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Megaureter and hydronephrosis: Consequences of ureteric dysfunction

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Abstract. The prevalence of "megaureter" among children can be as high as 20-25% and can be bilateral or unilateral; in some cases, the contralateral kidney is either absent or dysplastic. Megaureters can be categorized as obstructed, refluxing, obstructed and refluxing, or neither obstructing nor refluxing. Megaureter is likely to either transiently or permanently involve the kidneys, resulting in hydronephrosis or other medullary and cortical derangement. During routine student dissection of an 86-year-old female donor who died of atherosclerotic cardiovascular disease, we observed the presence of large ureters on both kidneys with the right-side ureters comparatively much larger than the left side. The upper and lower lobes of the right kidney were drained by independent ureters, which were encased in a thin, membranous connective tissue structure. Additionally, we also observed thinning of the renal cortex, renal pelvis, and caliceal dilation with total loss of medulla and lack of corticomedullary delineation. Importantly, reproductive structures such as uterus, fallopian tubes, ovaries. cervix and vagina were normal. This paper, in addition to providing a description of what was observed on dissection, will discuss various causes, pathophysiology, and alterations in the matrix composition of the ureter and kidney.

Keywords: hydronephrosis, megaureter, altered ureteric matrix, reflux, obstruction, anomaly, dysfunction, ureterovesical junction.

INTRODUCTION

This paper starts with a review of the development of the renal system, followed by a report of the association between megaureter and hydronephrosis and, finally, various ways megaureter develops and is classified. Analysis deliberating whether megaureter or hydronephrosis occurred first follows a description of the findings and morphometric measurements of the renal system in this case. The introduction and discussion provide solid foundations about the complications observed in the case.

Embryologically, the permanent kidneys develop from two sources: the ureteric bud (aka metanephric diverticulum) and the metanephric blastema

(aka metanephric mass). The ureteric bud is a diverticulum or an outgrowth from the mesonephric duct. The ureteric bud is the primordium of the ureter, renal pelvis, calices, and collecting tubules. The extending ureteric bud penetrates the metanephric blastema that forms the nephrons. The stem of the ureteric bud becomes the ureter, of which the cranial part undergoes repetitive branching to form the collecting tubules. The initial four branches enlarge and coalesce to form major calices, while the subsequent four coalesce to form minor calices (Moore et al., 2020). Additionally, the ureter undergoes changes in its matrix components, including types of collagen and longitudinal and smooth muscle content (Friedrich et al., 1987; Hanna et al., 1976; Hanna et al., 1977; Vlad, et al., 2007).

Congenital ureteric abnormalities, specifically megaureter, are a common and widespread pathology (Sharif, 2021); frequency varies between 20% and 40% of all malformations related to the urinary system. Megaureter is most often diagnosed in children and is also discovered in incidental findings when other problems are investigated. More common in boys than girls, megaureter occurs more frequently on the left side (Wilcox and Mouriquand, 1998), but arises bilaterally in 25% of cases (Shokeir and Nijman 2000; Manzoni 2002; Wilcox and Mouriquand, 1998). The disruption of urodynamics affected by megaureter makes possible the subsequent development of pyelonephritis or scarring of renal tissue that causes loss of physiological functions. A ureter is considered a megaureter if the lumen diameter is larger than 7-8 mm (Hodges et al., 2010; Baskin et al., 1994).

In general, an obstruction to the flow of urine, due either to intrinsic or extrinsic compression, produces hydronephrosis. The causes of intrinsic obstruction include renal stones, tumor, ureteropelvic junction narrowing, ureteral strictures from earlier infections, posterior urethral valves, prostatic hyperplasia, and neurogenic bladder, etc. The causes of extrinsic compression include pregnancy, pelvic/perineal cysts, malpositioned ureter, tumor, pelvic fibrosis, etc. (Thotakura and Anjum, 2022). Anatomic abnormalities, such as urethral valves or strictures, stenosis at the ureterovesical or ureteropelvic junction, or vesicourethral reflux, account for most cases in children (Capriotti and Frizzell, 2016). In pregnancy, rotation to the right (dextrorotation) of the uterus can cause compression of the right ureter, thus making hydronephrosis more common in the right kidney than left (Rasmussen and Nielsen, 1988).

