Herlyn-Werner-Wunderlich Syndrome

December 18, 2020

Herlyn-Werner-Wunderlich Syndrome

Objectives

The reader will be able to:

1. Understand what Herlyn-Werner-Wunderlich Syndrome is.
2. Identify the main symptoms of HWWS and how it affects the reproductive system.
3. Recognize how radiology plays a significant role in diagnosis.
4. Distinguish the different treatments suggested for HWWS.

I. Introduction

Herlyn-Werner-Wunderlich Syndrome is a rare congenital syndrome that affects the female reproductive and abdominal organs. This syndrome can affect a young woman's menstrual cycle and future pregnancies. HWWS is best treated surgically.

II. History

III. Genetics and Development

IV. Symptoms

A. Uterus didelphys

B. Obstructed hemivagina

C. Ipsilateral renal agenesis

V. Diagnosis

A. Classification 1

B. Classification 2

VI. Roles of Radiology

A. US

B. MRI

C. CT

D. Fluoroscopy/HSG

VII. Treatments

A. Surgery

B. Outcomes

C. Pediatrics

D. Untreated diagnosis and risks

VIII. Interview with Dr. Keith Hansen, MD

IX. Conclusion

Introduction

Herlyn-Werner-Wunderlich Syndrome, or HWWS, is a rare congenital syndrome that affects the reproductive system and kidneys of young women. Approximately 0.1% to 3.8% of women are affected by HWWS. The characteristics of HWWS include the three main abnormalities: uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis. Young women with HWWS are usually diagnosed around puberty age or after their first menstrual period. For diagnoses, physicians rely on imaging modalities such as ultrasound and MRI to depict uterine and renal anomalies. The most common treatment for HWWS is surgical excision

soon after diagnosis. Young women who have HWWS and are treated with surgery generally recover well and have successful pregnancies later in life. If left untreated, certain complications, such as endometriosis and issues with fertility, could arise. HWWS is newly referred to in literature as OHVIRA or Obstructed Hemivagina and Ipsilateral Renal Agenesis. Due to modern imaging and an increase in diagnoses, research and overall awareness of Herlyn-Werner-Wunderlich Syndrome is slowly but surely expanding.

History

In 1922, the first case of HWWS was said to be reported.[1] It was not until 1971, that German physicians, Herlyn and Werner had their first patient with an open Garner duct cyst, homolateral renal aplasia, and double uterus. About 5 years later, another German physician, Wunderlich, came across a woman with a bicornuate uterus, isolated hemocervix, and right kidney & ureter aplasia. The names of the three physicians (first names unknown) were combined to term these rare genetic cases of uterine anomalies: Herlyn-Werner-Wunderlich Syndrome.

Sixty years after the first diagnosed case, only 115 cases were reported in literature. In the last twenty years, a growing 170 cases were published. With ultrasound and MRI becoming more readily available, there is an increase of awareness of HWWS and uterine anomalies in general. These modalities will help with improvement in future research, diagnoses, and overall gynecologic care.[2]

There are several types of Müllerian duct system abnormalities, along with symptoms grouped into those anomalies. Herlyn-Werner-Wunderlich Syndrome can be classified as a more specific type of OHVIRA, or obstructed hemivagina and ipsilateral renal anomaly. OHVIRA is claimed to be the newer term in literature to generalize uterine anomalies, including HWWS.

Genetics and Development

Advanced research within the genetic component concerning HWWS is still yet to be found. Herlyn-Werner-Wunderlich Syndrome is a congenital syndrome and at this time, there are no known mutated genes directly related. Although, some researchers say that HOX genes could be somewhat related to this syndrome. The HOX genes are regulators of the Müllerian system

during embryonic development.[3] They are vital for the overall female reproductive system, which could explain why researchers are making the connection with HWWS.

In development, the Müllerian duct system is responsible for the fallopian tubes, uterine cervix, uterus, and part of the vagina. If the Müllerian ducts are disrupted or fail to fuse during development, abnormalities of the reproductive system can arise, such as HWWS.

During embryonic development, the internal organs of the embryo start to form in a stage named organogenesis. Organogenesis happens within the second to twelfth week of pregnancy. It is not until the third to eighth week of pregnancy that the embryo's reproductive system will begin to fully develop. Thus, in cases of HWWS, the embryo affected in this stage will start to develop uterine, vaginal, and renal anomalies.

Symptoms

The three main characteristics of Herlyn-Werner-Wunderlich Syndrome are recognized as the "triad" of anomalies: uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis. Being a congenital syndrome, these anomalies occur during embryonic development, specifically during organogenesis.

The first characteristic to distinguish HWWS is uterus didelphys. Uterus didelphys represents having two separate uteri and two cervices.[4] This is caused by the Müllerian ducts failing to fuse together during embryonic development. Two separate uterine cavities are then formed. Figure 1 demonstrates the difference between a normal uterus with one cervix and uterus didelphys along with two cervices. It will be discussed later in the Diagnoses section which classifications of HWWS have communicating or non-communicating uteri.

