

Herlyn-Werner-Wunderlich Syndrome: A Mini-review

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Herlyn-Werner-Wunderlich (HWW) syndrome is a rare congenital malformation syndrome that is characterized by a triad of uterine didelphys, blind hemivagina, and ipsilateral renal agenesis. There is a wide variety of phenotypic presentation which is recognized as a spectrum of disease rather than a separate entity. The exact incidence and pathogenesis of HWW syndrome are yet to be investigated. While this disease typically involves adolescent girls who present with abdominal pain or a pelvic mass that is secondary to hematocolpos, nowadays, a majority of potential patients with HWW are being prenatally screened for renal anomalies. Therefore, it is recommended to search for uterovaginal anomalies whenever a multicystic dysplastic kidney or the absence of a kidney is noted in a newborn female, and the role of pediatric nephrologists has become ever more important for early recognition of the disease.

Key words: Müllerian duct anomaly, renal agenesis, hemivagina, Uterus didelphys, female genital anomalies

Introduction

Herlyn-Werner-Wunderlich (HWW) syndrome is a combined anomaly syndrome with uterine didelphys, blind hemivagina, and ipsilateral renal agenesis^{1,2}. It is sometimes also referred to as obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome³. It was firstly reported in 1925 by Wilson⁴, and decades later Herlyn⁵, Werner⁵, and Wunderlich⁶ have elaborated on its clinical presentation. Although the exact incidence of HWW syndrome is not known, it is expected that a patient with double uterus has a renal agenesis in 63–81% of the cases and an obstructed hemivagina in 6%⁷. The etiology of müllerian anomalies, including HWW syndrome is controversial and yet to be investigated⁸.

Owing to the recent development in diagnostics, patients with a single kidney are being prenatally screened which consequently brought forward the age at diagnosis of HWW syndrome earlier than ever. In spite of such an advance in diagnostic technology, however, the significant heterogeneity of its clinical manifestation seems to hinder prompt recognition. Understanding the heterogeneous presentation of this syndrome is important also in that the clinical presentation and complications may differ between the variants. Since, nowadays, a majority of potential HWW patients firstly visit a pediatric clinic for prenatally detected renal anomalies, the role of pediatric nephrologists

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has become increasingly important for early recognition and proper diagnosis.

Clinical presentation and diagnosis

1. The classic triad and the variants

The classic triad of HWW syndrome includes uterine didelphys, obstructed hemivagina, and ipsilateral renal agenesis^{1,2}. Recently, however, anatomic variants have been introduced. Although HWW is characterized by a complete obstruction of the hemivagina, a body of literature reported that the vaginal septum may have a fenestration and thus the obstruction may be either partial or complete. In a case series by Fedele et al⁹, about 18% (16/87) of HWW patients had an incomplete septum in which the obstructed hemivagina was partially communicant with the contralateral counterpart. Moreover, in cases where the vaginal septum is very thin, the pressure from retained menstrual products over time can result in a spontaneous perforation, leading to communication between the two vaginas⁷. The presence of fenestration as such can delay the diagnosis because fully distended hematocolpos and its related symptoms may be absent on initial examination⁷. Uterine anomalies such as didelphys, bicornuate, septate uteri are considered to be on the same spectrum of disease, depending on how 'caudally' the müllerian ductal fusion occurs¹⁰. A likewise variation should be understood for vaginal anomalies. In addition, the uterine cervix may also have anatomical variation. Cervical atresias⁹ and double cervix with hemicervical obstruction with rudimentary hemiuterus may present like a single vagina¹¹. Moreover, although ipsilateral renal agenesis on the obstructed hemivaginal side is the most commonly accompanied renal anomaly, other renal anomalies, including dysplastic, multicystic, and/or ectopic kidney are reported as variant forms^{3,12}. Furthermore complete agenesis and severe ectopic dysplasia of unilateral kidney are usually not easy to discern since the dysplastic kidney may involute or atrophy over time.

2. Clinical presentation

In the classic presentation with natural history, dysmenorrhea with recurrent progressive lower abdominal pain after menarche is most commonly seen and often the ear-

liest appearing symptom³. Patients are usually asymptomatic until menarche^{13,14}, and the symptom presents over time, due to entrapment of menstrual contents within the obstructed hemivagina³. It is reported that most patients are diagnosed from 2 months to 1 year after menarche^{1,14,15}. In the presence of a menstrual outflow obstruction, hematometra, hematosalpinx, and endometriosis may be accompanied as the main reasons for cyclic pelvic pain and metromenorrhagia¹⁶. It is usually the degree of vaginal anomaly that defines the symptom and relates to the age at initial presentation. Patients with complete hemivaginal obstruction may visit the clinic earlier due to symptoms from hematocolpos, compared to patients with incomplete obstruction. It has been reported that HWW syndrome can present as early as the neonatal period¹⁴ depending on anatomy and cervical development.

In the nonclassic presentation, patients may initially present with a solitary kidney or a multicystic dysplastic kidney on prenatal ultrasonography (USG).

Previous studies have reported right side predominance of the affected laterality, with a ratio of 2:1^{8,16-18}.

