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Review Articles

Congenital Urethral Anomalies in Boys. Part I: Posterior Urethral Valves

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ABSTRACT

Introduction: The aims of this review are one, to consider that congenital urethral anomalies are not a simple disease entity in all patients. This is accomplished by reviewing the evidence for presence of posterior urethral valve subtypes and comorbidity of various unexplained clinical conditions in some children leading to chronic renal failure. The review's second aim is to describe the effects of fetal lower urinary tract obstruction on postnatal bladder function and the consequence of bladder dysfunction on the remaining postnatal renal function.

Materials and Methods: The literature was extensively reviewed concerning the different types of congenital urethral outlet obstruction presentations, diagnosis, different types of treatment modalities, morbidity, mortality, and new concepts for this old problem. These findings were compared with conventional approaches to these anomalies. The 739 published papers on posterior urethral valves were evaluated, and a quarter of those are addressed. All radiologic presentations and figures in this review were selected from among the records of Iranian patients treated by the author during the last 25 years.

Results: A significant overlap of presentation before antenatally diagnosed era was observed. The natural history of these anomalies is becoming clear and the hypothesis of posterior urethral diaphragm is popular among several investigators in comparison to the original valves classification by Young in 1903.

Conclusions: Further molecular investigation of the urinary tract is needed to better understand the pathophysiology of renal and bladder function in children who are born with antenatally diagnosed congenital urethral obstruction. These anomalies must be treated by urologists with a vast experience with valves and other rare congenital urethral anomalies.

KEY WORDS: urethral abnormalities, anterior urethra, posterior urethra, valves

This article is part of a review on the anomalies of the male urethra with unknown etiology or those believed to result from a androgen deficiency. It includes Part I: 1. posterior urethral valves and Part II: 2. anterior urethral valves, 3. lacuna magna (sinus of Guérin), 4. syringocele, 5. megalourethra, 6. urethral duplications, and 7. prostatic urethral polyps.

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Posterior Urethral Valves

Introduction

Posterior urethral valve (PUV) is one of the most common causes of lower urinary tract obstruction in male neonates. Although not precisely known, its prevalence is reportedly 1/8000 to 1/25000 live births.[1,2] PUV has been observed exclusively in boys,[3] but several reports in adults have been published.[4-7] The definitions of many of the disease manifestations have changed in recent years. Advances in the prenatal diagnosis of this disease and subsequent surgical treatment, either intrauterine or immediately after birth, have contributed to a better understanding of the pathophysiology and nature of this disease, as well as considerable improvement in the longevity of affected children.

The primary pathology is a mucosal membrane in the prostatic urethra, although secondary complications of this membrane result in injuries in the kidneys and the urinary bladder, which determine the fate of the children with this primary urethral membrane.[8-11]

Background

PUV was first described in 1515 and subsequently observed at autopsies. In 1802, the first definition for PUV was written and presented in an article on lithotomy.[12] The first report in British journals is found in the *Lancet*, in which Dr Budd reported a PUV in a 16-year-old boy who had died of renal failure.[13] He stated that severe dilation of the kidneys and the urinary tract, as well as renal failure, had all been due to the obstruction caused by the PUV.

In 1913, Young reported the first clinical case of PUV, before which all the cases had been diagnosed postmortem.[14] In 1919, he published a report of 36 cases from the papers of that time, 12 being his own patients and the other 24 from various other papers.[15] It was in this paper in which he presented a classification for the PUV. The numbers of case reports or case series of the patients continued to grow from the early 20th century, so that by 1949, there were 207 published cases of PUV worldwide.[16-18]

In the last 10 years, several hypotheses have been proposed regarding bladder function and its relationship with renal function following correction of the primary obstruction, as well as several urodynamic studies and their relation with renal function and treatment options, all of which has led to major progress in the field. Still, after 300 years since the initial diagnosis of this disease, more than one third of the affected children develop renal failure. In some cases, cystoplasty is needed to decrease the intravesical pressure.[19]

Anatomy and Embryology of the Posterior Urethral Valve

The normal male urethra extends from the bladder neck to the external urethral meatus and is anatomically divided into 2 or 3 portions: the prostatic and membranous portions or the *posterior urethra*, and the spongy portion or the *anterior urethra*. The prostatic urethra, from the base to the tip of the prostate, is the widest and the most distensible part. The urethral crest is a mucosal ridge that gives a specific form to the posterior urethra and is fully apparent in the urethral section. On each side of this crest there is a dip, known as *the prostatic sinus*. In almost half as long as the urethral crest, and there is the verumontanum (colliculus seminalis), a bulge on the posterior urethral floor on which there the foramen of the prostatic utricle lies. The urethral crest continues naturally below the verumontanum and binds from both sides as a small midline bridge. This membrane, extending laterally and downward, eventually vanishes.[3]

The shortest, narrowest, and least distensible part of the urethra is the membranous part, surrounded by the urinary sphincter. Embryologically, the prostatic urethra, up to the prostatic utricle, originates from the vesico-ureteral cloaca and adjoins into the terminal mesonephric duct. The rest of the prostatic urethra includes the urogenital sinus, which is the anterior cloacal portion and is divided by the urogenital septum. The anterior urethra, up to the glans, forms from urogenital fusion or the urethral fold.

The classic form of PUV is in the prostatic urethra, below or after the verumontanum (Figures 1A and 1B). Pathogenetically, PUV is a congenital phenomenon occurring sporadically, although familial forms also have been rarely reported.[20-22] This congenital anomaly is believed to occur due to a mixed effect of a few minor genes and cannot be ascribed to a single gene mutation. Therefore, it is recommended that

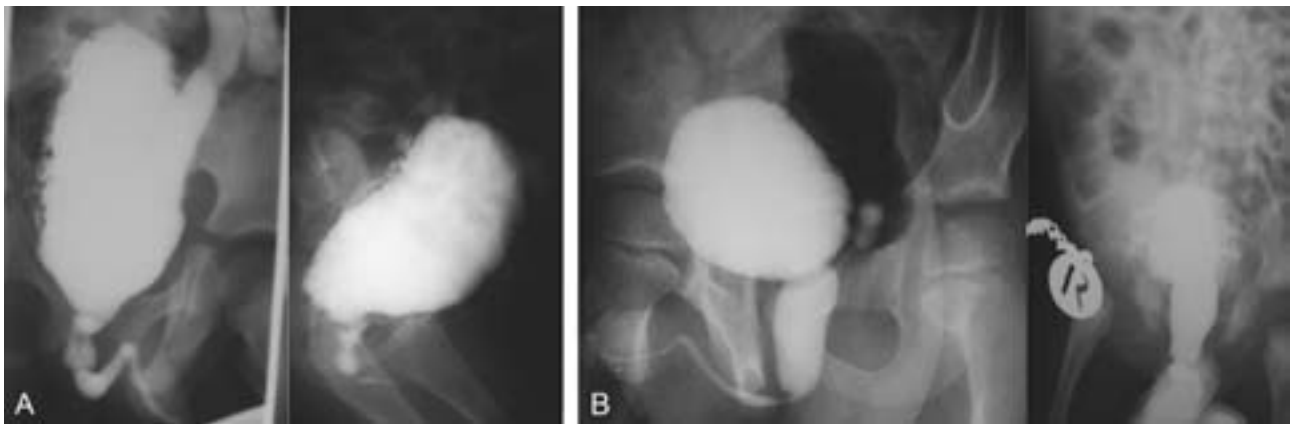

Fig. 1. A. Type I valves. Oblique view shows degrees of obstruction and dilatation of posterior urethra, **B.** Voiding cystourethrogram shows filling defect of obstruction by Type III valves.

all the brothers of the affected child (especially twins) be evaluated, even when asymptomatic, to prevent undiscovered renal damage.[22]

The precise embryologic mechanism of this disease process is not yet known.[23] In 1932, 4 theories were described by Campbell, which remained unchanged until today:

1. Hypertrophy of the urethral mucosal folds, proposed by Tolmatschew[24] in 1870
2. Bazy's theory,[25] the persistence and continuation of the urogenital membrane, proposed in 1903
3. Abnormal development of the Wolffian or Mullerian duct, proposed by Lowsley[26] in 1914
4. Fusion of the colliculus seminalis or the posterior urethral roof epithelium, proposed by Watson[27] in 1922.

None of these theories has been, however, complete and descriptive of the entire pathology of the urethral valve.