The second characteristic of the triad is an obstructed hemivagina. A hemivagina is the presence of a vagina with a septum or wall of tissue separating the vagina into two canals. The presence of two canals is commonly mistaken as having two or "double vaginas", which is not the case. There will not be two vaginas, but rather one vagina with a fused septum, bisecting the vagina. The obstructed hemivagina is also caused by the Müllerian and Wolffian ducts not properly fusing. While the vagina has two pathways leading into the uterus, it is highly possible for patients with HWWS to have an obstruction or hematocolpos on one side. The obstruction or hematocolpos is a buildup of menstrual blood that causes an obstruction within the vagina.

The third characteristic of the HWWS triad is ipsilateral renal agenesis. Ipsilateral renal agenesis is the absence of one kidney. “Because the embryologic origins of the female reproductive system and the urinary system develop in tandem, the anomalies in HWWS are ipsilateral (same side)”.[5] This means whichever side the vaginal obstruction is located, the same side will correlate to which kidney is missing. If there is an obstruction on the left side of the vagina, there would be a left kidney missing. If there is an obstruction on the right side of the vagina, the patient would be missing her right kidney.

This triad of symptoms are also associated with other common symptoms that can help lead to the diagnosis of HWWS. These symptoms include acute to chronic abdominal and pelvic pain, dysmenorrhea (pain with menstruation), irregular or intermenstrual bleeding, and the presence of palpable masses. Some less common symptoms might include fever, amenorrhea (absence of menstruation), dyspareunia (pain during intercourse), urinary retention, abnormal vaginal discharge, and ruptures of the hematocolpos.[1] While physicians rely on the main triad of characteristics to diagnose HWWS, a patient can have a wide variety of the minor symptoms listed along with the triad.

Diagnosis

HWWS is typically diagnosed around puberty age or after the first menstrual period. Diagnosis of HWWS is oftentimes delayed due to a number of factors. One common factor would be having dysmenorrhea or pain during periods. Almost 85% of women have some kind of pain during their periods, making HWWS difficult to diagnose. “With normal external genitalia, diagnosis is often delayed until after menarche with most affected patients presenting with progressive dysmenorrhea and a suprapubic mass on abdominal exam”.[6] Unknowingly, birth control can sometimes play a factor into controlling symptoms of pain and bleeding, but not for treatment. It is common for patients taking birth control to have the absence of pelvic pain, abdominal pain, or irregular bleeding, thus delaying diagnosis as well. Some patients are not aware of any irregularities of HWWS until issues of fertility or their pregnancy arise.

There are two different classifications of HWWS that researchers have developed within the last few years: Classification 1 and 2. Within each classification lies two subtypes researchers could categorize the detailed symptoms into.

Classification 1 is characterized as HWWS with a completely obstructed hemivagina. Classification 1.1 is specifically characterized with a blind hemivagina. “The hemivagina is completely obstructed; the uterus behind the septum is completely isolated from the contralateral uterus; no communication is present between the duplicated uterus and vagina”.[7] Hematocolpos are common to appear a few months or years after the first menstrual period. Figure 3 demonstrates HWWS-Classification 1.1

Classification 1.2 is characterized with an obstructed hemivagina, with a cervicovaginal atresia without communicating uteri. “The hemivagina is completely obstructed; cervix behind the septum is maldevelop or atresic; and menses from the uterus behind the septum cannot outflow through the atresic cervix”.[7] This classification is important as to how providers continue with treatment compared to the other classifications. Figure 4 depicts HWWS-Classification 1.2.

Classification 2 is recognized as an incompletely obstructed hemivagina. Classification 2.1 is characterized with partial reabsorption of the vaginal septum. “[There is] a small communication between the two vaginas, which makes the vaginal cavity behind the septum incompletely obstructed; the uterus behind the septum is completely isolated from the contralateral uterus”.[7] HWWS-Classification 2.1 is displayed in Figure 5.

Classification 2.2 is distinguished with communicating uteri. “The hemivagina is completely obstructed, and a small communication exists between the duplicated cervices”.[7] Both types of Classification 2 have been termed “newer” classifications that clinicians are hoping to diagnose sooner and provide treatments for in different ways of those classifications with completely obstructed hemivaginas.[7] Figure 6 illustrates HWWS-Classification 2.2.

Age is a significant factor with diagnosing HWWS. As stated before, HWWS is usually diagnosed after puberty age or after menarche (first menstrual period). Researchers claim female infants and children who have renal agenesis should be considered for having uterine anomalies.[1] The earlier the diagnosis is found, the better to prevent uterine complications and preserve fertility of younger female patients. Similar to most medical plans, physicians consider the safest and most appropriate approach when it comes to pediatric patients. This will limit radiologic imaging such as CT scans and fluoroscopic exams. Relying on ultrasounds and MRI is key for pediatric patients.

Depending on the patient and patient age, it is important to note whether or not the female is sexually active and if she would like to bear children in the future. As later mentioned

within Treatments, this will help the physician devise the best medical plan and journey for patients with HWWS.