Based on the international classification of nomenclature, the megaureters can be classified as obstructive, refluxing, obstructed and refluxing, or neither obstructing nor refluxing (Report of working party to establish an international nomenclature for the large ureter 1977). Primary obstructive megaureter occurs when the ureter is too narrow at the point where it enters the bladder; peristalsis of the ureter proves insufficient and blockage results. An obstructive process characterizes **secondary obstructive** megaureter occurring secondary to elevated intravesical pressure of some other cause such as neurogenic bladder, ectopic ureter, ureteral vesicular junction problem, retroperitoneal mass and enlarged prostate and others (Shokeir and Nijman, 2000; Khoury and Bagli, 2007; Berrocal et al., 2002). The **primary and secondary refluxing** megaureters represent a refluxing ureter that happens to be dilated. This may be associated with abnormalities of uretero-vesicular junction problem. In the **refluxing obstructed megaureter,** some degree of obstruction occurs, perhaps due to ectopic insertion of the ureter into the neck of the bladder (Weiss and Lytton, 1974).

In the light of what is known about megaureter and hydronephrosis and what is observed in the present case, the authors will attempt to explain the possible causes of the megaureter and hydronephrosis seen in the female donor.

MATERIALS AND METHODS

Case report

We report on pathology seen in a donated body that was obtained from the willed body program; it was intended for medical student dissection and learning at Cooper Medical School of Rowan University. During students' dissection of an 86-year-old female Caucasian donor who died of atherosclerotic cardiovascular disease, we observed megaureter of both kidneys; the right ureter was much larger with hydronephrosis of the right kidney. Unfortunately, the students randomly dissected the kidneys before the authors had a chance to carefully dissect, document and display the abnormalities. Despite this, we performed a detailed study of the anomalous renal system presented here.

Declaration: The authors state that every effort was made to follow all local and international ethical guidelines and laws that pertain to the use of human cadaveric donors in anatomical research.

Results and observations

The right kidney was primarily affected; the magnitude became noticeable when comparing it with the less-involved left kidney and its ureter. An Illumifun elec-

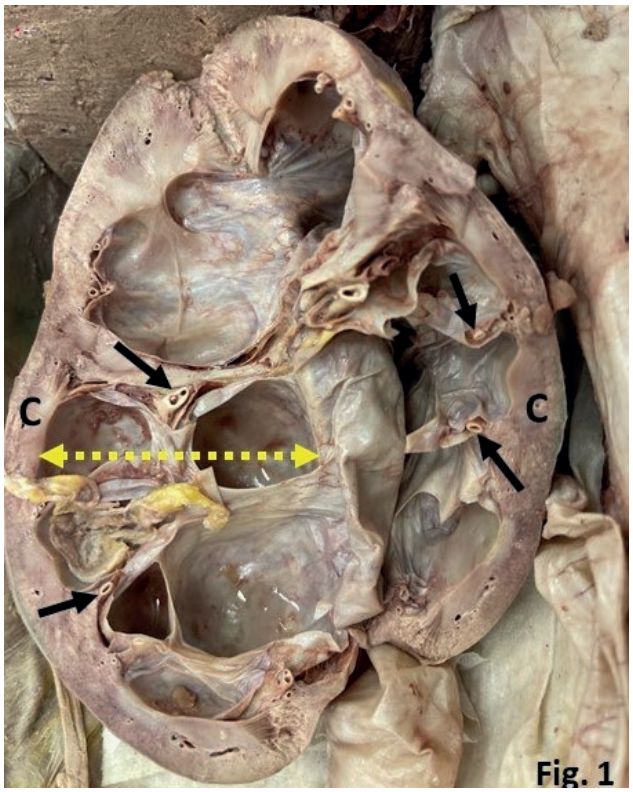

Figure 1. Longitudinal section of the right kidney showing hydronephrosis, cortex thinning, renal pelvis and caliceal dilation with total loss of medulla and lack of corticomedullary delineation. C=Cortex; Short black arrows pointing to vasculatures and double headed yellow arrow indicates renal pelvis and caliceal dilation with total loss of medulla and lack of corticomedullary delineation.

Table 1.

