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NEED FOR RECLASSIFICATION OF EXISTING CONGENITAL MULLERIAN DUCT ANOMALY ALONG WITH RENAL ANOMALIES

Urology

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ABSTRACT

Background: The system use to classify various Mullerian Duct Anomalies [MDA] has been the American fertility society [AFS] classification and various other scientists have tried to come up with their versions but none of them were comprehensive. Around 30% of cases of MDAs have features of renal anomalies. The commonly used AFS classification is too simplistic and does not account for renal congenital defects along with MDA. It also significantly excludes many patients with utero-vesical fistulae, cervico-vesical fistulae, obstructed hemivaginas/vaginal atresia, etc. **Methods:** The study aimed at reviewing the literature to find the various classifications used to classify MDA and to identify the cases which do not belong to any specific classification. A thorough search was done on PubMed for topics named renal anomalies with Mullerian duct anomalies, present classifications of MDA such as ESHRE, VCUAM, ASRM, etc. Papers on the embryological basis for the development of the urogenital system were also looked at to accurately cement the need for consideration of renal and genital organogenesis together. **Results:** A total of 48 papers were reviewed out of which 16 cases were found to be unclassified in the existing classification. In those 8 patients had anomalies common to our index patient. **Conclusion:** Despite so many classifications and cases proving an association, the fact remains that many patients still do not find a place in the literature currently available. This lack of standardization severely impacts the treatment, management, and diagnosis of many such patients. A more comprehensive and consistent classification is required so all patients suffering from these conditions have access to completely functional treatment options. It is important to diagnose these anomalies at the right time as it affects their future prognosis. We aim to provide a new classification as an add on to the existing one, that encapsulates a broader picture of MDAs and their common associations with the renal/urinary tract, vertebral system, and urogenital sinus derivatives as seen in our index patient along with other reported cases in the literature.

KEYWORDS

Mullerian duct anomaly, renal anomaly, renal agenesis, hematocolpos, congenital vesicouterine fistula

BACKGROUND

Isolated MDAs occur with a frequency of 7% in the general population and 17% in women with spontaneous abortions [1]. The urogenital sinus has an association with MDAs and is commonly affected together [2]. Multiple types of classifications have been put forth in order to enhance the ability to diagnose and treat Mullerian anomalies. The AFS classification was the earliest and remains the easiest way to classify MDAs. Unfortunately, it does not account for the multiple variations in the very anomalies it classifies, and neither does it take into factor other systems that can be affected. ESHRE [3] and VCUAM [4] systems also seem to go in-depth about uterine anomalies along with gonad and tubal but it lacks an analysis of the urological tract. Most if not all of them have multiple variations within uterine maldevelopment but none as such with the renal deformities that occur alongside MDAs. While the recent ASRM classification certainly offers an accessible means to search and classify MDAs, it sidelines the renal component of MDAs. The prevalence of renal anomalies occurring with MDAs is at least 30%; the most common being renal agenesis along with a unicornuate uterus and vaginal atresia [5]. This statistic signifies that it is essential for the entire urogenital tract to be looked at as a whole. For example, some patients of MDAs present with cyclical menouria, which is a classical indication of a vesicouterine fistula; but this has no place in any of the classifications thus mentioned. Due to the embryological proximity of the paramesonephric ducts and the mesonephric ducts, maldevelopment at any stage could result in a fistula, agenesis, dysplasia, etc. The Mullerian ducts develop in 3 stages- specification, invagination followed by elongation [6]. The Mullerian ridge is known as the region on the mesonephric duct where Mullerian precursors are found. At the 7th week, the caudal portions of paramesonephric ducts join to form the uterus and vagina. The caudal end of the mesonephric duct, known as the ureteral bud induces differentiation of the surrounding mesenchyme which ultimately forms the metanephros, a precursor to a fully functioning kidney. During this organogenesis, if damage occurs during ureteral budding, it complicates the epithelial-mesenchymal transformation of the metanephros. Thus, the development of the genitourinary system is intertwined in a complex manner and must be considered complementary to each other. These present in different ways in contrast to isolated MDAs which may be diagnosed only during reproductive years. An atypical patient presentation featuring urinary/CKD symptoms may be missed as a solely urological case when it could be a part of an MDA as well. Many patients are still unclassifiable despite the availability of multiple classifications. Our classification aims to bridge this very gap.