Roles of Radiology

Imaging plays a significant role in helping diagnose HWWS. The images from different modalities are vital in providing doctors and physicians the tools to establish a diagnosis or better care plan. Ultrasound and MRI are primarily relied on with HWWS, while CT and fluoroscopy are quick to follow if needed.

Ultrasound is usually the first imaging modality used to diagnose HWWS. This modality is well-liked due to the procedures being non-invasive and the use of no radiation or contrast. Transabdominal ultrasounds are first used for more of an overall evaluation of the abdomen and pelvis. If the transabdominal ultrasound is completed or not at all suggested, a transvaginal ultrasound will follow. A transvaginal ultrasound will be used to further depict anatomy and better detect anomalies.[1] The first distinction of uterus didelphys and/or double uteri are recognized with ultrasound.[4] Some physicians may suffice making the diagnosis with a transvaginal ultrasound.[9] Doctors are to keep in mind that with diagnosing a pediatric patient or a young patient who is not sexually active, a transvaginal ultrasound is not recommended. Nonetheless, both ultrasound procedures benefit by being referenced together. “Ultrasonography can show uterovaginal duplication, hematocolpos or hematometrocolpos, along with the absence of ipsilateral renal kidney”.[10] Ultrasound is important for the initial evaluation of the pelvis and symptoms associated, but not enough to clearly identify the anatomic abnormalities in the patient.[8]

Similar to ultrasound, MRI procedures are also non-invasive and use no radiation. MRI is said to be more accurate than fluoroscopy and ultrasound, by evaluating uterine contours, shapes of each cavity, course of the vaginal septum, and detection of acute and chronic complications.[1] MRIs provide multiplanar image acquisition that provides more details.[7] MR imaging is also able to distinguish any communication between two cervices or two vaginal canals.[10] MR contrast media via IV is not routinely used but could be used in rare cases of infectious complications or incidental findings. Figure 2 shows an MRI scan (in coronal view) of a patient with HWWS, demonstrating uterine didelphys, absent left kidney and a left sided hematocolpos.

CT, or computed tomography, is not always preferred in diagnosing uterine anomalies. More disadvantages are risked with CT scans. CT requires radiation exposure and contrast administration, making this modality undesirable for young female patients as well as pediatric patients. CT imaging does not easily depict pelvic anatomy as MRI, but may be used when abdominal ultrasounds are not conclusive. Though as a benefit, CT scans can help find cystic lesions, which could possibly lead to obstructions in the reproductive system.[1]

Fluoroscopy, or specifically, a hysterosalpingogram exam (HSG), is not typically a front-line procedure suggested with uterine anomalies. Like CT, an HSG uses radiation exposure and contrast material that is injected via the cervix. A catheter is inserted into the cervix. A balloon attached to that catheter is inflated, as contrast fills up the uterine cavity. An HSG will contribute information regarding the interior cavity of the uterus, but will fail to demonstrate external evaluation and any non-communication between uteri.[1] Figure 7 shows an HSG exam with uterus didelphys and double cervices. Access to the uterus will be dependent on the patient or on a case-by-case basis. Specifically with patients of Classification 2.2, the iodinated contrast during an HSG could pass through the communication between the duplicated cervices to the opposite uterus and any cavities lying posteriorly.[7]

With past cases of HWWS, other procedures were said to be rare but still used in special instances. A hysteroscopy allows direct visualization of the intrauterine cavity.[1] It unfortunately does not demonstrate external contours or evaluation of the uterus. The procedure is invasive and requires anesthesia, making it inappropriate for diagnosing pediatric patients. Similar to a hysteroscopy, a laparoscopy or laparotomy could be suggested in rare HWWS cases. Both procedures are again invasive, expensive, and require the use of anesthesia. Some researchers and physicians claim that a laparoscopy is the preferred procedure in evaluating the female reproductive system for suspicion of uterine anomalies. A laparoscopy can identify endometriosis, pelvic infection, and adhesions.[1] However, any invasive surgery will still come with surgery-related risks.

Another uncommon imaging exam used is an IVP, or intravenous pyelogram. This will require contrast to be injected through the veins. The contrast will then travel to the kidneys and urinary tract. After abdominal x-rays are taken of a patient with HWWS, images will show the absence of one kidney and contrast flowing into a present kidney contralaterally. Due to more modern technology and the radiation used with x-rays, IVPs are rarely used today.

Treatments

There is no current cure for Herlyn-Werner-Wunderlich Syndrome. Currently, the most effective treatment of HWWS is surgery. The surgical plan for these cases is to resect the vaginal septum as much as possible for patients with Classification 1.1, 2.1, and 2.2.[7] In addition, drainage of any obstruction, or hematocolpos, in the vagina would take place. It is stated that of patients with Classification 1.1, the best time for surgery would be during menstruation or when a hematocolpos develops. This distends the tissue of the vaginal septum, making it easier to excise.[1] Figure 8 shows the removal of the vaginal septum in a patient.

As mentioned before with cases of Classification 1.2 (cervical atresia), a different treatment is recommended. With cases of cervical atresia, researchers suggest an ipsilateral hysterectomy. Resecting the vaginal septum with these cases would not relieve the symptoms of obstructions. Towards the end of the surgery, a stent will be placed into the vagina to keep the canal open, noting whether or not the patient is sexually active.