	R. Kidney	L. Kidney
Length	122.2 mm	139.9 mm
Width	51.3 mm	55.4 mm
Thickness	44.8 mm	60.6 mm
Medulla	Non-existent	Fairly defined
Cortex at Hilum	8.3 mm	19.4 mm
Ureter Luminal Diameter		
Lower lobe: proximal part	247 mm	201 mm
Lower lobe: middle part	316 mm	n/a
Lower lobe: distal part	119 mm	15.1 mm
After uniting	146 mm	n/a
Upper lobe	21.3 mm	n/a
Ureter Length		
Length:		241.5 mm
Upper lobe	132 mm	n/a
Lower lobe	130 mm	n/a
After uniting	63 mm	n/a
Bladder		
Wall thickness		1.4-1.7 mm
Inter ureteral orifices distance		21.7 mm
Ureteral orifice to internal urethral opening		34.7 mm

tronic digital vernier caliper was used to make all measurements reported here.

The right kidney was slightly smaller compared to the left kidney in all the dimensions measured (see Table 1: length (122.2 mm vs 139.9 mm); width at the hilum (51.3 mm vs 55.4 mm); and thickness measured at the hilum (44.8 mm vs 60.6 mm). The right kidney additionally exhibited medullary cavitation due to loss of the integrity of pyramid and caliceal systems and cortical thinning [see Figure 1].

Both right and left ureters exhibited dilation and contortion, the right far more than the left [see Figure 2].

Measurements listed in Table 1 clearly show that the right ureter luminal diameter was considerably larger (mega) and more misshapen in comparison to the left ureter, though that was also enlarged [see Table 1 and Figure 1].

Though initially separate, a clear, thin membranous connective tissue sheath wrapped the ureters from the upper and lower lobes of the right kidney together. Distally, the ureters joined as a single ureter prior to reaching the bladder posterolaterally. Ureter length of the upper lobe is 130 mm; the lower lobe was 130 mm before uniting and 63 mm after uniting. The left ureter length was 241 mm, was less contorted and ran parallel with the large left ovarian vein, which drained into the left renal vein.

In the medulla of the right kidney, the renal pyramid and papilla were unrecognizable [see Figure 1].

The renal caliceal system of minor and major calices and the renal pelvis appear to have lost their histology and physical configurations. The interlobular vascular system appears intact, allowing a viable cortex, even though the thickness of the cortex is diminished in size (see Figure 1). Cortex thickness across from the hilum was 8.3 mm on the right and 19.4 mm on the left [see Figures 1 and 3].

The medulla of the left kidney is acceptably well defined and the caliceal system is recognizable when viewed with higher magnification (see Figure 4). Measured at two different sites, the bladder wall thickness was between 1.4 and 1.7 mm. Normally, bladder wall thickness is 2.76 mm when the bladder is almost empty and 1.55 mm when it is distended. The inter-ureteral orifice was 21.7 mm apart (normal 13-41 mm) and the distance between the ureteral orifice and the urethral opening was 34.7mm (normal 17-40 mm) (see Figure 4).

