Journal of Pediatric Surgery 55 (2020) 1377–1380

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Preventing the O in OHVIRA (Obstructed Hemivagina Ipsilateral Renal Agenesis): Early Diagnosis and Management of Asymptomatic Herlyn–Werner–Wunderlich Syndrome☆

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ARTICLE INFO

Article history:
Received 10 April 2019
Received in revised form 13 May 2019
Accepted 7 June 2019

Key words:
Herlyn–Werner–Wunderlich syndrome
OHVIRA syndrome

ABSTRACT

Introduction: Herlyn–Werner–Wunderlich syndrome (HWWS) is a rare variant of Mullerian ductal anomaly associated with ipsilateral renal agenesis. Most patients are diagnosed after menarche with complications of uterovaginal obstruction, genitourinary infection and pelvic adhesions. Patients often undergo additional operations for misdiagnosis or treatment of complications. Our institution manages several HWWS patients diagnosed before symptoms by screening for antenatally-diagnosed renal agenesis. This study aims to improve the presymptomatic management of HWWS patients.

Methods: We carried out retrospective case review of patients diagnosed with HWWS from 2010 to 2017 on patient demographics, symptoms, clinical course and operative management and summarize the sparse literature published to date.

Results: There were 8 patients with HWWS but only 2 symptomatic patients presented acutely with hematocolpos requiring urgent vaginal surgery. The other six patients had early diagnosis through postnatal ultrasound screening. No patient required further operation for diagnosis or complications related to obstructed hemivagina.

Conclusion: Our case series and literature review show that the majority of prepubertal patients with HWWS do not require early gynecological surgery. We recommend that female babies with renal agenesis should be screened for HWWS syndrome with ultrasound. Early diagnosis and presymptomatic elective surgery may prevent urogynecological complications that cause fertility and renal impairment.

Study design: Case series, level IV evidence.

The Herlyn–Werner–Wunderlich syndrome (HWWS) is a rare variant of Mullerian ductal anomalies characterized by the presence of hemivaginal septum and uterine anomaly, predominantly didelphys, associated with ipsilateral renal agenesis [1,2]. HWWS constitutes only 0.16%–10% of all Mullerian duct anomalies, which have an incidence of 2%–3% [3]. However, the very low reported incidence of this syndrome may be because of underdiagnosis related to poor awareness of this condition. Current literature comprises small retrospective case series of adolescents and women diagnosed after menarche, when they present with symptoms related to complications of obstructed hemivagina [4,5]. A significant proportion of these patients underwent unnecessary operations before diagnosis and delayed treatment resulted in gynecological complications with potential future obstetric problems.

There is generally excellent antenatal care in Singapore and most local expectant mothers receive a routine second trimester antenatal ultrasound screen for anomalies. Our institution is the national maternal and child hospital and the main referral center for congenital anomalies. Several of our patients with HWWS are diagnosed before puberty, through postnatal screening for concomitant uterovaginal anomalies in patients with antenatally-diagnosed renal agenesis.

1. Aim

The aim of our study was to review the cases of HWWS managed in our institution and summarize the published literature to improve presymptomatic management of HWWS patients.

2. Methods

Upon institutional review board approval (Singhealth IRB 2019/2041), we carried out a retrospective review of case records of all patients diagnosed with HWWS at our institution from January 2010 to October 2017. Data were collected on patient demographics, symptoms, clinical course, management and follow-up.

☆ Conflict of interest: We declare no conflict of interest.

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https://doi.org/10.1016/j.jpedsurg.2019.06.006
0022-3468/

2.1. Case series (Table 1)

There were 8 patients and all had antenatal diagnosis of renal anomaly. HWWS was recognized in 6 patients (75%) through postnatal screening for associated gynecological abnormalities (5 as neonates and one at 3 years old). In these 6 patients, two neonates had hydrocolpos and were managed conservatively with subsequent resolution on follow-up scans. The patient diagnosed at age 3 years old (Patient 6) was on regular follow-up and elective surgery was carried out after menarche before she developed symptoms. Both post pubertal patients in our series (Patients 7 and 8) were diagnosed when they presented with symptoms of hematocolpos and required vaginal surgery to relieve the obstruction.