Classification of Posterior Urethral Valves

Young described 3 types of PUV.[14] Types 1 and 2 are presented as a bicuspid valve of mucosal folds that attach to the verumontanum in 2 different ways. In the first type, the valve extends from the verumontanum distally, while in the second type, it extends from the verumontanum toward the bladder neck. The third type is in the form of a mucosal web. This third type was the first definition of PUV described in 1856 by the French physician, Jarjavay. The common belief in the current century for the posterior valve is also consistent with the membrane, or the third type definition. In a study reported in 1995 by Kajbafzadeh and colleagues[28] from the United Kingdom, 80% of these valves were of the membranous type, and the other 20% also were initially membranous but ruptured during catheterization for cystography or in the fetal period due to high bladder pressure, which led to its final presentation in the type 1 form, the bicuspid valve.

The issue proposed here is that in some children, although catheterized, one may still observe an unruptured membranous valve. The theory suggested states that the foramen of the membranous valve is not always located peripherally; sometimes it is located centrally, with the catheter passing occasionally through the central foramen without being able to rupture it. A virgin urethra phenomenon has been proposed in this case, stating that if the urethral valve is diagnosed in the fetal period and before birth, and a suprapubic 6-F catheter for cystography is placed immediately after birth without manipulation of the urethra, 80% of the valves appear to be of the virgin type, with a totally different pathophysiology from type 1, which probably ruptured in the fetal period into a bicuspid form.[29]

The above phenomenon was tested in 1969 by Robertson during autopsies of children who had died of this anomaly. At first, he isolated the entire urinary tract including the kidneys, ureters, urinary bladder, prostate, and the entire urethra, and noted that the nature of the PUV was membranous or the third type. He stated that the bicuspid valves were not anatomically correct.[30] The same results were obtained 5 years later in a similar report.[31]

In another study based on the theory of a virgin urethra (urethra not manipulated by a catheter or other device) performed by the author

at a children's medical center on over 30 patients with PUV before birth, the same theory was established–that the PUVs exist in the form of a complete membrane with a small peripheral foramen. At the time, the valve is confirmed by antegrade cystography, and urethroscopy is performed by direct videoscopic view; the posterior valve is seen as a complete diaphragm. It is interesting that a 1-time passage of a urethral catheter causes a rupture of the valve into the triangular bicuspid form or the type 1 in Young classification. Therefore, it seems that all posterior valves are initially of the diaphragmatic type (type 3), which convert into type 1 after the passage of a fine catheter. The type 2 valve does not exist, and it seems that mucosal folds are seen in children with sphincteric dyssynergia due to neurologic or nonneurologic injuries. The distended posterior valve and the folded membranes of the urethral floor that extend from the bladder neck toward the verumontanum have no anatomic relation with the PUV and seem to be a mere clinical flaw (Figure 2A).

Type 4 valves are not true valves but typically presented with a Prune-belly syndrome (Figure 2B). More than 12 radiologic patterns of PUV are shown in Figure 3. It is worth noting that classification of the PUV has no clinical value with regard to treatment and prognosis, and the clinical symptoms are not related to the valve type.[32]

Pathophysiology of the Posterior Urethral Valve

The importance of the posterior valve is based on 2 things: first, the secondary effects of urinary outflow obstruction of the fetal bladder, and second, the secondary effects of bladder function on the fetal kidney, as well as its effects after birth or even after elimination of the urethral valve.

Disorders of Renal Function in the Posterior Urethral Valve

There are multiple mechanisms for renal dysfunction and valve effects on the kidneys. These include the following:

1. Primary renal dysplasia
2. Dysplasia due to urinary outflow obstruction in the fetus and its detrimental effects on nephrogenesis
3. Intrauterine hydronephrosis and secondary destructive effects of obstruction on nephron production in the fetal period, probably due to backward pressure to the fetal kidneys
4. Postnatal urinary tract infections with or without reflux
5. Persistent bladder dysfunction after valve elimination

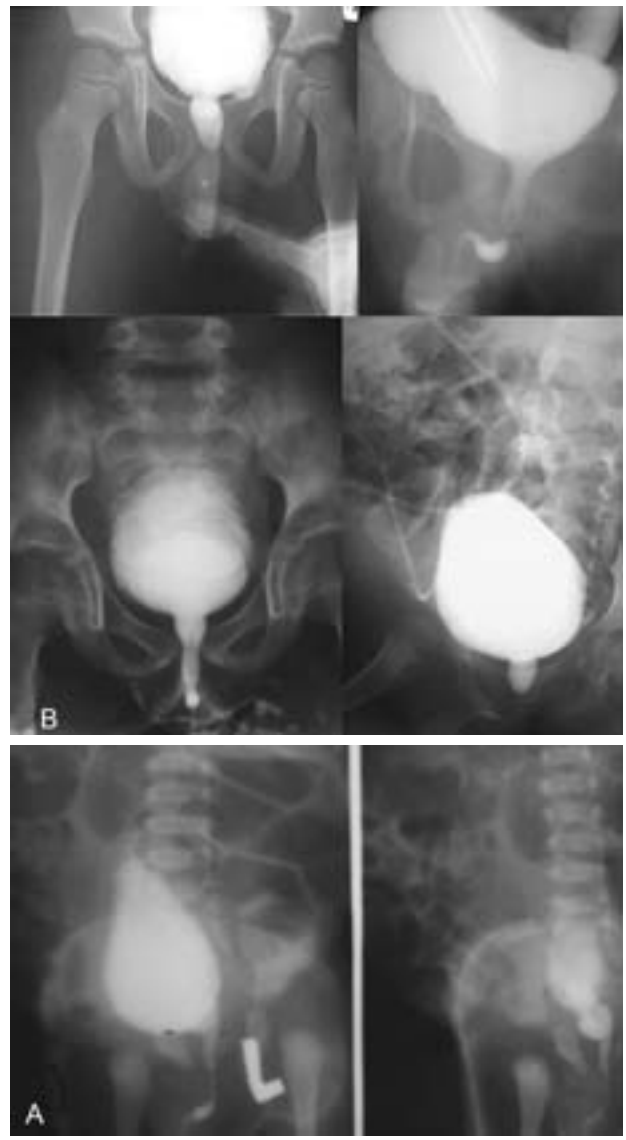

FIG. 2. A. Type II valve prostatic urethral dilatation and mucosal folds are seen in children with sphincteric dyssynergia due to myelomeningocele neuropathic bladder. **B.** Type IV valve in Prune-belly syndrome.

Renal Dysplasia

The simultaneous occurrence of renal dysplasia and PUV is a known fact, although their cause and effect relation is not yet known.[33] Renal dysplasia can be due to either obstruction or teratogenic effects of the valve. Renal dysplasia with urinary reflux is a known phenomenon. In the first evaluation of the children with PUV,