Other uncommon surgical treatments include endoscopic ablations, hemi-hysterectomies, and metroplasties. An endoscopic ablation procedure will remove the lining of the uterus. It is minimally invasive and helps achieve successful results. A hemi-hysterectomy, or excising half of the uterus, with or without a salpingo-oophorectomy (removal of ovaries and fallopian tubes) is another option. This is suggested if resecting the vaginal septum is not successful in relieving symptoms, such as dysmenorrhea, and to prevent endometriosis.[12] A metroplasty will reconstruct any uterine anomalies. This specific surgery may benefit women with a uterine septum and recurrent pregnancy loss.[1] It is vital for the physician and patient to note whether she would want to have children in the future or not, to provide the best plan for any excisional surgery.

Studies have shown that full resection of the longitudinal vaginal septum, the typical treatment for Classifications 1.1, 2.1, and 2.2, has produced good outcomes regarding fertility and pregnancy.[10] Patients typically come out asymptomatic post-surgery. A few cases noted irregular menses post-surgery, but physicians and researchers suggest continuing birth control if symptoms occur. Birth control will help with dysmenorrhea or excessive bleeding if present.

For pediatric patients diagnosed early with HWWS, surgical treatments are not always recommended and most of the time avoided. In some cases, pediatric patients will be given birth control or anti-inflammatory drugs to suppress symptoms of dysmenorrhea and/or irregular

bleeding. Close observation of symptoms is likely recommended if HWWS is diagnosed around puberty age. Similar to most pediatric medical plans, physicians will usually take the conservative approach.

There are potential risks of HWWS if it is to be left untreated. If the patient refuses to be treated, symptoms of pain can only worsen and bleeding can become heavier or even more blocked to the point of blood reflux. Reflux of blood into a woman's reproductive system could lead to endometriosis and permanently affect fertility or pregnancies in the future. Not draining or excising hematocolpos can also lead to the obstructions randomly tearing or even bursting apart. So far, early diagnoses and surgical treatment are strongly recommended.

Interview

For the purpose of this research paper, an interview was conducted with Dr. Keith Hansen. Keith Hansen, MD, is an obstetrician/gynecologist (OB-GYN) who has specialized in reproductive endocrinology and infertility for over 20 years. In his experience, Dr. Hansen has worked with over 40 HWWS cases. Although forty cases may seem like many for a rare congenital syndrome, Dr. Hansen was referred patients by other physicians from other cities and states for the evaluation of Herlyn-Werner-Wunderlich Syndrome.

As previously stated, HWWS has physical malformations that relate to, not just having uterine anomalies, but also vaginal and cervical anomalies. Some of these symptoms or anomalies include: double uterus and/or cervix, long vaginal septum that divides a present vagina, two separate uterine horns, obstructions in the vagina and cervix, and many others as mentioned before. OHVIRA can possess different variations of these anomalies, as being discovered in current ongoing research.

Dr. Hansen explains Herlyn-Werner-Wunderlich Syndrome as a rare condition where there are abnormalities or malformations in the genital tracts of young women. Dr. Hansen begins, "Something, which we do not know yet, disrupts the fusion of the uterus and cervix, and also the breaking down of the vaginal septum. Patients will also most likely have a missing kidney." Dr. Hansen stated that these young women with HWWS will normally have two normal ovaries, two normal uterine horns, and two normal fallopian tubes. What is abnormal with the reproductive system is that there will sometimes be two cervices and/or uterine didelphys bicollis with a longitudinal vaginal septum that is obstructed. As mentioned before, uterine didelphys is a

Müllerian duct anomaly in which the uterus is developed into two separate horns.[4] The longitudinal vaginal canal is separated by a septum as well, in which one side of the septum may or may not be obstructed by buildup of menstrual blood.

Dr. Hansen said this buildup of menstrual blood can lead to the development of hematocolpos, hematometra, and hematosalpinx. Hematocolpos is blood in the vaginal space. Hematometra is blood buildup in the uterus, and hematosalpinx is blood in the fallopian tubes. All of these effects, Dr. Hansen believes, can cause reflex or even endometriosis. He added that whichever side in the vagina is obstructed, associates to which kidney is missing. “Obstructed left vagina, missing left kidney, and vice versa. The opposite kidney or kidney present will be enlarged and hypertrophied”.

Symptoms of HWWS are likely to be found early. According to Dr. Hansen, “Pain in the pelvic area with periods or absence of periods all together are usual signs of these obstructions.” It is common in patients of puberty ages of twelve to thirteen. These obstructions can develop as blue bulges, in which some can even develop large enough to be seen through the labia.

The longitudinal vaginal septum is a wall-like separation of tissue that can divide the vagina into left and right canals. Having a vaginal septum can be commonly mistaken for having two or “double vaginas”. Young women with HWWS, will have one vagina that is separated by a wall. Dr. Hansen stated that the septum can be located towards the upper, mid, or lower vagina, depending on the length. In order to fix this abnormality, the septum can be excised out with surgery. A stent could also be placed to keep the vagina open, especially if patients are around puberty age or not sexually active.