All 8 patients had ultrasound (US) as the primary form of imaging while 1 patient underwent additional magnetic resonance imaging (MRI) to aid diagnosis. Seven patients had uterine didelphys and 1 patient had bicornuate uterus. The renal abnormalities included multicystic dysplastic kidney (MCDK) in 2 patients and renal agenesis in 6 patients, with laterality 3 on the left and 5 on the right. Three patients had contralateral urological involvement (2 vesicoureteral reflux and 1 dysplastic duplex kidney). Four patients underwent urological surgeries but only 1 patient had renal impairment.

3. Discussion

The syndrome of obstructed hemivagina and ipsilateral renal agenesis syndrome (OHVIRA), earlier described as Herlyn–Werner–Wunderlich syndrome (HWWS), was first reported by Purslow in 1922. Pathogenesis is presumed to occur during the eighth week of gestation owing to embryologic arrest involving the Mullerian (paramesonephric) and Wolffian (mesonephric) ducts [2]. Regression of the Wolffian duct, in particular the ureteric bud and metanephric blastema, results in ipsilateral renal maldevelopment, commonly manifesting as agenesis or MCDK [6]. Malposition of the paired Mullerian ducts leads to uterine didelphys as the two hemiuteri/hemicervices fail to unite. Lastly, the failed development of the ipsilateral mesonephric duct at the urogenital sinus contributes to the underdevelopment of the distal vagina, which results in obstruction.

Awareness of this rare congenital anomaly remains limited. Most of the published literature comprises individual case reports and few retrospective case series with ≫5 patients. Table 2 provides a summary of these 8 studies describing a total of 201 female patients: the majority presented shortly after menarche with symptoms of pelvic pain, pelvic mass/hematocolpos and occasionally vaginal discharge or acute urinary retention. Some young women had additional complications of hematometros, endometriotic ovarian cysts, pelvic adhesions and genitourinary infections.

Most authors highlighted that clinicians lack awareness of the association of uterine abnormalities with unilateral renal anomalies [10,14,15]. To date, there have been only 2 case reports [7–8] and 3 case series [12,14,16] that describe early recognition and diagnosis in prepubertal girls, while the rest [9–11, 13, 15] are retrospective case series of symptomatic post pubertal patients. The poor awareness of HWWS has led to 2 potentially preventable complications. Firstly, up to 20% of patients [15] have undergone prior unnecessary laparotomies or laparoscopies for misdiagnosed pelvic mass. Additionally, delayed diagnosis led to other gynecological complications apart from hydrocolpos/hematocolpos, such as abscess formation and endometriosis from retrograde menstrual flow. Capito et al. [12] reported that 5 of 24 patients diagnosed after puberty required hysterectomy in view of infection, while none of the 8 patients diagnosed before puberty required additional intervention other than vaginoplasty. Unnecessary operations and infective complications increase the risk of developing intestinal adhesions and tubal blockage that contribute to subfertility, which compounds the problem of higher pregnancy loss rates in patients with Mullerian duct anomalies [17].

In our case series, while all 8 patients had antenatal diagnosis of renal abnormalities, only 6 received postnatal screening for concomitant uterine abnormalities. They are younger compared to the 2 patients diagnosed at puberty, which reflects improved clinician recognition of this condition in recent years. We hope that early recognition of this condition and elective vaginal septum resection at menarche (similar to management of Patient 6), should result in improved outcomes for the rest of our patients without gynecological complications or impact on subsequent fertility.

US pelvis and/or MRI have been recommended for the diagnosis of OHVIRA syndrome, while MRI allows better delineation of the type of uterine anomaly and vaginal septum to aid surgical planning [18,19]. Laparoscopy at the time of vaginal surgery is favored by some authors [9,11] for improved anatomical diagnosis and permits concomitant therapeutic drainage of intraabdominal abscesses, pelvic adhesiolysis and endometriosis surgery. These recommendations have been made for symptomatic patients presenting with immediate surgical indications. Han et al. [14] suggested that it is not cost-effective to screen all patients with unilateral MCDK or renal agenesis for HWWS because of the low incidence (1.9%). We differ in our management since there is easy access to high quality US at our institution. Since we routinely do postnatal US scans for confirmation and subsequent monitoring of antenatally diagnosed unilateral kidneys, it is a simple addition to screen for associated uterovaginal anomalies. Early diagnosis of HWWS would facilitate planning of elective surgery before patients develop complications. In our series, all asymptomatic prepubertal patients were diagnosed and regularly followed up with US while MRI was reserved for preoperative planning. Pediatric patients less than the age of

Table 1
Patient characteristics.