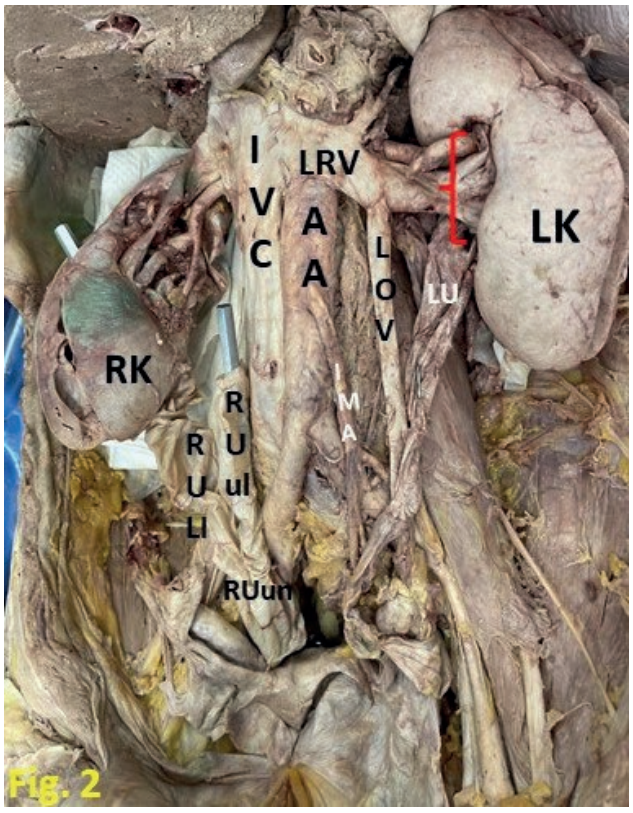

Figure 2. Megaureter –Right kidney: In situ view showing markedly large and tortuous ureters of both upper and lower lobes that fused distally forming a single ureter that entered the bladder posterolaterally. Left kidney (LK) Ureter is less large and less twisted. RK= Right kidney; RULl= Right ureter lower lobe; RUul=Right ureter upper lobe; RUun= Right kidney upper and lower lobe ureters united; IVC=Inferior Vena Cava; AA=Abdominal aorta; IMA=Inferior mesenteric artery; LRV-Left renal vein; LU=Left ureter; LK=Left kidney.

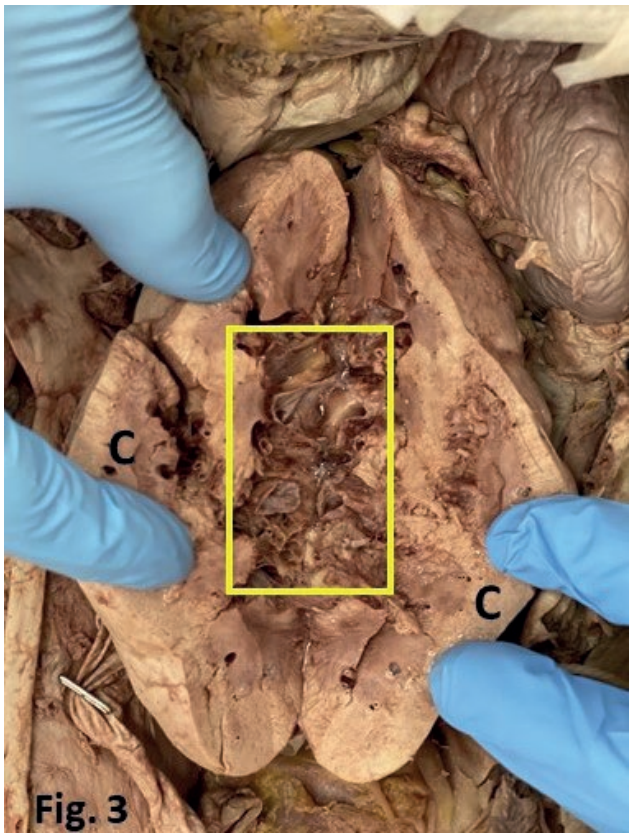

Figure 3. Left kidney: vertical section showing normal caliceal system and cortex and in general larger than the right kidney. C=Cortex; The vertical block of medulla is enlarged and shown in figure 4.

The trigone (or Lieto Triangle), which is the triangular portion of the bladder floor, was the site of the anti-reflux mechanism [see Figure 5].

One ovary showed fibrosis and the uterus showed age-related reduction in size; otherwise, the reproductive structures were within normal limits.

DISCUSSION

Megaureter

Epidemiologically, occurrence of congenital primary megaureter (PM) is unclear; however, it is the second most common cause of neonatal hydronephrosis (Younsi 2020). A primary congenital megaureter means a dilatation of the ureter with a ureteric diameter ≥7 mm (normal 3-5 mm) due to a structural or functional obstruction of the ureterovesical junction (Younsi 2020). The male to female ratio is nearly 4:1 and the left side is more often affected than right (1.6-4.5 times) (Braga et al., 2016). Most cases are non-refluxing and unobstructed. The frequency of obstructed megaureter is 1/10,000 (Farrugia et al., 2014). Primary megaureter has been classified in many ways, based on functional impediment. The Pfister–Hendren classification established in 1978 was based on the morphological appearance: Type I involved the distal ureter without associated hydronephrosis; Type II extended to both ureter and pelvis; and Type III was associated with severe hydroureteronephrosis and ureteric tortuosity (Pfister and Hendren, 1978; Weber et al., 1971). Using the Pfister–Hendren classification, we assign the findings in this case as Type III hydronephrosis with megaureter and ureteric tortuosity.