Methods

A thorough review of all relevant articles was done on PubMed with the topics searched including renal anomalies with Mullerian duct anomalies, present classifications of MDA such as ESHRE, VCUAM, ASRM, etc. Case reports of patients unable to be classified under these systems were specifically sought. Papers on the embryological basis for the development of the urogenital system were also looked at to accurately cement the need for consideration of renal and genital organogenesis together. A total of 48 papers were reviewed out of which 16 cases were found to be unclassified in the existing classification. In those 8 patients had anomalies common to the index patient.

DISCUSSION

The index patient, was a 14-year-old, who presented with bilateral recurrent colicky pain associated with cyclical hematuria. On examination, the abdomen was mildly tender bilaterally in the iliac fossa. She had a normal urethral and anal opening with a dimple in the vaginal area. Imaging findings such as USG showed uterus didelphys, hematocolpos, lower one-third hypoplastic vagina, and partially organized collection in the right iliac fossa, mostly representing

hematoma, which was confirmed by MRI. CT Urography was done and it showed dilated right lower ureter and its opening into the proximal urethra. Cystourethroscopy revealed the right ureteric orifice, just distal to bladder neck opening into the proximal urethra, and normal left ureteric orifice. Bilateral retrograde pyelography suggested mild right lower hydroureter. CT also revealed an anomaly of the 12th vertebrae. While reviewing the management for this case, 16 reports were read of similar unclassifiable grouped anomalies which found no place in the available scientific literature. In those, 8/16 (50%) had anomalies common to the index patient [Table 1]

Table 1- Case Reports Showing Mullerian Duct Anomaly With Other System Anomaly

	AGE	CYCLICAL HEMATURIA	AMENORRHEA	URINARY INCONTINENCE	ABDOMINAL PAIN	UTERINE ANOMALY	RENAL ANOMALY	CERVICAL ANOMALY	VAGINAL ANOMALY	OTHERS
1	18	Yes	Yes	No	No	Absent	Not studied	Absent	Atresia	Imperforate anus
2	18	Yes	Dyspareunia	No	Yes	Absent	Not studied	Absent	Atresia	Short stature
3	27	Yes	Yes	No	No	Absent	RK-Agenesis LK-malrotation	Atresia	Upper 1/3 atresia	No
4	14	Yes	Yes	No	No	Small unicornuate uterus	Absent	Absent	Atresia	Recurrent UTI
5	21	Yes	Yes	No	Yes	Bicornuate uterus	Absent	Agenesis	Dimple only	No
6	16	Yes	Yes	No	Yes	Absent	Absent	Absent	Distal agenesis	NO
7	15	Yes	Yes	No	Yes	Bicornuate uterus	RK-Agenesis LK- Mild Hydronephrosis	Absent	Distal atresia	Imperforate anus
8	19	Yes	Yes	No	Yes	Absent	LK-Agenesis	Absent	Distal atresia	Fecal incontinence

It is mandatory to look for genital anomalies if a patient has renal anomalies and vice versa [7]. It is difficult for these patients to seek treatment and find a scientifically sound answer when the standardization of the data available is poor. A new classification combining the renal anomalies along with the Mullerian anomalies is of utmost value to ensure that neither are missed out during diagnosis, along with the fact that multiple variations can occur within the urogenital sinus, kidneys, and uterus. During embryogenesis, the paramesonephric ducts grow parallel to the mesonephric ducts. They meet in the midline, near the mesonephros, to form the uterovaginal duct and this fusion leads to the formation of a full cavity. If this fusion does not occur, the uterine cavity can get duplicated – leading to uterus didelphys. Due to its proximity to growth factor stimulation, multiple numbers of renal anomalies can also occur at the same time. After fusion of the paramesonephric ducts, they move caudally to connect with the urogenital sinus to form the Mullerian tubercle. This caudal movement of the tubes can also lead to numerous congenital defects like vaginal atresia, hemivaginas, transverse or longitudinal septa, and cervico-vesical fistulas. Congenital Utero-vesical fistulas presenting as cyclic menouria, abdominal mass, and ectopic openings of the ureter must be looked at in conjunction with the uterine and urological point of view. These must be classified in a way that is constructive and homogenized so that a simplified surgical plan may be created for the multitude of patients that live with these anomalies. Several studies have been conducted which prove that there is an association between renal and uterine anomalies [8]. In this study conducted in China, they found 65/76 cases of patients with uterine anomalies and renal anomalies on the ipsilateral side. A case report and review [9] done by Baylor College of medicine shone a light on the misdiagnosis of 8 of their patients and incorrect referrals of didelphys uterus with hemivaginas. All 8 of their cases had concomitant renal agenesis. Due to this being a rare diagnosis, a high degree of clinical suspicion must be maintained. A long-term follow-up study of 45 women with didelphys uterus was carried out in Finland, and 23% of them had renal anomalies [10]. After reviewing the literature, it is noticed that there are a variety of classifications, and placement of all patients into a particular category is not possible. Earlier the classifications were based on embryological development but still could not answer any abnormalities. It's been seen that all these are based on Mullerian development processes, hence are not sufficient to explain some of the complex female genitourinary malformations. The most widely used American Fertility Society classification is also based on Mullerian development. Recently other classifications which are based on the combination of anatomy, embryological development, and functional anatomy have been proposed, but are discouraged due to their complexity. A few years ago, updated systems were thought of to keep up with the varying involvement between the genitourinary development [11], and more and more case studies and reports must be pooled together to ensure a transparent system to include as many variations as we can.