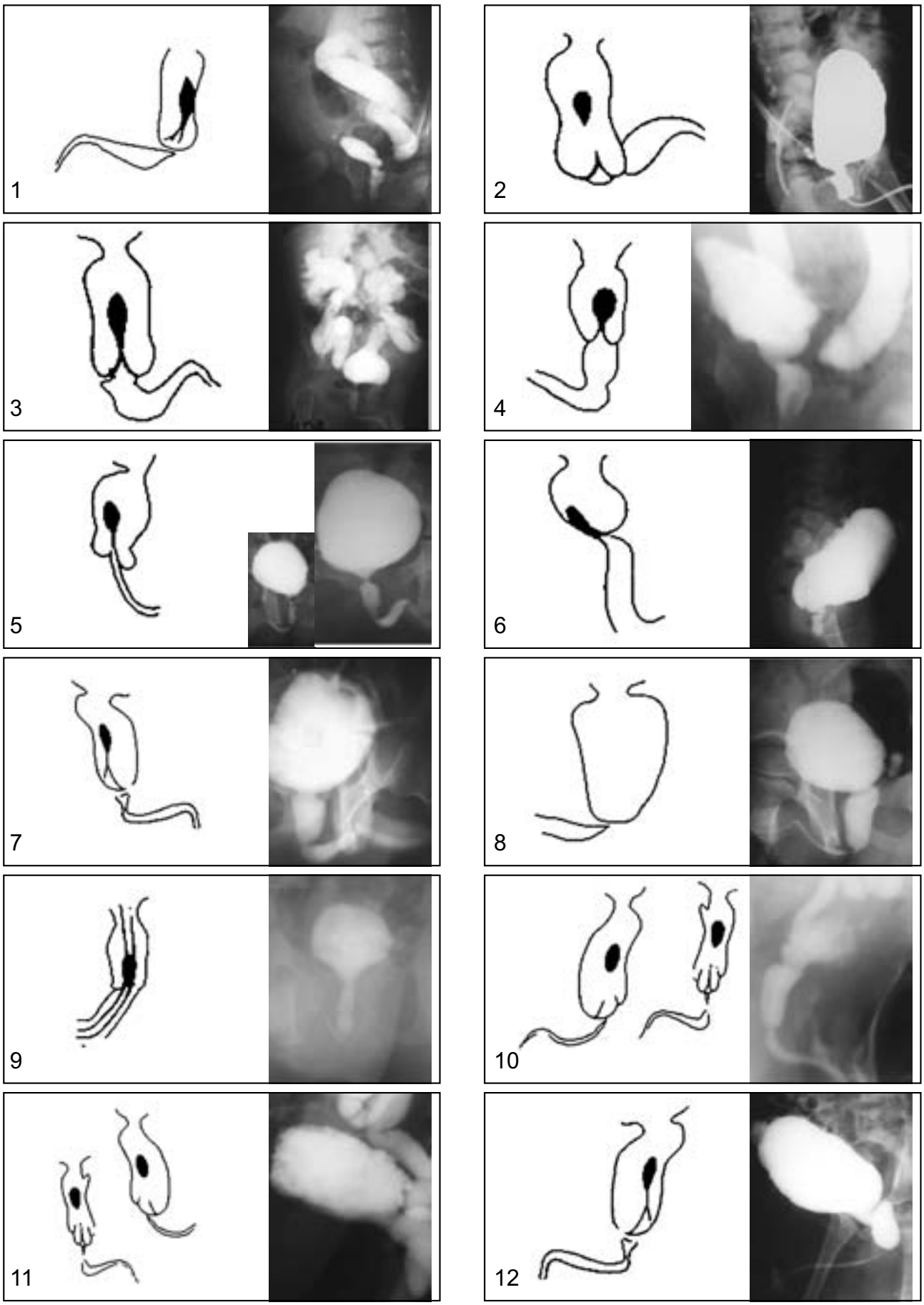

Fig. 3. Tracing of filling defects caused by urethral valves in 12 different urethrograms showing variations in radiograph pattern.

reflux was seen in 30% to 70% of cases.[34] It seems that the presence of reflux at the time of nephrogenesis might cause dysplastic changes in the kidneys. On the other hand, a cystic dysplastic change in a kidney affected by reflux has been reported.[35]

According to some researchers, renal dysplasia is an accompanying feature with PUV and not a secondary cause.[33] In another report on PUV and reflux, histologic findings of 32 kidneys were studied (14 kidneys from autopsies and 18 from nephrectomies of nonfunctioning kidneys of patients with PUV). This study showed that 24 of the kidneys had been dysplastic.[36] Another study confirmed dysplasia, histologically, in 22 nephrectomized renal units.[37] The very important point in this study was that there is a direct relation between the location of the ureteral opening in the bladder and the degree of dysplasia; that is, the higher the grade of dysplasia, the more lateral was the ectopy of the ureteral opening. This study confirms that the cause of dysplasia is a developmental phenomenon rather than a direct effect of reflux or urinary outflow tract obstruction.

Urinary Concentration Disorder in Posterior Urethral Valves

Loss of urinary concentrating power leads to production of a large volume of dilute urine, as observed in children with urinary valves.[38] The prevalence and severity of antidiuretic hormone-resistant nephrogenic diabetes insipidus is not known. In an assessment of 28 patients in 1970, Waldbaum and Marshall observed 2 patients with polydipsia and polyuria, suggestive of nephrogenic diabetes insipidus.[39] There are various other records of the urethral valve and nephrogenic diabetes insipidus in the literature.[40,41] Some researchers have noted that in most children developing renal failure because of PUV, hemodialysis is needed much later, if this failure is accompanied with polyuria.[42]

On the other hand, most children with PUV develop ureteral dilatation following valve resection, due to a 2- to 4-fold increase in urine volume.[43] This group of patients doesn't respond to a 14-hour water restriction. Treatment of these children is very difficult, and they quickly present symptoms of dehydration and acidosis with a minor stress or a gastroenteritislike disease.[44]

Classification of the Upper Urinary Tract Anatomy in Urethral Valve

Hendren classifies the pathology of kidneys and ureters in patients with PUV into 4 groups as follows:

Group 1: no secondary changes are seen in patients with urethral valves in the ureters and kidneys, including paraurethral diverticula, reflux, or upper urinary tract dilatation

Group 2: mild dilatation of the upper urinary tract

Group 3: severe reflux and renal destruction is seen

Group 4; severe destruction of the kidneys, together with hydroureteronephrosis, megaureter, and often azotemia[45]

This classification was used in a group of children with urethral valves (124 cases), with 43% going into group 1, 34% into group 2, 14.5% into group 3, and 8.5% into group 4.[46]

Initial Diagnosis and Clinical Manifestations

Two types of symptomatic presentation and clinical manifestations are seen in these children. The first group shows obstructive symptoms including straining during urination, intermittent voiding with reduced urinary flow rate, and a palpable midline bladder. The second group presents with infectious signs including septicemia, failure to thrive, and urinary tract infections, which are the most prominent features of this disease. In the neonatal and infantile periods, the primary obstructive symptoms are more prevalent, while at older ages, the infectious signs are dominant.[47]

In a study of valve diagnosis, 26% appeared in the first month of life, 23% in the first year, and 51% between the ages of 1 and 15 years.[48] In another report, one third occurred in the first month, one third in the first year, and the rest after 1 year of age. Two decades ago, when diagnostic and treatment advances were performed on fetuses, fetal uropathies were diagnosed and patients affected by PUV could be diagnosed (Figures 4A, 4B, 4C, and 4C).[49]

Initial reports on fetal-stage diagnosis of PUV show a better prognosis for those patients diagnosed prenatally as compared with those occurring after birth.[50] Diagnostic evidence of the urethral valve appears in children presenting with severe bilateral hydronephrosis and