The Society for Fetal Urology (SFU) classification specified five grades of hydronephrosis which, in addition to renal parenchyma, describes the ureter (Fernbach et al., 1993). Based on the SFU classification, the findings in

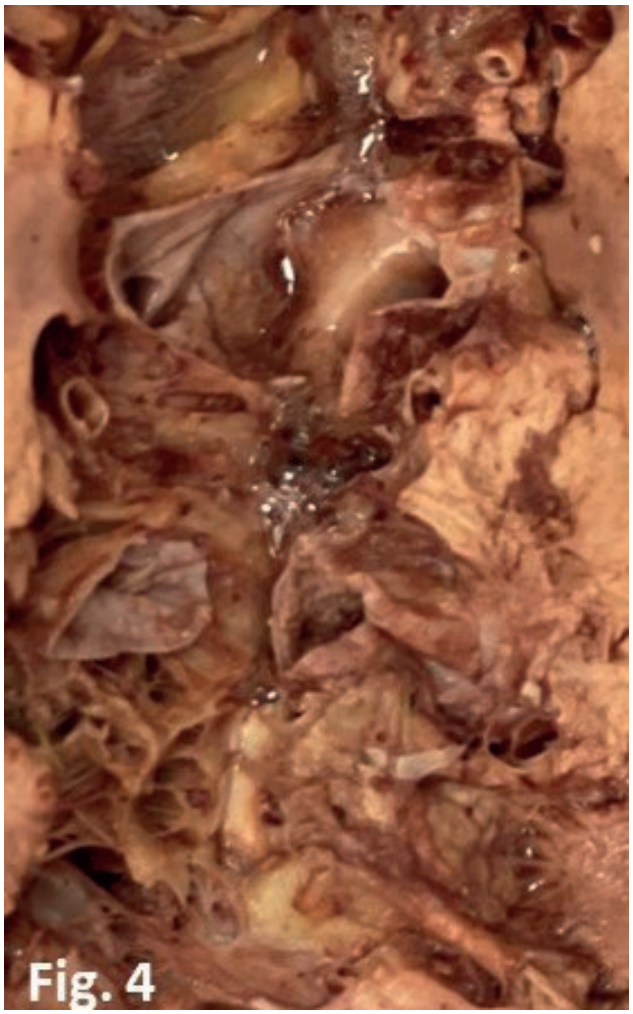

Figure 4. Left kidney= An enlarged vertical section from figure 3 showing normal caliceal system.

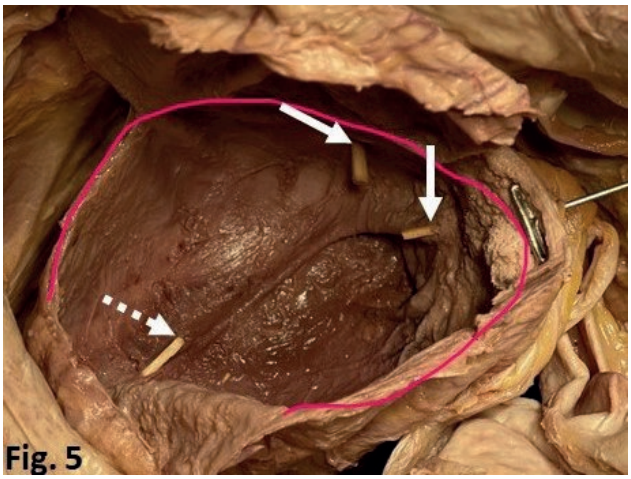

Figure 5. Urinary bladder= The ventral wall removed to display the dorsal 'trigone' region. The open bladder wall is marked by red outline. The solid white arrows pointing to the ureteral entrance with wooden picks. The dotted white line and wooden picks indicate the urethral opening.

Figure 6. Schematic diagram based on the actual dissection showing gross dilation of the ureter, pelvis, and calyces; loss of papillary impressions; thinning of cortex and ureteral tortuosity.

this case can be classified as grade V hydronephrosis with megaureter and ureteric tortuosity [see Figure 6]. Figure 6 here was drawn to show what was observed during the dissection, similar to what is seen in Fernbach et al.