Vertebral associations with the Mullerian ducts and renal parenchyma are due to the common intermediate mesoderm they originate from. Various studies have been conducted to gauge the accompanying anomalies associated with congenital scoliosis and other vertebral defects. Types of spinal defects are Failure of fusion, formation, segmentation, and hemivertebrae. A study [12] showed 27.8% of associated genitourinary pathologies with congenital scoliosis. The various renal anomalies possible are ectopic kidney, fusion defects, and renal agenesis. In a case study Invalid source specified. of 11 cross-fused kidneys, 10 of them showed vertebral anomalies. A complete physical exam and imaging are vital to diagnosing all the co-existing findings.

Our classification's [Figure 1] aim is to add on to an already diagnosed patient with an MDA.

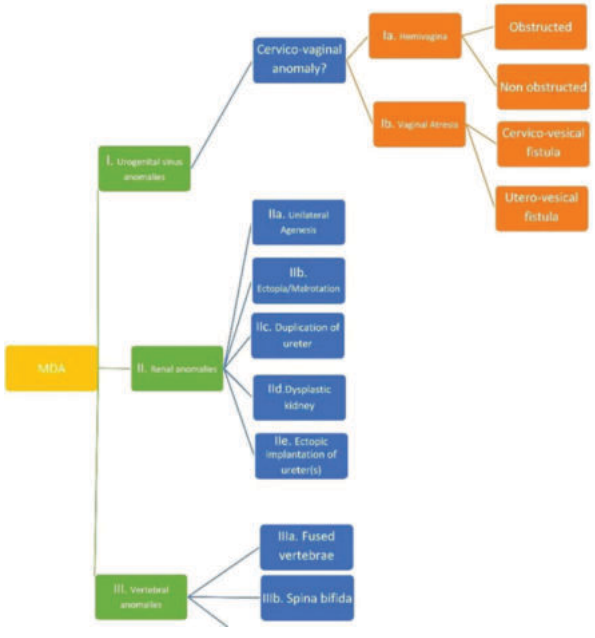

Figure 1- Shows Our New Classification Of Mullerian Duct Anomaly Considering Urogenital Sinus Anomalies, Renal Anomalies And Vertebral Anomalies.

Once an MDA has been identified, it must be at the back of the mind of the diagnostician to look for a renal, urogenital sinus, and or vertebral anomaly. Not only does this affect the treatment of the patient at the current time, but it also affects the future functioning of the patient with respectto chronic kidney disease and cardiovascular risk factors such as hypertension. A renal anomaly associated with an MDA may also lead to adverse outcomes in pregnancy such as preeclampsia and gestational hypertension. A study conducted to evaluate the same showed that 42% of women with UNILATERAL AGENESIS + MDA had hypertension during pregnancy [13]. Thus, it is of paramount importance to ensure a proper workup has been done in a case of an MDA. A renal anomaly must be looked for through an MRI involving

genitourinary system as whole. Urography phase is more beneficial than the latter as it allows us to look for a ureteral orifice and where it drains if it does so ectopically. As the patients are young, serum creatinine values can also contribute to a diagnosis without causing too much harm. A range of renal anomalies may co-exist and they all are able to be diagnosed. Urogenital sinus anomalies can include the distal 1/3rd of the vagina and cervix. Hemivaginas may become obstructed, presenting as hematometra, cyclical abdominal pain, and mass. Our index patient had a case of vaginal atresia with the uterus forming a fistula with the bladder, which presented as cyclical menouria. Multiple case reports have highlighted such patients not being able to be classified in current systems.

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