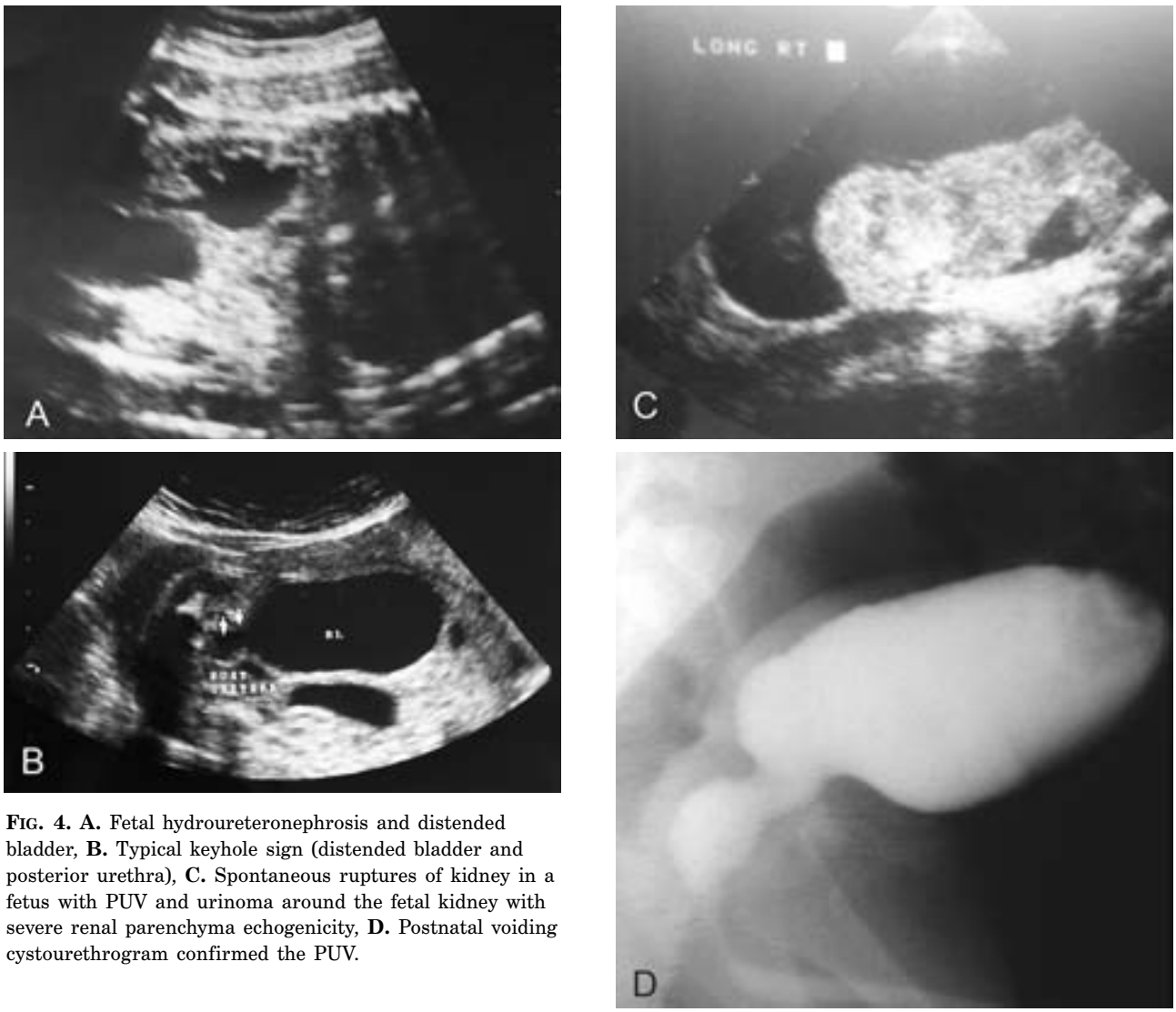

Fig. 4. A. Fetal hydroureteronephrosis and distended bladder, **B.** Typical keyhole sign (distended bladder and posterior urethra), **C.** Spontaneous ruptures of kidney in a fetus with PUV and urinoma around the fetal kidney with severe renal parenchyma echogenicity, **D.** Postnatal voiding cystourethrogram confirmed the PUV.

increased serum creatinine, with or without respiratory problems. Respiratory symptoms in a newborn with PUV might be related to oligohydramnios, which is accompanied by severe pulmonary hypoplasia.[51] These respiratory disorders are more prevalent in children with urine ascites due to spontaneous renal rupture in the fetal period. Diagnosis at older ages seems to come with a better prognosis, as those with renal failure present their symptoms quite early.

Differential Diagnosis of the Posterior Urethral Valve

The differential diagnoses of the posterior urethral valve include the following:

1. Perirenal urinary extravasation[52]
2. presacrococcygeal teratoma[53]
3. Urethral duplication[54]
4. Megalourethra[55]
5. Anterior urethral valve or diverticulum[56]
6. Syringocele and Mormon's ring[57]
7. Prune belly syndrome[58]
8. Urethral hypoplasia
9. Urinary retention
10. Ectopic ureterocele
11. Urethral strictures
12. Anterior or posterior myelomeningocele

Whenever bilateral hydronephrosis with a thick-walled, persistently full bladder is observed in the fetal period, urethral valve should be the first diagnosis. However, the Prune-belly syndrome and neuropathic bladder should also be considered.[58]

Treatment

It is best to drain bladder urine immediately after diagnosis. Placement of a suprapubic 6-F urinary catheter is feasible in most centers after local anesthesia with topical anesthetic creams, and without general anesthesia. When the bladder is empty, normal saline can be infused

into the bladder through the meatus, without urinary catheterization. The advantages of suprapubic catheter placement are that first, it does not lead to urethral infection with its consequent strictures and complications, second, the urethra remains virgin, third, cystography can be performed suprapubically as the catheter can be fixed with a suture, with little chance of its spontaneous displacement, and fourth, a suprapubic catheter can be maintained for a longer period of time.

An important advantage of using a suprapubic catheter is during physiologic urodynamic studies before and after valve destruction, in which vesical pressure measurements can be made in various positions without the use of a urethral catheter. A novel option is fetal surgical intervention for posterior valve and placement of a shunt in the fetal bladder and the amniotic fluid, which can be performed in specific cases by a special team in fetal surgery.

Immediately after placement of the suprapubic catheter after birth, a urine sample can be taken for urinalysis, urine culture, and other parameters. An appropriate antibiotic should be administered thereafter, and in case of the absence of infection, prophylactic antibiotics should be given, especially if a urinary reflux is also present. Hypercalcemia and acidosis are severe and prevalent problems in children with PUV.

Before the invention of fine endoscopic instruments for neonates, various options were suggested for urethral valve removal including perineal urethrotomy,[59] suprapubic cystostomy,[60] and valve destruction using Fogarty balloon,[61] all of which were accompanied by severe complications including urethral rupture, urinary incontinence, and urethral strictures.[9]

A major revolution occurred with the production of neonatal cystoscopes, numbered 7.5 to 8, in which the valve can be operated primarily at every age and at any weight. A hook was made by Whitaker, which could be connected directly to an electrocautery device, that could approach and reach the valve directly and destroy it.[62] Cystography must be performed after valve destruction to ensure complete valve removal. In some children, the creatinine level does not change much even after 2 weeks of bladder drainage.[63]

If there is no change in renal and ureteral dilation by precise sonographic measurement of the diameters, supravesical urinary diversion must be considered. If the pelvic and ureteral diameters are reduced, a vesicostomy may be performed after 2 weeks. If valve destruction is not feasible, as in cases of urethral hypoplasia, where a cystoscope cannot be passed, a vesicostomy may be performed. However, if severe pelvic and ureteral dilation still persists, ureterostomy or pyelostomy should be considered.[63]

Vesicostomy can be closed 1 or 2 years later, and a suprapubic vesical catheter can be fixed. With this, bladder drainage and the status of the urethra may be assessed. If the urethra is back to its normal state and bladder drainage is complete, the catheter may be removed. In a comparison between vesicostomy and primary urinary diversion in the treatment of PUV in neonates and in children who have been initially operated on for valve resection, it has been shown that bladder dysfunction is greater in the first group than those whose valves had been initially operated on. The status of the urethra can be described as either favorable or unfavorable.[34]

The urethra is said to be in a favorable state when the creatinine level decreases quickly, and renal function is good on isotope scan. The presence of a pop-off mechanism reflects a positive prognosis. Conversely, in case of azotemia and renal malfunction on sonography, the child's prognosis must be viewed unfavorably.[53] In all, if the renal failure continues despite all the measures, renal transplantation should be considered, although initially, chances of success in these patients was believed to be less.[64,65] However, if the bladder function and urodynamic and other parameters are fully assessed and the bladder problems treated, there is no difference in transplant outcome in these patients.

Late Complications of the Urethral Valve

Every child with a resected PUV must undergo long-term surveillance and follow-up until puberty and afterward. Parameters like urethral patency, renal function, bladder function, reflux, and urinary tract infections must be considered. One month after valve destruction surgery, serum creatinine level measurement together with cystography and renal ultrasonography and isotope (DMSA) scan must be repeated. If there

TABLE 1. *Long-term follow-up for children with posterior valves*

Types of evaluation	Intervals
Blood pressure measurement	Routinely in every visit
Growth and weight	Routinely in every visit
Creatinine and electrolyte measurements	Initially every 3 months then yearly
Urinary tracts ultrasonography	One month, 3 months, 1 year postoperatively, and then yearly
DTPA isotope scan	At the ages of 3 months and 1 year then yearly
Urodynamics-uroflowmetry	Yearly, since urinary continence
Indirect cystography	At the time of DTPA isotope scan
DMSA isotope scan	Yearly, if UTI and reflux are present
Voiding cystourethrography	1 month after valve resection and yearly for 3 to 4 years

is still an obstruction in the urinary outflow tract, a proper decision must be made and a repeat evaluation be done after 3 months. If the obstruction persists, cystoscopy should be performed. Measurement of the glomerular filtration rate (GFR) with the isotope method (EDTA chromium) gives an accurate portrayal of renal function.[66] Table 1 gives the means of long-term follow-up for children with PUV.