Dr. Hansen mentions that HWWS is somewhat difficult to diagnose with young women. Women who have HWWS are said to experience incredible episodes of pain. The symptoms first start as pain associated with periods, which is common for women. Dr. Hansen claimed to have treated patients who had to once stop on the side of the road and reportedly pass out from the extreme pain. It is also hard for patients to distinguish regular pain and pain from an obstruction in the cervix or vagina. Dr. Hansen also stated that bleeding is strongly affected as well, aside from the regular monthly menstruation. “Obstructions can sometimes cause lots of bleeding or prolonged bleeding in between periods.”, Hansen states.

For newly diagnosed patients, Dr. Hansen recommends a treatment similar to other doctors and researchers caring for patients with HWWS. He advocates for a surgical route as

soon as the condition is suspected on imaging. Patients will undergo anesthesia and doctors will first exam the anatomy of the abnormal reproductive system. The team will then cut out the longitudinal vaginal septum and let any obstruction drain. Most likely needed, they will place a stent in order to keep the opening of the vagina dilated. What is important to be aware of, according to Dr. Hansen, is whether or not these women are willing to bear children in the future. If bearing children is in the patient's future plans, it is important for the surgical team to make sure there is no scar tissue or any signs of endometriosis. This will interfere tremendously with fertility and pregnancies in the future.

Due to the nature of how young HWWS patients typically are, Dr. Hansen states that the women diagnosed with HWWS recover well physically. His recovery plan post-surgery is to rest, recover, and observe any symptoms. To take preventative measures, Dr. Hansen suggests women with HWWS continue to take birth control post-surgery. For women who have endometriosis along with HWWS, birth control will help suppress some of those symptoms. When deciding to have children, birth control can obviously be stopped.

Dr. Hansen expresses that although it is common for women with HWWS to have successful pregnancies post-surgery, there are chances of complications with pregnancies concerning uterine anomalies in general. Some of these complications could be preterm labor and delivery, recurrent miscarriages at any trimester, and intrauterine growth restriction (which can cause babies to become breeched). Fortunately from his own research and experience, Dr. Hansen states the syndrome itself does not cause infertility.

Conclusion

Herlyn-Werner-Wunderlich Syndrome is a rare congenital syndrome affecting the reproductive tract and kidneys of young women. The most common symptoms of HWWS reign as the "triad" of characteristics which include: uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis. Patients may experience other symptoms which include dysmenorrhea and a presence of a pelvic or abdominal mass. There are currently two different classifications of HWWS: Classifications 1 and 2. Each classification is described into two subtypes of specific cervical and vaginal anomalies. Young women are usually diagnosed with HWWS around

puberty age or until realization of fertility issues. Ultrasound and MRI are consistent imaging procedures to help diagnose HWWS. The most effective treatment today is surgical excision of the vaginal septum and drainage of any obstruction. Surgery is the most common treatment with patients with HWWS, though if left untreated issues with fertility and future pregnancies could occur. Herlyn-Werner-Wunderlich Syndrome is incredibly rare, affecting only up to 3.8% of women, making research cases of the syndrome more infrequent.

Images

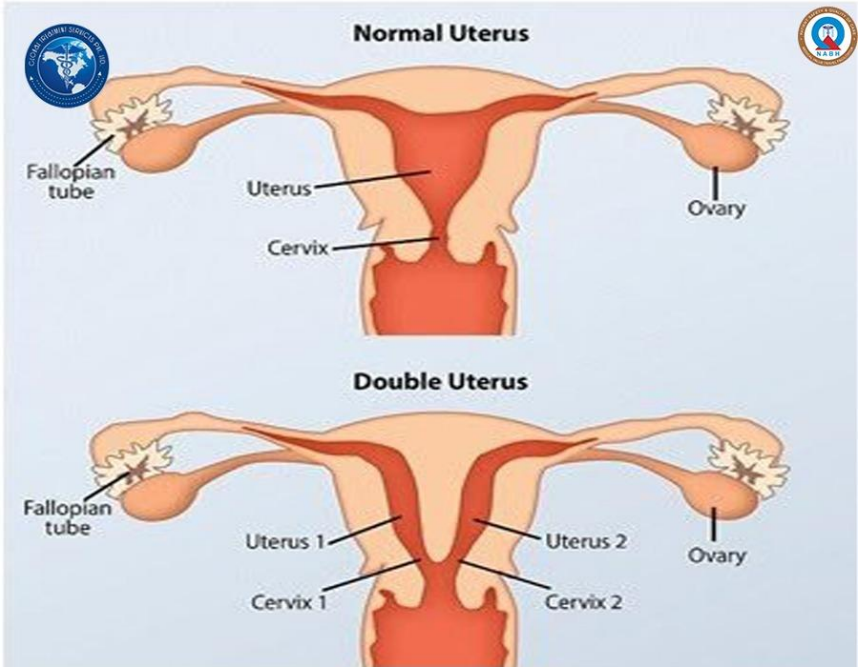


Figure 1: Two images demonstrating a normal uterus and a double uterus, or uterus didelphys. There are two uteri and two cervices present. Uterus didelphys is one of three main characteristics of HWWS.