Patient Index	Current Age (Year, month)	Age of diagnosis	Primary Imaging	Renal abnormality	Laterality	Contralateral kidney	Urological surgery	Uterine abnormality	Vaginal surgery	Follow up (months)
1	2 y	Perinatal	US	MCDK, ectopic ureter	Left	Normal		Didelphys	N	22
2	2 y, 6 mo	Perinatal	US/MRI	Agenesis	Left	Normal		Bicornuate	N	28
3	7 y, 2 mo	Perinatal	US	Agenesis	Right	Dysplastic duplex kidney with ureterocele	Ureterostomy (contralateral)	Didelphys	N	86
4	7 y, 6	Perinatal	US	Agenesis	Right	Normal		Didelphys	N	90
5	6 y	Perinatal	US	Agenesis	Right	Normal		Didelphys	N	70
6	11 y, 5 mo	3 y	US	Agenesis	Right	VUR	Reimplantation (contralateral)	Didelphys	Y Septum resection	88
7	17 y, 8 mo	11 y	US	MCDK, ectopic ureter	Left	Normal	Nephroureterectomy (ipsilateral)	Didelphys	Y Septum resection	54
8	20 y, 4 mo	12 y	US	Agenesis	Right	VUR	Reimplantation (contralateral)	Didelphys	Y Septum resection	100

Table 2
Summary of case series with ≫5 patients.

Author Year	No of patients (prepubertal)	Median age of diagnosis (range)	Renal abnormality	Uterine abnormality	Symptomatic	Surgery ([a]Urological operations were reported only in the series with prepubertal patients)	Primary imaging modality
Zurawin 2004 [9]	8	14.5 y (11–22)	8 Agenesis	Didelphys	8 had dysmenorrhea	8 had vaginoplasty 5 had laparotomy/laparoscopy for endometriosis or infection 2 required hysterectomy	CT, MRI
Smith 2005 [10]	27	14 y (10–29)	20 Agenesis 3 MCDK	Didelphys	23 had abdominal pain	26 had vaginoplasty 4 required second stage procedure 4 prior laparoscopy for endometriosis	US, MRI
Gholoum 2006 [11]	12	13 y (11–15)	10 Agenesis	Didelphys	11 had abdominal pain / pelvic mass 7 had dysmenorrhea 4 with menometrorrhagia 2 with intraabdominal abscesses	All had vaginoplasty 1 required laparotomy and salpingectomy for abscess	US
Capito 2008[a] [12]	32 (8)	Prepubertal: 6 mo (0–6 y)	6 Agenesis 2 MCDK	Difficult to assess 19 Didelphys	7 hydrocolpos	7 vaginoplasty (4 nephrectomies for ectopic ureters)	US
		Pubertal: 14 y (11–17)	22 Agenesis 2 MCDK	3 Septated uterus	11 acute abdomen 13 had vaginal discharge, dysmenorrhea and menometrorrhagia	24 had vaginoplasty 5 required hysterectomy for infection	
Tong 2013 [13]	70	21 y (10–50 y)	All agenesis	Didelphys	45 dysmenorrhea 28 mucopurulent vaginal discharge 18 metromenorrhagia 14 acute pelvic inflammation 12 endometriosis	All had vaginoplasty 9 required laparotomy / laparoscopy for pelvic adhesions, abscesses, or endometriosis	US, MRI
Han 2016[a] [14]	43 (43)	1.3 mo (0.1–3.6 mo)	28 MCDK 15 Agenesis	38 Didelphys 2 Bicornuate 3 Single uterus	2 protruding mass 1 urinary incontinence 1 Abdominal pain 1 Hydroureteronephrosis	3 vaginoplasty (4 nephrectomies)	US, MRI, CT
Kapczuk 2017 [15]	18	13.1 y (11.4–18.2)	Agenesis	16 Didelphys 2 Complete uterine separation	13 Abdominal pain 2 Dysmenorrhea	18 had vaginoplasty 4 prior unnecessary surgeries for misdiagnosed of adnexal mass	US, MRI
Noviello 2018[a] [16]	6 (2)	9y (2mo–15y)	Agenesis	Didelphys	4 Abdominal pain and hematocolpos	All had vaginoplasty	US, MRI
Our series[a] 2018	8 (6)	Prepubertal: 1 mo (0.1–3 y) Pubertal: 12 y (11–12 y)	6 Agenesis 2 MDCK	7 Didelphys 1 Bicornuate	2 Abdominal pain and hematocolpos	3 had vaginoplasty (1 nephroureterectomy)	US

[a] Series includes prepubertal patients.