The correct treatment for severe cases of valve, reflux and urinary tract dilation is still debatable. The time for ureteral reimplantation in cases of severe reflux or megaureter is not known. Some believe that the reflux and dilation of the ureter and kidney will resolve spontaneously if the valve is completely removed and if bladder function is normal according to urodynamic studies.[36]

Approach to Reflux in Children with Posterior Urethral Valves

It is not yet certain whether reflux is an anatomically accompanying feature of the urethral valve or is secondary to it. The prevalence of urinary reflux from the bladder to the kidneys is reportedly to be 26% up to 72%. In some initial reports, reflux prevalence was reported as 44%, with 16% being bilateral and 28% being unilateral.[67,68] There is a direct relation between the reflux and the age of disease incidence. The key question is why is the presence of reflux such a determining factor in children with urethral valves. In answer to this, the following are suggested[34]: first, the presence of infection and reflux could lead to scarring and a greater decrease in renal function; second, reflux might have unfavorable effects on bladder function; and third, during voiding, most of the urine enters the kidneys, and the child is said to void in his place and into his kidneys. The dilatation of the posterior urethra in children with PUV and severe reflux is much more evident than it is in a child without reflux (Figures 5A and 5B). After voiding, a high volume of urine flows from the kidneys into the bladder, refilling it immediately. Fourth, it aggravates the function of a dilated ureter; and fifth, if the voiding pressure is high, renal destruction might also be greater.

Reflux is spontaneously resolved in 35% to 50% of cases.[66,68]

Some believe that patients with reflux need not to be operated on, as it will automatically resolve as soon as the bladder function returns to normal.[36] Others believe that the bladder needs to be operated on if the reflux is accompanied by recurrent urinary tract infections.[45] This can occur when the urodynamic performance of the bladder is normal.[1] It must be noted, however, that ureteral reimplantation in a thick bladder is very difficult, several complications are possible, and the chance of failure is very high.[69]

In another study on 82 boys with urethral valves who had long-term follow-up, unilateral reflux by ipsilateral dysplasia continued in 21%, after successful valve surgery. Ten of the cases had a dysplastic kidney upon nephrectomy.[70] It must be noted here that a dysplastic kidney with severe reflux on the same side is a safety valve mechanism for the bladder, so that sometimes, after nephroureterectomy of the dysplastic kidney, bladder pressure increases and the contralateral kidney develops new reflux, a phenomenon referred to as the valve's ureteric reflux and dysplasia (VURD) syndrome.

Prognosis is excellent in children with this syndrome. On the other hand, one must know that if the child is in need of a cystoplasty in the future, the method of choice would be ureterocystoplasty with the use of the dilated

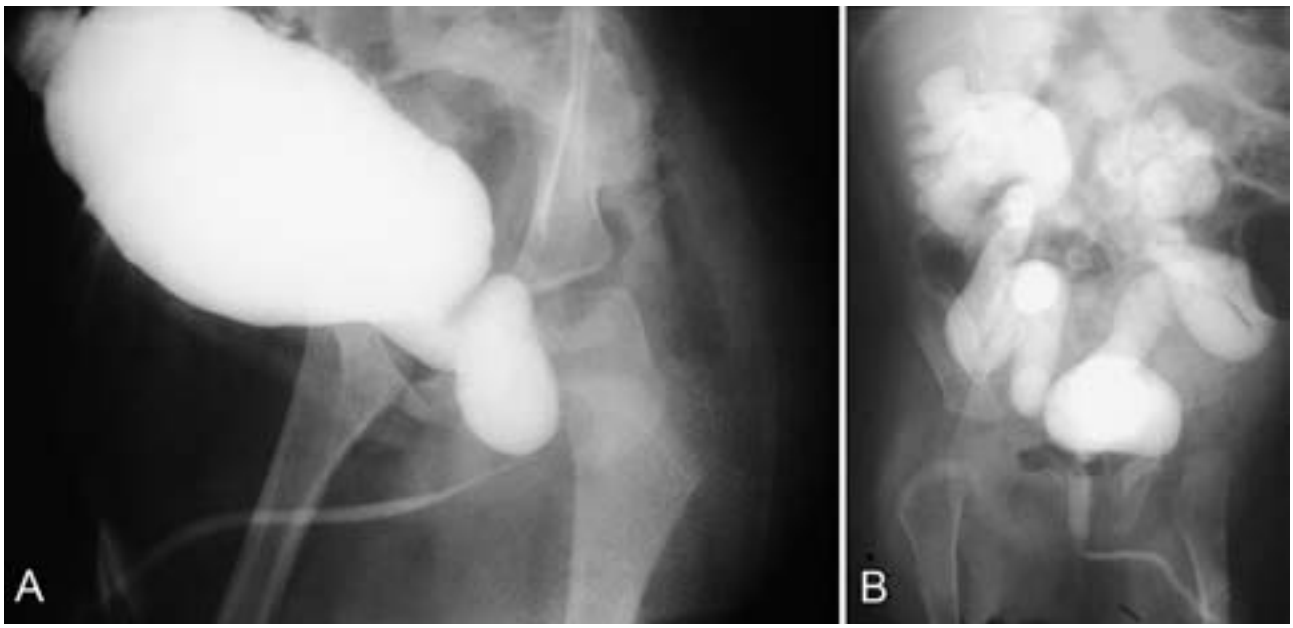

Fig. 5. A. Severe posterior urethral dilatation in a child with PUV and no VUR, **B.** high-grade VUR and less dilatation of posterior urethra in spite of typical PUV.

ureter. In another report of 6 cases of nephroureterectomy, it was observed that a dysplastic kidney can sometimes lead to renal failure.[71] Another long-term study has shown that the presence of reflux in the dysplastic kidney has protective effects on the other kidney, and it is generally advised that nephroureterectomy of the dysplastic kidney be carried out with caution.[72]

Urethral Stricture Following Urethral Valves Resection

All methods of valve surgery carry the risk of a urethral stricture, with a reported prevalence of 8% to 28%.[73,74] The use of a large, unsuitable cystoscope, inappropriate urinary catheter, and especially valve resection in a dry urethra (when there is a vesicostomy) all increase the chance of a stricture.[73] The prevalence of urethral stricture is currently very low.

Undescended Testis and Sexual Function in Boys with Urethral Valves

The prevalence of undescended testis is 12% in these patients. Boys with a PUV might have retrograde ejaculation after puberty, due either to the anatomy of the urethra and the bladder neck, or to valve surgery complications.[48] Fertility is possible for children with a history of valve surgery. However, slow ejaculation is seen in 38% of these children.[10] At times an absence of ejaculation due to an obstruction of the ejaculative tracts has been reported. Paramo has also reported a case of sterility due to retained ejaculation in the posterior urethra.[75]

Prognosis of Children with Posterior Urethral Valves

The prognosis of these children is quite poor. In long-term follow-up, at least one third of such children have a poor outcome with respect to renal function.[76] In one study, 26% of patients older than 18 years with a history of urethral valve had a renal failure.[8] In another study, 50% of children whose valve had been diagnosed before the age of 1 year showed some degree of renal failure.[77] If the patient has a protecting mechanism at birth, the prevalence of renal failure reaches 5%. These factors are valve bladder syndrome, large bladder diverticulum, and fetal urine ascites due to bladder or kidney rupture.

Mortality of the Patients Affected by Posterior Urethral Valve

Mortality of these children was reported to be 40% to 50% in the previous two or three decades,[57,78] having reduced to zero in the previous decade.[53] This improvement is mainly due to a higher awareness of this disease among the physicians, prompt treatment of the urinary tract infections, improvement in surgical instruments and medical treatments, and dialysis and renal transplantation in small children.

Bladder Function in Children with Posterior Valves

The lower urinary tract consists of the bladder and urethra, which compose a single unit. Each part has two functions, reserving urine, and disposing thereof,[79] which is under neural tract support, as well as smooth and striated muscle. The nerves effective in voiding include somatic and autonomic (sympathetic and parasympathetic) nerves. There is no evidence of disordered innervation in urethral valve cases. In these children, the determining point in bladder function is the amount of collagen types I, III, and IV, whose ratio significantly changes because of an outflow tract obstruction of the compliant fetal bladder. This plays a major role in bladder function even after valve removal.

Normally, the bladder fills without any increase in its internal pressure. This occurs because of the bladder's relaxing ability, under the effect of central and local nerves. Paucid vesicoelastic structures, also, enable it to be filled at low pressures. This relation between the change of intravesical pressure (dP) and the change of volume (dV) is referred to as the compliance (C = dP/dV). A change of bladder morphology due to collagen ratio or muscular hypertrophy leads to a reduced compliance.