According to Baskin et al., primary megaureter results from a functional or anatomical abnormality involving the ureterovesical junction, whereas secondary megaureter results from abnormalities that involve the bladder or urethra. It appears to be most commonly due to an abnormality or delay in the development of the muscle in the distal ureter adjacent to the ureterovesical junction at 20 weeks gestation. This results in the formation of an aperistaltic segment which leads to functional obstruction (Baskin et al., 1994).

Primary obstructive megaureter (POM) is a congenital dilatation of the ureter due to an adynamic segment of vesicoureteral junction obstruction (Hamid et

al 2022). Megaureters may be primary or secondary and the dilatation may be due to obstruction or reflux or both. Hamid et al. found that refluxing or obstructive types of megaureter occurred 58% and 18.5% of time respectively and the distribution of ureteral diameter varied from 5-30 mm (Hamid et al., 2022). The cause of primary obstructed megaureter is the aperistaltic and narrowed pre-vesical portion of the ureter. The inner sheath of the terminal ureter generally shows a reduced amount of longitudinal smooth muscle bundles and an increased amount of collagen (Merlini and Spina, 2005). Primary obstructive megaureter (POM) is an uncommon disease in adults, it is defined as an intrinsic congenital abnormality at the lower segment of the ureter in the ureterovesical junction (Ibrahimi and Ziani, 2020). Refluxing PM is caused by a short or absent intravesical ureter, congenital para-ureteric diverticulum or other derangement of the vesico-ureteric junction. Obstructed PM is a functional obstruction arising from an aperistaltic jucstavesical segment 0.5-4cm long that is unable to transport urine at acceptable rates. Causal theories include excessive collagen deposition, hypertrophy of ureter muscle, thick periureteral tissues or a circumferential segment devoid of muscle (Merlini and Spina, 2005). Primary megaureter is not known to be hereditary, but families with more than one affected member have been described (Farrugia et al., 2014). A recent publication (Ayad Y Khudair, 2020) brings to light numerous studies related to both embryology and pathophysiology of megaureter. Sharif writes, "It is believed that the ureters has an aperistaltic jucstavesical (adynamic) segment, which leads to insufficient peristalsis of the ureter and, therefore, to urinary outflow. This distal segment was examined histologically, and it was found to contain elevated collagen levels of types I and III (mainly type I). It is this increased fibrosis that is connected with the disturbance of intercellular connections and leads to arrhythmias and ureteric obstruction. Some scientists have proved the atrophy of internal longitudinal muscles in these segments of the ureter (longitudinal muscles transmit peristalsis) and hypertrophy of external compressive circular muscles, which leads to obstruction. " (Sharif, 2021) (Hanna et al., 1976; Merlini and Spina, 2005, Hill, 2015). The muscular layer of the ureter consists of longitudinal and circular smooth muscles that create the peristaltic contractions to move the urine into the bladder without the aid of gravity (Hill, 2015).

While there are many scientific studies explaining the histological origin of megaureter, the results often varied from one another. However, they all showed an increase of connective tissue in the megaureter (Hanna et al., 1977; Vlad et al., 2007). A quantitative study showed that the collagen to smooth muscle ratio in the normal ureter is 0.52, while in obstructive and reflux megaureters, it is 0.78 and 1.99 respectively (Lee et al., 1998). Other researchers have shown the presence of smooth muscle cells in these ureters, which produce abnormally increased amount of collagen (Hanna et al., 1977). It has also been shown that muscles in these segments of the ureter have an abnormal response to neurotransmitters, emphasizing the atypical behavior of these cells (Hanna et al., 1977; Vlad et al., 2007; Lee et al., 1998; Mackinnon, 1977; Mackinnon et al., 1970).

