute UTI is possible ***(Ismaili et al., 2006).***

Less than 1% of the general population has a duplex kidney, and VUR is the most commonly associated anomaly found in duplex kidneys, especially in those presenting with a UTI (70%) ***(Guy et al., 2012)***. VUR almost always occurs in the lower pole moiety, due to its lateral entry and shorter intravesical pathway. If VUR is also seen in the upper pole, one must suspect an incomplete duplication or an ectopic orifice in the bladder neck or urethra and misplacement of the transurethral catheter at the time of the VCUG.

VUR in duplex kidneys can resolve, but it will take longer than in a single system. Surgery, including the eventual correction of the ureterocoele of the upper pole, is challenging but provides excellent results ***(Thomas, 2008)***.