During natural bladder filling, the pressure increases very slightly or does not increase at all, and this is known as normal compliance.[79] In adults, the raise in bladder pressure after filling with 300 mL of water must be less than 10 cm H2O and at final volume less than 15 cm H2O.[80] The high compliance of the bladder allows it to receive a large volume of urine at a low pressure. Low compliance, on the contrary, means that the bladder receives a low volume of urine at a very high pressure, which predisposes the urinary tract to infections, renal dilation and dysfunction, and renal failure in due course.[38]

These definitions are given according to the international association for disease control. For example, the term "unstable bladder" is used when the bladder contracts automatically during filling and the patient tries to avoid urination.[79] The stimulating factors for this state could be rapid filling, change of position, and coughing. Such contractions are considered involuntary when detrusor contraction pressures exceed 15 cm H2O.[81]

In one study, the results of which were published recently, it was shown that bladder dysfunction in children with PUV is a determining prognostic factor in the probability of developing renal failure in this group of patients. A bladder with poor compliance and myogenic failure has a poorer prognosis, while children with bladder instability will have the lowest prevalence of renal failure following valve removal (Figures 6A and 6B). Some investigators agree that long-term bladder free drainage (vesicostomy) could cause long-term bladder dysfunction.[79]

Bladder Capacity in Children

Normal bladder capacity in children has been calculated by many, eventually giving the following formula for the calculation of bladder capacity with age[82-84]:

Bladder capacity (mL) = (age in years + 2) × 30

Normal bladder capacity of the neonate is given by the following formula:

Newborn's bladder capacity (mL) = weight in kilograms × 7

Natural History Voiding in Children

The voiding phenomenon is a response to increased urine volume in the bladder, in which urethral relaxation and detrusor contraction

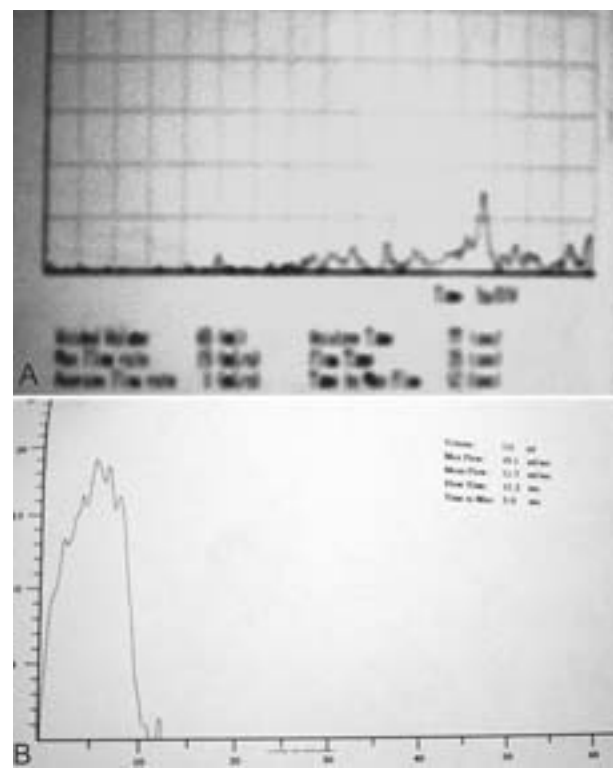

FIG. 6. A. Initial uroflowmetry shows obstructive pattern in a 6-year-old boy with Type III valves. **B.** Uroflowmetry following valves ablation in the same child with a Type III PUV.

occur simultaneously with pelvic floor muscle relaxation and funneling of the bladder neck. This neuromuscular phenomenon is very complex. The relation between bladder pressure and urine flow rate has been studied extensively. One researcher, in 1970, calculated the maximal voiding pressure of the bladder in children as equal to 73.6 cm H2O.[85] Others, however, have calculated this pressure in the adult population as 40 cm H2O to 60 cm H2O.[86]

Urodynamics in Children Affected by Urethral Valves

Urodynamics, one of the most important tests, is the study of lower urinary tract function. Urodynamic studies include the following assessments[87-92]:

1. Urinary history
2. Frequency volume chart
3. Uroflowmetry
4. Urodynamics in the forms of:
   Videourodynamics
   Physiologic urodynamics
   Isotope urodynamics
5. Uroflowmetry and pelvic floor EMG

History is the most important part of the urodynamic assessment. During history taking, one must consider intermittent voiding, narrow-stream voiding with high or low pressure, such that the patient urinates on the scrotum. Moreover, urination with force, severe crying, and squatting during voiding are among the most important issues and initial points in urodynamic studies.

To make a frequency volume chart, the child's parents are asked to calculate the volume of voided urine in every session and record the time and volume in a table. If the child is using diapers, estimated urine volume can be obtained by weighing the diaper before and after each episode of urination. Using this method, the number of voids in 24 hours, average volume of urination, and total daily urine volume are obtained.

Physical Examination

Only rarely is an abnormal point found in the physical examination of children with urethral valves. However, the observation of abnormal hair growth on the skin over the sacral bone, perineal sensory disorders, or abnormal tendon reflexes can all be signs of a neurogenic lesion of the bladder rather than the urethral valve. Urinary flowmetry in children who have reached the age of urinary continence is a very simple and noninvasive test, in which the volume, urine curve form, and maximal voiding in one second must be noted (Figures 7A and 7B). [93]

Ultrasonography of the Urinary Tract

Ultrasonography of the upper and lower urinary tracts, before and after voiding, is of paramount importance in the evaluation of these children. Calculation of residual urine volume,

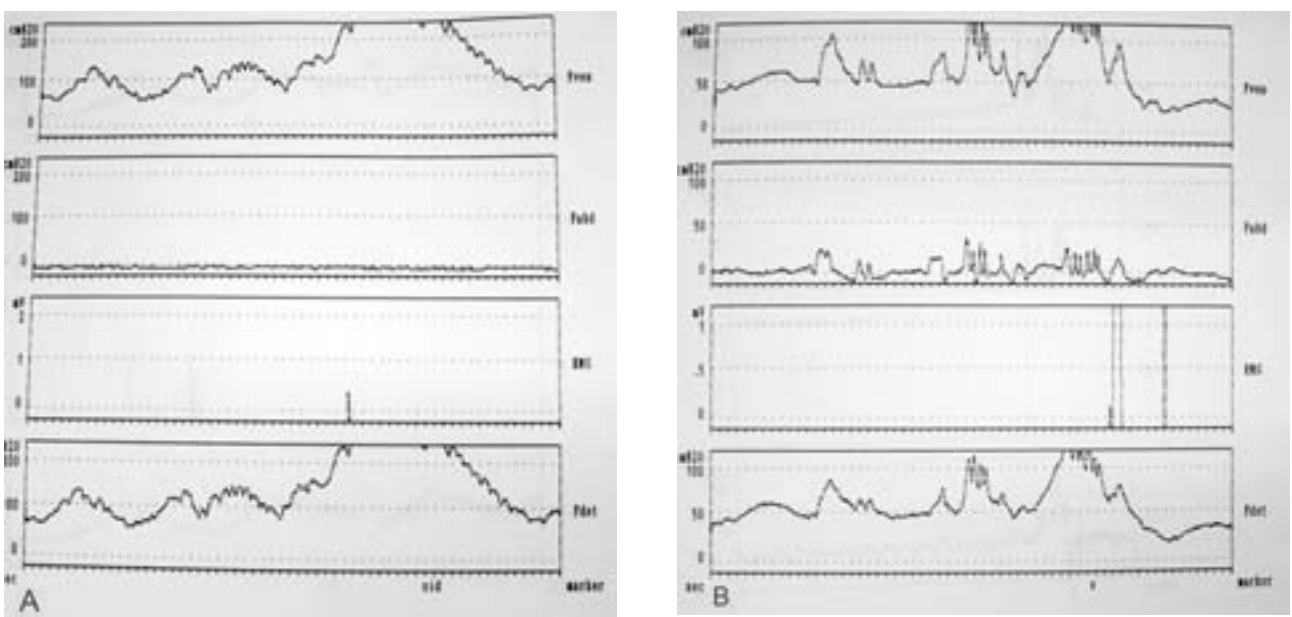

FIG. 7. A. Urodynamic study before valve ablation (maximum voiding pressure = 320 cm H2O) and **B.** after valve ablation in the same child with Type III valves (maximum voiding pressure = 112 cm H2O).