Congenital megaureter is considered to be related to the expression of transforming growth factor β, which might lead to a lack of post-natal muscle dysplasia (Ozturk et al., 2012; 2016). According to Nicótina et al., the primary megaureter should be attributed to a segmental developmental delay of the terminal ureter arising at about 20 weeks of gestation, with a possible pathogenetic involvement of autocrine TGF-β overexpression (Nicótina et al., 1997). Mackinnon et al. theorized that an absence of longitudinal muscle in the distal ureter led to the functional obstruction, which was accepted by number of other researchers (Mackinnon et al., 1970). Notley utilized an electron microscope to observe the normal nerve distribution and hyperplasia of collagen fiber in the muscular layer of megaureters, which was believed to be the primary cause of megaureter (Notley 1972). Furthermore, Tokunaka and Koyanagi and Tokunaka et al. described a small subgroup of megaureters with muscle dysplasia that affected the dilated part of the ureter; and the muscle dysplasia was thought to be the primary cause leading to the dilatation (Tokunaka and Koyanagi, 1982; Tokunaka et al., 1984). In light of the evidence, we, like other researchers, believe that multiple factors contributed to the congenital megaureter.

Hydronephrosis

The renal parenchyma, which produces urine, and the pelvicalyceal system, which collects and conveys the urine into the ureter, comprise the two functional segments of the kidney. Hydronephrosis occurs due to two distinct causes: ureteropelvic junction problems or vesicoureteral reasons (Onen 2020). It happens when there is either a blockage of the outflow of urine or reverse flow of urine that is already in the bladder (vesicoureteral reflux), contraction of bladder detrusor muscles (neurogenic bladder) that can cause the renal pelvis to become enlarged (Thotakura and Anjum, 2022). Furthermore, structural defects of the connections between the kidney, ureter and bladder can also lead to hydronephrosis. Oth-

er causes that result in hydronephrosis are due to renal stone, congenital causes, scarring from infections or earlier surgery, cancer, enlarged prostate, and pregnancy, to name a few (Thotakura and Anjum, 2022). Common causes of upper urinary tract obstruction include kidney stones at the ureteropelvic junction (UPJ) and blockages caused by intrinsic narrowing of the ureters or extrinsically caused by overlying renal blood vessels. Ureteropelvic junction obstruction (UPJO) is primarily a congenital condition that results in diminished urine flow from the renal pelvis into the ureter; this can cause hydronephrosis and, if untreated, may result in complete functional loss of the affected kidney (Jackson et al., 2018; Sulemanji and Vaklit, 2013). Reflux of urine into the kidney (e.g., neurogenic bladder or ureteral obstruction) causes impairment in the lower urinary tract (Thotakura and Anjum, 2022). In pregnancy, towards the end of 2nd trimester, physiological dextrorotation (rotation to the right) of the gravid uterus and engorged right ovarian vein that drain into the right renal vein can cause compression on the right ureter, thus making hydronephrosis more common in the right kidney than the left (Rasmussen and Nielsen, 1988). Hydronephrosis or hydroureter is a normal finding in pregnant women. The renal pelvises and caliceal systems may be dilated due to effects of progesterone and mechanical compression of the dilated ureters against the bony pelvic brim (Rasmussen and Nielsen, 1988. According to Rasmussen and Nielsen (1988), pregnancy-induced hydronephrosis recedes in 80% of women, but persists in 20%. It is possible that, in the case of the female donor, it did not return to normal, as seen in the right-side kidney.

Other congenital causes of hydronephrosis include ureteral hypoplasia that may lead to an aperistaltic segment of the ureter due to abnormal arrangement of the smooth muscle layer, which in turn will impair the urine drainage from the renal pelvis into the ureter and cause functional obstruction, rather than mechanical [Jackson et al., 2018; Sulemanji and Vaklit, 2013]. High insertion of the ureter into the renal pelvis can result in urine failing to empty from the pelvis into the ureter. Entrapment of the ureter by a crossing accessory renal vessel occurs most commonly from the lower pole. This results in kinking of the proximal ureter, interrupting the free flow of the urine and, rarely, a malrotated kidney can cause UPJO. UPJO is estimated to occur 1 in 1000-1500 cases. [Jackson et al., 2018; Sulemanji and Vaklit, 2013].