http://blog.gtsmeditour.com/uterinedidelphys/

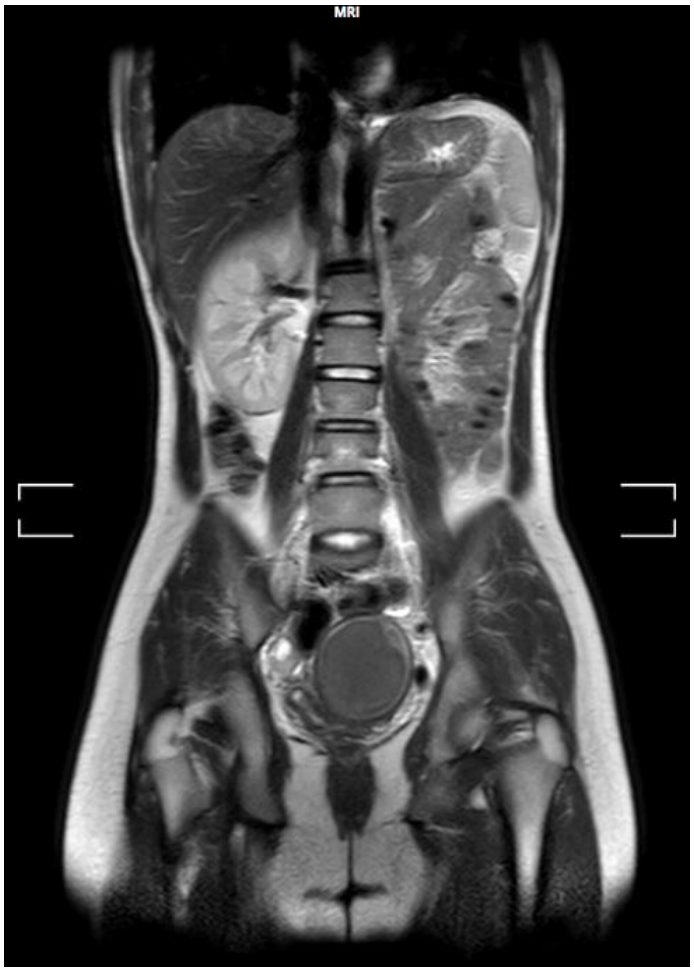


Figure 2: MRI (Coronal T2). Image of uterine didelphys, left sided hematocolpos, associated with absent ipsilateral kidney (absent left kidney). The uterus and vagina on the right side of the patient are normal.

https://radiopaedia.org/cases/herlyn-werner-wunderlich-syndrome-3

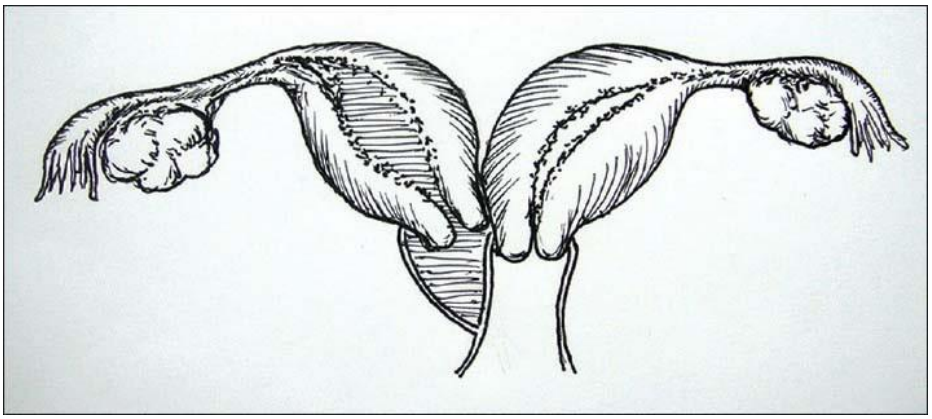


Figure 3: Classification 1.1 - completely obstructed hemivagina with blind hemivagina.

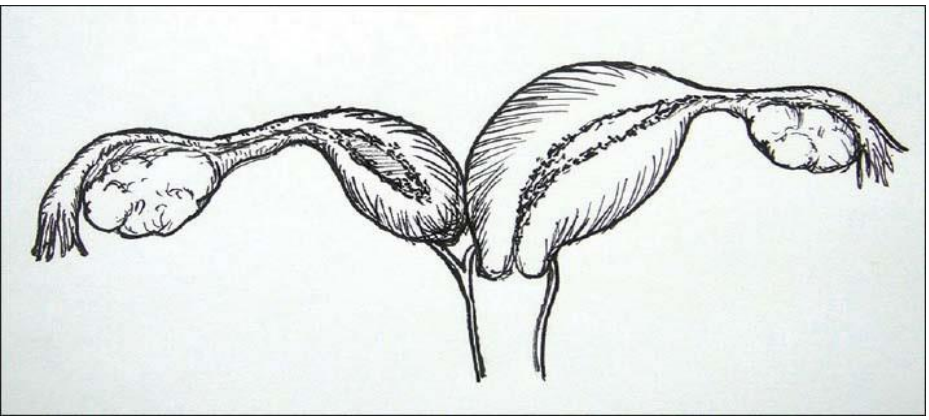


Figure 4: Classification 1.2 - completely obstructed hemivagina with cervicovaginal atresia, without communicating uteri.