assessment of renal pelvic and ureteral diameters before and after bladder drainage with a thick bladder wall, voiding time, and posterior urethral diameter are among the most important points to be considered in ultrasonography. Ultrasonography of the urinary tract is the first assessment in the newborn with a history of bilateral hydronephrosis and a distended bladder during the fetal period. Isotope study of the urinary tract is a further specific study in patients with urethral strictures. Intravenous urography has no role in the evaluation of PUV.[94]

Cystometry

Determining the relation between the bladder volume and pressure is a valuable test essential in every child affected by a valve. Some young physicians think that cystometry is the same as urodynamics, being the first step in the study of the urinary tract. However, with respect to all initial issues, cystometry is the last part of the urodynamic studies. For cystometry, a catheter must be placed in the bladder to measure its pressure, another catheter must be placed in the rectum to measure the perivesical pressure, which is transferred from the abdomen to the bladder muscles. The device obtains the detrusor pressure by a simple subtraction of these two pressures.[88] It must be kept in mind that some of the urodynamic findings change with the amount and rate of bladder filling and the temperature of the fluid entering the bladder.[89,90]

Video-urodynamics was first suggested by Bates in 1970, giving more information including visualization of the bladder's function at the same time as the pressure measurements.[91,92] In this method, the status of the diverticulum, bladder neck, urethra, reflux, and involuntary contractions during bladder filling can be compared by measuring intravesicular pressure changes.

Obstructive Bladder Changes Due to Urethral Valve

The bladder muscles show a wide range of different responses to degrees of outflow obstruction. These changes are important, not only morphologically, but also with respect to bladder function.[95] These responses have been observed in experimental studies on the rabbit bladder, too, and the above changes studied both for the period of obstruction and the period after its relief.[96]

The first response to obstruction is bladder distension, followed by a thickening in the bladder wall. This thickening is at first due to a submucosal swelling, later replaced by an increase in collagen and the muscular mass eventually substituted by connective collagen tissue. This point is more prominent in the fetal bladder. The degree of hypertrophy depends on the severity of obstruction. In other words, muscular hypertrophy leads to a moderate obstruction, and hyperplasia is seen when the obstruction is severe. In the bladder of the growing rabbit, if an outflow tract obstruction is made, at first the bladder smooth muscles are doubled, enlarging to as much as 6 times their normal size within 8 weeks. A 10-time hypertrophic muscular increase is seen in the obstruction of the mature rat. These lesions show that the amount of bladder collagen increases to 4 times its initial amount.[97, 98]

Apparently, the bladder's elasticity increases with increasing collagen.[99] These morphologic changes lead to a hardening of the bladder wall.[38] Morphologic studies in the bladders of the patients with outflow tract obstruction confirm similar changes.[100] In cases in whom an obstruction in the urethra occurs, the force of voiding increases and the urine flow rate decreases at the same time. The signs of instability are observed in 64% of cases and the bladder end-filling pressure reaches 55 cm H2O.[101] Studies of the bladder nerves show that in obstruction the amount of autonomic nerves in the detrusor muscle is reduced.[102] In another study, the same changes are described in the bladder facing an outflow tract obstruction.[103]

Such changes are also seen in men affected by prostate enlargement, in 45% of whom involuntary contractions are seen. After obstruction relief, these involuntary contractions are relieved in 62% of the patients only.[104] In urinary postprostatectomy urinary incontinence, involuntary contractions (instability) are seen in 66% of the patients.[105] In a similar study, such disorders are reported in 60% after prostatectomy.[106] The more severe the obstruction, the prevalent are the involuntary bladder contractions.[107]

Unfortunately, studies in animal models of fetuses are very difficult because severe

obstruction of the fetal urethra is accompanied by oligohydramnios, which leads to fetal pulmonary hypoplasia and death, making the postnatal study impossible.[108] Another problem in animal models is fetal bladder decompression due to urethral obstruction because of automatic opening of the urachus.[51] Until now, most of the studies centered on the assessment of effects of urethral obstruction on the kidneys [108,109], but recently the researcher's attention has moved toward the effects of urethral obstruction on the bladder, in experimental animal fetuses.

In one study, urethral obstruction in the sheep fetus at mid-pregnancy led to a 4-fold increase in bladder weight, together with hypertrophy and hyperplasia of the bladder muscles, with a reduced compliance in cystometric evaluations.[110]

In these animal models, the maximum vesical pressure, as well as the amount of residual urine, increases.[111] These changes are due to increased gestational proteins of the cellular matrix and collagen production in response to obstruction.[112]

The VURD Syndrome

Urethral valve in children causes evidences of urethral outflow tract obstruction, similar to the urinary tract obstruction in benign prostatic hyperplasia in adults.[113] However, there are considerable differences between these two age groups (children and adults) with respect to the effects of obstruction on the developing kidney and the forming bladder in the fetus and the newborn.[114]

It was reported about 70 years ago that 70% of children with a urethral valve have urinary incontinence, which was thought to be caused by bladder overflow of urine. Forty years later, Williams reported that two thirds of these patients have some degree of urinary incontinence.[68] At the same time, another theory was proposed for these children's wetting, suggesting bladder dysfunction as being responsible for the urinary incontinence in children with a urethral valve.[115]

In 1977, the first urodynamic studies showed that the external sphincter is normal, rejecting the theory that urinary incontinence after valve surgery is due to traumatizing of the external sphincter.[116] At the beginning of this study, 5 types of bladder function in children affected by a valve were introduced[116-119]: normal bladder, myogenic failure, increased voiding pressure, uninhibited contraction, and low-volume high-pressure bladder.

An interesting study was done on persistence of ureteral dilation after valve resection.[117] In this study, upper tract urodynamics were performed and 3 urodynamic classes were found for the renal pelvis and the dilated ureters. For this, a fine catheter was introduced percutaneously into the renal pelvis and the pelvic and ureteral pressures were studied in 3 positions with an empty and a full bladder.

This study was performed in children whose ureteral dilation had not been relieved after relief of the urethral obstruction. These dilated ureters are classified, urodynamically, into 3 obstructive types: type 1, obstructive; type 2, nonobstructive with a full bladder; and type 3, nonobstructive with an empty bladder. The study showed that most nonobstructive dilated ureters exist at the time of bladder emptying and become obstructed upon bladder filling. This phenomenon, in which and increased bladder wall resistance and pressure leads to a resistance to urine flow from the ureter to the bladder was introduced as the valve bladder.[118]

The important point is that placement of a Foley catheter can itself be considered as a foreign body and a means of pressure on the trigon, so that the ureteral distension might not be relieved after drainage through a Foley catheter. Now, if a Nelaton catheter replaces this catheter, the effect on ureteral drainage will improve.[119]

In general, the high intravesical resting pressure is one of the important reasons for persistence of ureteral and pelvic dilation following valve surgery.[120] On the other hand, if the urinary incontinence persists after the age of 5 years, this is considered a poor prognosis for renal function. The urodynamic evaluation of children affected by urethral valve shows 3 types of urinary disorders after valve surgery[120]: myogenic failure, bladder hyperreflexia, and hypertonic bladder. These findings prove that sphincter disorders are rare, and that the children with urinary incontinence face severe renal and ureteral disorders.[9] There is a direct relation between disordered voiding, reduced compliance, and the risk of renal failure.[122] Increased voided urine volume and the loss of renal urine concentrating capacity aggravate signs of lower urinary tract disorders.[81]

Renal dysfunction in the long run is well known in myelomeningocele patients,[123,124] which is due to a low-volume high-pressure bladder that causes a disordered urine emptying from the ureter into the bladder, especially if this is concomitant with detrusor-sphincter dyssynergia. Also in urethral valve, it seems that the higher the bladder pressure, the lower the GFR.[125]

This critical pressure is, by definition, 40 cm H2O, which can eventually destroy the kidneys.[126] In subsequent studies, the bladder's resting pressure (20 cm H2O to 25 cm H2O) is also claimed to be hazardous for the kidneys.[113,127,128] Almost 4% to 5% of children with a urethral valve have persistent bladder dysfunction resistant to therapy, requiring augmentation cystoplasty.