3. Mode of diagnosis

The mainstay of diagnosing HWW is radiologic findings. If there is typical hematocolpos, ultrasonography (USG) often shows a hypoechoic mass between the bladder and the rectum¹⁴. Although several reports have suggested that magnetic resonance imaging (MRI), hysterosalpingogram (HSG) and laparoscopy could aid in the accurate diagnosis¹⁹⁻²¹, careful gynecological examination and USG may result in correct and timely diagnosis in the great majority of cases¹¹. However, the presence of hematocolpos frequently distorts the anatomy and makes the diagnosis on USG quite challenging in which cases MRI is recommended⁷. MRI is also advocated as a useful tool to discern renal variants with dysplasia and/or ectopia, incomplete vaginal duplication and uterine anomalies with variations in which discrete images are required. Even in such cases, given the high accuracy of MRI, laparoscopic exams or HSG are reserved for very limited cases³.

Nowadays, renal agenesis or multicystic dysplasia is usually a prenatal or neonatal diagnosis. It is therefore advisable for female newborns with renal malformations - a multicystic dysplastic kidney or the absence of a kidney-

to be looked for genital anomaly. However, the small size and tubular shape of the uterus in infancy makes it extremely challenging to evaluate the uterine anomaly¹⁾. It is therefore recommended that asymptomatic neonatal patients with renal malformations receive follow-up USG examination for potential uterovaginal anomaly until the end of puberty¹⁾.

Complications

1. Gynecologic

When the vaginal septum is thin, it is easy to have a spontaneous fenestration and the partial hemivaginal obstruction with communication may present with metrorrhagia or chronic vaginal discharge due to delayed menstrual passage from the partially obstructed side⁷⁾. Moreover, the presence of perforation may allow ascending migration of pathogenic bacteria, leading to infection of the hematocolpos and even pelvic inflammation²²⁾.

When the vaginal septum is thick, the thick septum limits the ability of the hemivagina to distend distally⁷⁾ which consequently can cause retrograde bleeding into the peritoneal space, leading to endometriosis^{1,7,23)}. Endometriosis has been reported with rates of 17%–35% among women with uterus didelphys^{24,25)} and 23% in patients with HWW or OHVIRA^{2,3,22,23)}. Literature reports that if decompression is timely performed, endometriosis could be prevented^{7,16)}.

2. Renal/urologic

As well as renal anomalies ipsilateral to the vaginal obstruction, the reported prevalence rate of contralateral renal anomalies, such as dysplastic or polycystic kidney is up to 50%²²⁾. In addition, ipsilateral anomalies of the urinary system such as, ectopic or duplicated ureters have been reported^{3,26)}. There are reports of an ectopic ureter with insertion into the obstructed hemivagina^{27,28)}, which should be suspected when the patient complains of persistent urine leakage or incontinence²⁸⁾.

Since the hyperfiltration hypothesis implies that children with solitary functioning kidney are at risk to develop hypertension, proteinuria and chronic kidney disease²⁹⁾, the follow-up of these patients must avoid factors that may

aggravate existing congenital renal damage. Accompanied urologic anomalies can cause recurrent urinary tract infections which may aggravate the renal function. Consultation with urology is highly recommended for any renal anomaly⁷⁾. Regular monitoring for renal function and proteinuria as a marker of glomerular damage is recommended, especially during the peri-pubertal period where the impairment of renal function may exacerbate due to rapid somatic growth.

3. Infertility

Since the ovarian function is theoretically preserved, it is considered that primary infertility among women with HWW syndrome may be caused by factors such as endometriosis and pelvic abscesses rather than the anatomical anomaly itself⁶⁾. Although the exact statistics with regard to infertility in HWW patients is not available, it has been reported that women with uterine didelphys have comparable reproductive performance as that of women with a unicornuate uterus³⁰⁾. However, if proper management was not timely provided, complications leading to endometriosis, pyosalpinx or pyocolpos, and subsequent pelvic adhesions may present with infertility or miscarriage^{14,22,31,32)}. Early diagnosis and timely decompression of vaginal obstruction could avoid complication and preserve reproductive capacity^{14,15)}.

Treatment

Currently, the preferred surgical approach for patients with HWW syndrome is resection of the vaginal septum^{7,14)}. The resection is usually not an emergency, except for rare cases complicated with infection⁷⁾. To date, the curative procedure is recommended to be performed around the pubertal period given the lack of long-term data regarding excision of vaginal septum in the prepubertal age⁷⁾. In cases complicated by cervical atresias or other structural anomalies, the surgery may be postponed even after the puberty and in such cases, gonadotropin-releasing hormone analogs may be a good option for maintaining amenorrhea and reducing complications¹⁶⁾. Laparoscopic surgery is indicated for patients with complications such as endometriosis or abscess¹⁶⁾. Overall, timely performed surgical

removal of the obstructing vaginal septum can provide rapid relief of symptoms, prevention of complications, and preservation of fertility in majority of the cases.

Conclusion

Herlyn-Werner-Wunderlich syndrome should be suspected in cases with cyclic pelvic pain and also in neonatal cases with any renal malformations. Understanding its broad spectrum of phenotypic presentation may aid screening out the over-looked population. The patients need to be searched for urologic, gynecologic problems and regularly monitored for renal function. Prompt diagnosis based on clinical suspicion and timely intervention is essential for prevention of potential complications.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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