7 years typically require general anesthesia to keep immobile for the time taken for MRI image acquisition, hence delaying the MRI until older age avoids unnecessary general anesthesia.

The two commonest ipsilateral renal anomalies described in HWWS are renal agenesis and MCDK with variable prevalence rates. The largest prepubertal pediatric retrospective review of 43 patients by Han et al. [14], showed a higher prevalence of MCDK (65.1%), compared to our case series of 25.0%, while Tong et al.'s review of 70 postmenarche patients [13] only reports renal agenesis with no MCDK. There are 2 possible explanations for this phenomenon. Firstly, earlier definition of OHVIRA only included cases with renal agenesis and older series may have excluded cases associated with MCDK. Alternatively, the natural history of antenatally diagnosed MCDK has a spontaneous involution rate of 53.5% by ten years of age [20]. Hence, the greater prevalence of renal agenesis in series with older patients could be due to involuted MCDK being classified as renal agenesis. Other urological associations include ipsilateral ectopic ureteral insertion into the obstructed vagina which can give rise to incontinence and infection, requiring ureterectomies or ligation of ureters. A significant proportion of patients have contralateral urinary abnormalities, most commonly VUR [14].

Due to the delayed diagnosis of this condition until puberty, there is little guidance on infant and prepubertal childhood management for asymptomatic patients. Han et al. [14] evaluated the natural course of OHVIRA in 43 infants with mean age of 1.3 months (median IQR 0.1–3.6 months) with mean follow-up of 25 months. Six patients (14.0%) required surgical intervention (either nephrectomy or vaginal surgery or both) at a median age of 31 months. Four (9.3%) of them had vaginal aspiration with or without septum resection for prolapsing mass or contralateral urological obstruction. Of the remaining patients, 12 had complete resolution, 7 partial resolution and the rest had persistent vaginal distension at the end of the study period. There were 6 patients with contralateral VUR in their series but there was no elaboration on management.

In our study, there was no prepubertal vaginal intervention: Two infants had vaginal distension prior to 6 months of age and achieved complete resolution without treatment. On the other hand, four patients (50%) required urological surgeries. One patient with MCDK underwent ipsilateral nephroureterectomy for urinary tract infection and 3 patients (33.3%) required contralateral urological surgery (one ureterostomy creation for duplex dysplastic kidney with ureterocoele and 2 patients vesicoureteral reimplantation for VUR.)

This suggests that the majority of cases of HWWS diagnosed in the perinatal period can be safely managed conservatively in early childhood without need for vaginal surgery. Once transmitted maternal hormone stimulation ceases, perinatal hemivaginal blood collection typically resorbs without problems if it remains sterile. It is likely that the exceptions are patients with ipsilateral MCDK associated with an ectopic ureter opening into the obstructed vagina where it causes continued urine accumulation and predisposes to infection [21].

In our institution, for asymptomatic cases diagnosed via perinatal screening, we presently adopt a 6-monthly follow up till 2 years of age, followed by annual or biennial clinical review with renal and pelvic US. More frequent reviews are undertaken as required for symptomatic patients, as well as those close to puberty in order to avoid complications of hematometrocolpos. At puberty, multidisciplinary care allows smooth transition to adult care: the nephrologist is involved for renal protection while vaginal surgery is undertaken together with the adolescent gynecologist who subsequently manages counseling for future pregnancy [22] when the adolescent is emotionally ready.

4. Conclusion

We recommend that female babies with renal agenesis or MCDK should be screened for HWWS syndrome with US. The majority of prepubertal patients with HWWS do not require vaginal surgical intervention while some may require ipsilateral or contralateral urological surgery. Early diagnosis and presymptomatic elective surgery may prevent urogynaecological complications that cause fertility and renal impairment.

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