No matter what causes hydronephrosis, staging of the condition is important in planning a treatment protocol. With ultrasound (US), it has become possible to detect and stage hydronephrosis. Onen and his group studied the hydronephrosis for several years; in 2020, they published an article with staging of hydronephrosis (Onen 2020). From the US images in Onen, it is easy for us to stage the donor kidney's functional status and explain what has been exposed in our dissection (see Figures 5 and 6). The anterior-posterior thinning (44.4 mm vs 60.6 mm) parenchymal thinning indicates a possible severe functional loss. Onen (2020) further distinguished the parenchymal thinning into medullary thinning and cortical thinning. In the right kidney of the donor (see Figure 1), we also observed pelvis plus caliceal dilation, total medulla loss, cortical thinning, and no recognizable corticomedullary differentiation, resulting in progressive and permanent damage to the right kidney.

ANALYSIS

The following analysis pertains to the case presented here; it is based on our observations, findings and on available published research studies on megaureter and hydronephrosis. Deciding which came first, the megaureter or hydronephrosis, is analogous to the "chicken or egg" conundrum. Resolving the question requires consideration of the following: the donor was an 86-year-old female with complete internal reproductive structures whose right side of the renal system was primarily involved. Due to donor confidentiality, we do not know whether she was married or had children. Any conclusion drawn in the discussion is the authors' assumption or based on available published materials.

As mentioned earlier, megaureter may be caused by a structural or functional obstruction of the ureterovesical junction; it represents the second most likely cause of neonatal hydronephrosis (Younsi 2020). According to Merlini and Spina (2005), abnormality or delay in the development of the longitudinal muscle bundle and an increased amount of collagen in the distal ureter adjacent to the ureterovesical junction results in the formation of an aperistaltic segment that leads to functional obstruction. It is believed (Ayad Y Khudair, 2020) that the ureters have an aperistaltic jucstavesical (adynamic) segment, which leads to insufficient peristalsis of the ureter and, therefore, to urinary outflow (Ayad Y Khudair, 2020). Other reasons such as expression of transforming growth factor β, which might lead to a lack of post-natal muscle dysplasia (Ozturk et al. (2012; 2016); a possible pathogenetic involvement of autocrine TGF-β overexpression (Nicótina et al., 1997), or abnormal changes in the collagen to smooth muscle ratio (Lee et al., 1998). In agreement with other researchers, we feel that multiple factors contributed to the development of the congenital megaureter in this donor.

Hydronephrosis occurs for two reasons: ureteropelvic junction or vesicoureteral causes (Onen 2020). Any number of reasons can cause the renal pelvis to become enlarged: a blockage of the outflow of urine or reverse flow of urine already in the bladder (vesicoureteral reflux), contraction of bladder detrusor muscles (neurogenic bladder) at the ureteropelvic junction (UPJ); renal stone, congenital cause, scarring from infections or earlier surgery, cancer, enlarged prostate, pregnancy, etc. (Thotakura and Anjum, 2022).

Based on the Pfister–Hendren classification and what was observed in this donor, we consider that the findings in the case presented here can be classified as type III hydronephrosis with megaureter and ureteric tortuosity of the right-side renal system (Pfister and Hendren 1978). Additionally, we also observed Onen's Grade 4 hydronephrosis with cortex thinning, renal pelvis and caliceal dilation with total loss of medulla and lack of corticomedullary delineation (Onen 2020).

Our report does not include histological appearance of the vesicoureteral junction or distal ureter due poor preservation of such details in an embalmed cadaver tissue. However, there are studies that report that defective vesicoureteral junction and loss of muscles at the distal ureter and increased connective tissues caused aperistaltic distal ureter and retrograde flow of urine from the bladder towards kidney, resulted in dilated ureter and hydronephrosis (Nicótina et al., 1997; Lee et al., 1998).

CONCLUSION

With the available information about the donor, who lived for 86 years, had complete reproductive structures to ovulate, conceive, and carry a fetus to full term, and the fact her megaureter and hydronephrosis are on the right side, we assume that she carried a fetus to full-term. In pregnancy, in the late second semester, the gravid uterus rotated to the right side, causing compression of the right ureter and gonadal vein. This compression of the right ureter initiated the hydronephrosis. Hence, we believe that the megaureter came first and caused the hydronephrosis.

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The authors state that every effort was made to follow all local and international ethical guidelines and laws that pertain to the use of human donors in anatomical research.

For research using human subjects, American Association for Anatomy endorses the protections embodied in the Basic Principles of the Declaration of Helsinki and their expansion in the regulations governing research supported by the U.S. Government (45 CFR Part 46; 56 FR 28003).

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