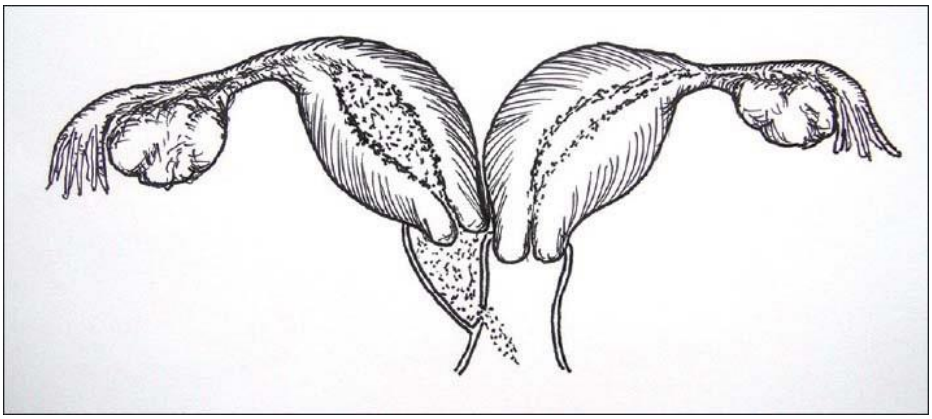


Figure 5: Classification 2.1 - incompletely obstructed hemivagina with partial reabsorption of the vaginal septum.

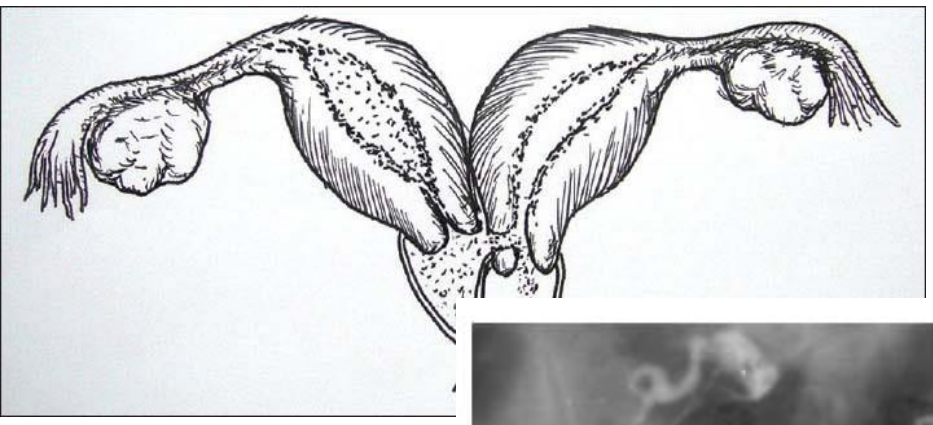
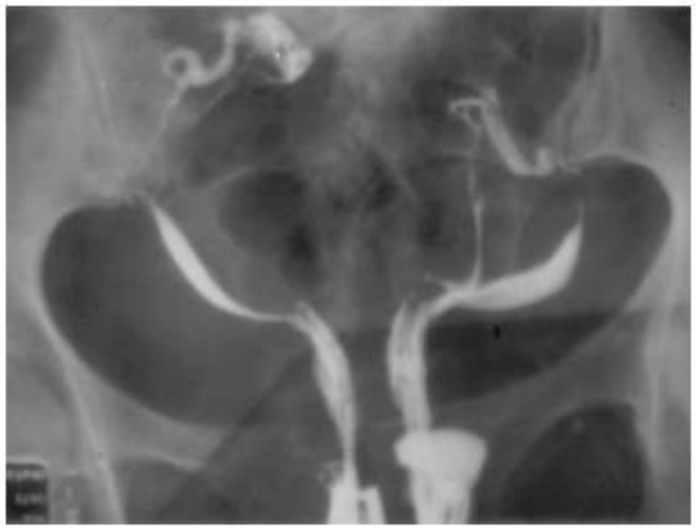


Figure 6: Classification 2.2 - incompletely obstructed hemivagina with communicating uteri.

Zhu L, Chen N, Tong JL, Wang W, Zhang L, Lang JH. New classification of Herlyn-Werner-Wunderlich syndrome. Chin Med J (Engl). 2015;128(2):222-225. doi:10.4103/0366-6999.149208



Baramki. Hysterosalpingography. Fertil Steril 2005.