It is interesting that in 1 of our studies 40% to 50% of these patients have normal voiding after cystoplasty, without a need for urinary catheterization.[129] In the urodynamic assessment of neonates who are diagnosed prenatally, a fine, 2-mm, suprapubic catheter is introduced into the bladder immediately after birth, connected to the urodynamics device, and the bladder function monitored for 12 hours.

In this study, the voiding pressure had risen to up to 350 cm H2O in some children. Interestingly, this pressure did not changed much after valve resection, although radiologically and clinically, the urine flow had been normal and the urethra had no obstruction. Still more interesting is that if the urethra is not catheterized at birth, cystography can be performed through a suprapubic catheter leaving the urethra intact. Almost 80% of the urethral valves in this group appear to be of the third type, which is in contrast with existing reports.

There is as yet no report of urethroscopy without catheterization. It has been shown in these patients that if the bladder is catheterized with a 6-F catheter, the valve changes from type 3 into type 1, explaining the higher prevalence of the type 1 valve.[128] In the urodynamic study before and after valve resection at birth, the intravesical voiding pressure does not change, whereas the residual urine disappears.

All these patients have hypocompliant bladders, with a formed entity after the age of 1 year, which is classified as described earlier.[129,130]

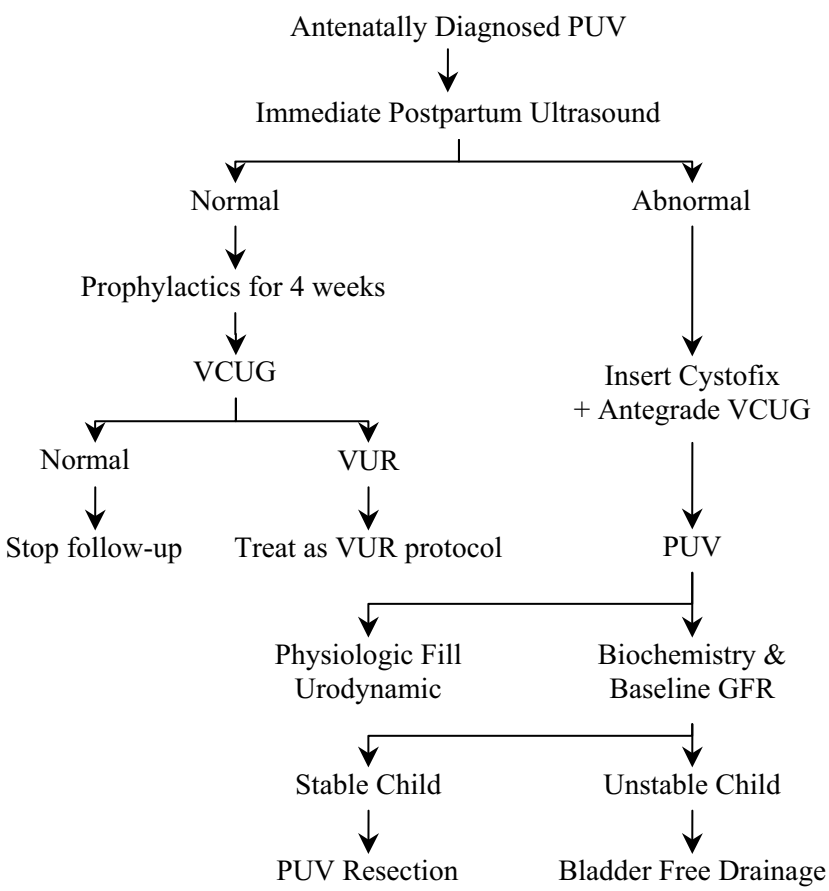

FIG. 8. Diagnosis and treatment protocol of posterior urethral valve.

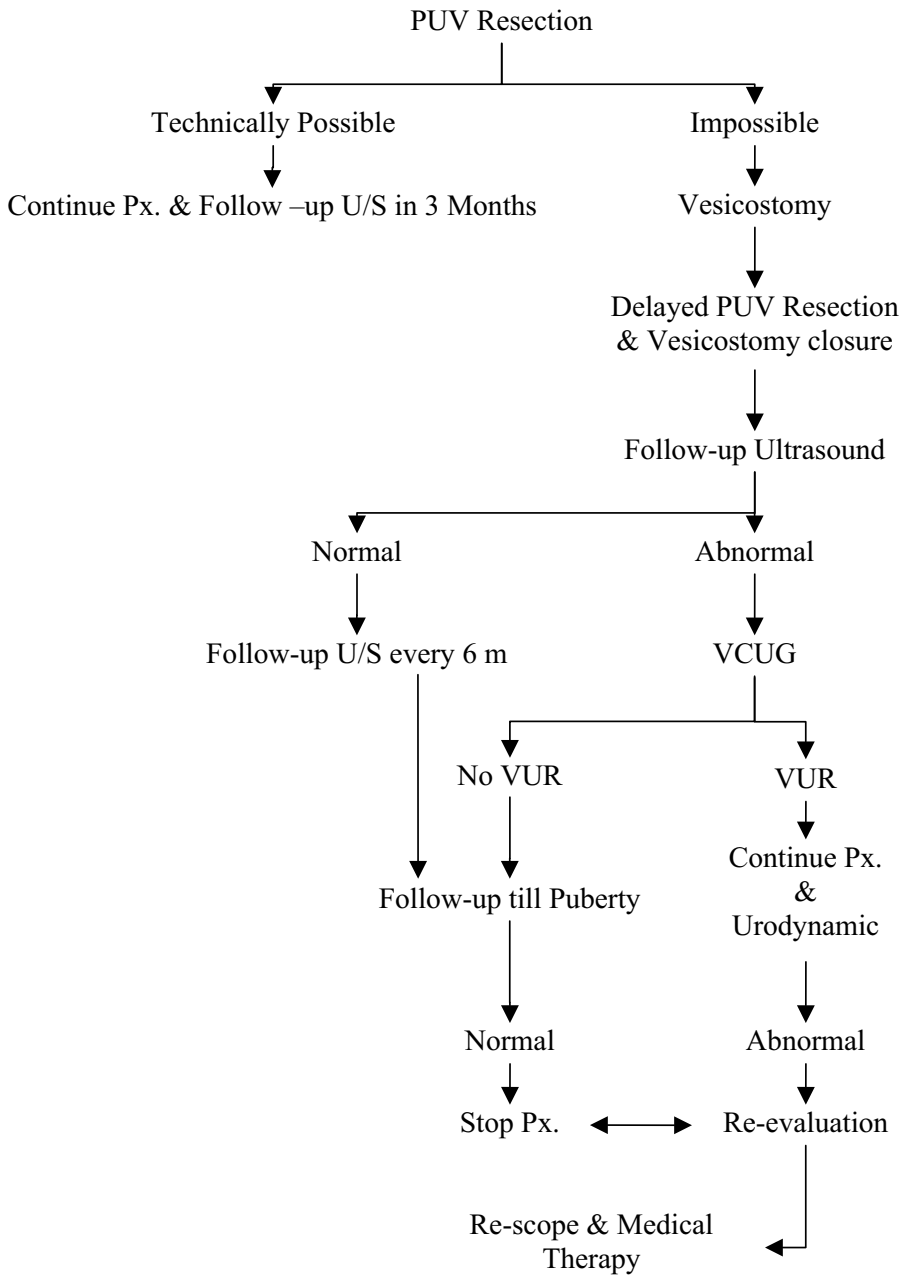

FIG. 9. Treatment protocol in cases in which resection is not possible.

There are several reports regarding prenatal diagnosis of PUV in the previous 2 decades. Whenever bilateral hydroureteronephrosis with a large, full bladder is shown on the renal ultrasonography of a fetus, a PUV must be considered. If the diagnosis is made before 24 weeks of gestation, the prognosis is poor, and if oligohydramnios is also present, the status of the fetus is even worse and needs to receive a treatment from an expert team.

The basic point, anyway, is that there is no need to terminate pregnancy or have a premature delivery as the neonate may actually die at birth of lung underdevelopment at any gestational age. Bilateral pneumothorax might occur in these children upon the first inspiration after birth, which requires specific treatments, proper action, and care if the child's life is to be saved.[28,93,94,128-133]

The protocol presented in Figures 8 and 9 is used in the division of Pediatric Urology Children's Medical Center, Tehran, Iran.[131]

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