Figure 7: An hysterosalpingogram (HSG) illustrates two uteri and two cervices being filled with contrast. Two cannulas and catheters were used with this patient.

https://www.fertstert.org/article/S0015-0282(05)00551-0/pdf

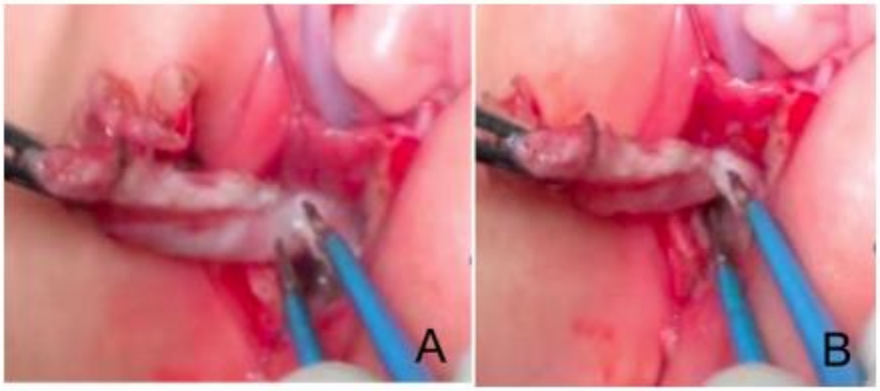


Figure 8: Resection of the vaginal septum.

R. Angotti, F. Molinaro, A.L. Bulotta, E. Bindi, E. Cerchia, M. Sica, M. Messina, Herlyn–Werner–Wunderlich syndrome: An "early" onset case report and review of Literature, International Journal of Surgery Case Reports, Volume 11, 2015, Pages 59-63, ISSN 2210-2612, https://doi.org/10.1016/j.ijscr.2015.04.027.

References

1. Lopes Dias J, Jogo R, Lopes Dias J, Dias JL. Herlyn-Werner-Wunderlich syndrome: pre- and post-surgical MRI and US findings. Abdominal Imaging. 2015;40(7):2667-2682. doi:10.1007/s00261-015-0421-0

2. Smith NA, Laufer MR. Obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome: management and follow-up. *Fertil Steril*. 2007;87(4):918-922. doi:10.1016/j.fertnstert.2006.11.015

3. Taylor HS. The role of HOX genes in the development and function of the female reproductive tract. *Semin Reprod Med*. 2000;18(1):81-89. doi:10.1055/s-2000-13478

4. Mehra S, Chamaria K, Garga UC, Kataria A, Ahuja A. Imaging Diagnosis of Herlyn-Werner-Wunderlich Syndrome- An Extremely Rare Urogenital Anomaly. J Clin Diagn Res. 2015;9(5):TD06-TD8. doi:10.7860/JCDR/2015/11123.5891

5. Ellspermann R, Sirhari C, Chapin E, Nelson M. Point-of-care Ultrasound Aiding in the Diagnosis of Herlyn-Werner-Wunderlich Syndrome. Clin Pract Cases Emerg Med. 2017;1(4):370-373. Published 2017 Oct 18. doi:10.5811/cpcem.2017.7.34089

6. Girardi Fachin C, Aleixes Sampaio Rocha JL, Atuati Maltoni A, et al. Herlyn-Werner-Wunderlich syndrome: Diagnosis and treatment of an atypical case and review of literature. *Int J Surg Case Rep*. 2019;63:129-134. doi:10.1016/j.ijscr.2019.08.035

7. Zhu L, Chen N, Tong JL, Wang W, Zhang L, Lang JH. New classification of Herlyn-Werner-Wunderlich syndrome. Chin Med J (Engl). 2015;128(2):222-225. doi:10.4103/0366-6999.149208

8. Karaca L, Pirimoglu B, Bayraktutan U, Ogul H, Oral A, Kantarci M. Herlyn-Werner-Wunderlich syndrome: a very rare urogenital anomaly in a teenage girl. J Emerg Med. 2015 Mar;48(3):e73-5. doi: 10.1016/j.jemermed.2014.09.064. Epub 2014 Dec 8. PMID: 25499400.

9. Pellerito JS, McCarthy SM, Doyle MB, Glickman MG, DeCherney AH. Diagnosis of uterine anomalies: relative accuracy of MR imaging, endovaginal sonography, and

hysterosalpingography. *Radiology*. 1992;183(3):795-800. doi:10.1148/radiology.183.3.1584936

10. Hamidi H, Haidary N. Late presentation, MR imaging features and surgical treatment of Herlyn-Werner-Wunderlich syndrome (classification 2.2); a case report. BMC Women's Health. 2018;18(1):N.PAG. doi:10.1186/s12905-018-0655-4

11. De Jesus, Jeneane M. "Interview with Dr. Keith Hansen, MD", Sanford USD Medical Center. 22 Oct. 2020.

12. Anderberg M, Bossmar T, Arnbjornsson E, Isaksson J, Persson J. Robot-Assisted Laparoscopic Hemihysterectomy for a Rare Genitourinary Malformation with Associated Duplication of the Inferior Vena Cava – A Case Report. *European Journal of Pediatric Surgery*.:1. doi:10.1055/s-0029-1241842