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Research Article

Swyer Syndrome: Challenging Diagnosis and Literature Review

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Abstract

Introduction: In normal human genetics, male sex chromosomes are represented by the chromosomes X and Y, whilst the female sex chromosomes are represented by X and X. Swyer syndrome is a condition in which people with one X chromosome and one Y chromosome (normally present in males) have a female appearance. People with Swyer syndrome are usually raised as females, have a female gender identity, have typical female external genitalia, and have a normal uterus and Fallopian tubes but in place of functional gonads (ovaries or testes), they have undeveloped, residual gonadal tissue (streak gonads). Streak gonads have a tendency to become cancerous, so they are usually surgically removed as early as possible to reduce any chances of malignancy. Hormone replacement therapy is another option of management. In this article We demonstrate the importance of excessive screening and searching for Mullerian structures, given the difficulty to find them, and the importance of laparoscopy for the correct and complete diagnosis of Swyer's syndrome. We also highlight the difficulties and challenges in making a differential diagnosis between Swyer's Syndrome and androgen insensitivity syndrome.

Material and Method: Case report study, showing clinical and image results of a particular case of Swyer's syndrome, with the agenesis of Mullerian structures (vagina), the hypoplasia of Mullerian structures (hypoplasic uterus) and the normal and complete development of other Mullerian structures (Fallopian tubes).

Results and Conclusions: This case demonstrates that cytogenetic analysis is not sufficient for the differential diagnosis between these 2 syndromes and that visualization of Mullerian structures is difficult. It is through these findings that the importance of performing diagnostic laparoscopy with histopathological examination of gonadal tissues that a clear differential diagnosis between these 2 syndromes can be obtained

Keywords: *46 XY; Infertility; Amenorrhea*

Introduction

Typical sex development is multifactorial and requires the involvement of several genes, hormones and hormone receptors. 46 XY Sexual Development Disorders are caused either by testicular developmental disorders or by disorders involving the male hormone, androgen. The conditions that fall into sexual development disorders with 46 XY karyotype include:

- 46, XY Complete gonadal dysgenesis (Swyer syndrome).
- 46, XY partial gonadal dysgenesis (46, XY PGD), (Deny-Drash Syndrome Frasier syndrome).
- Ovotesticular disorder of sexual development (DSD).
- Testicular Regression Syndrome (Testicular dysgenesis syndrome).

- Hypoplasia/Leydig cell aplasia (due to anomalies of hCG or LH receptors).
- T cell deficiency defects.
- Disorders of androgen synthesis and action
    - StAR deficiency (StAR)
    - P450scc deficiency (CYP11A1)
    - Deficiency of 3-b hydroxysteroid dehydrogenase type II, 3βHSD type II (HSD3B2)
    - Deficiency of 17α-hydroxylase and deficiency of 17,20 hydroxylase (17α-hydroxylase/17,20-lyase (CYP17).
    - Isolated deficiency of 17.20 hydroxylase.
    - Deficiency in POR P450 oxidoreductase gene.
    - Deficiency of 17b-hydroxysteroid dehydrogenase type III.
    - Abnormalities in the POR gene (poor P450C17 activity).
    - Mullerian dysfunctional persistence syndrome (abnormalities in AMH gene receptors or AMH genes).
    - Deficiency of 5 alpha reductase type 2 (5α-reductase type 2).
    - Full or partial insensitivity syndromes to androgen.
    - Mutations of the AMH and AMH receptor type II (AMHR-II) genes.
- Disorders of androgen excess
    - 21α-hydroxylase (CYP21).
    - 11βHSD1 (HSD11B1).
    - P450 aromatase (CYP19).

Diagnosis of Swyer's syndrome may be challenging, because visualization of Mullerian structures is sometimes difficult, and genetic mutation analysis is not useful for the differential diagnosis between Swyer's Syndrome and the Complete Androgen Insensitivity Syndrome. Previous studies have described cases of complete androgen insensitivity syndrome in individuals with 46 XY karyotype in which no imaging mullerian tissues have been visualized after hormonal treatment, the appearance of a uterine tissue was detected, making important the differential diagnosis between these 2 syndromes. Swyer's Syndrome was first described in medical literature by Dr. Swyer in 1955 [1]. It is a rare syndrome. Swyer Syndrome occurs in about 1 in 80,000 people. People who suffer from Swyer syndrome have typical female genitalia. Affected individuals, with 1 X chromosome and 1 Y chromosome in each cell, typical for male gender, have female external genitalia. Uterus and fallopian tubes are normally formed, but gonads (ovaries or testicles) are not functional. People affected by this syndrome have developed incomplete structures called "streak gonads" [2]. Due to lack of gonadal development, Swyer's syndrome is also called complete gonadal dysgeusia 46 XY. Residual gonadal tissue often becomes cancerous, so it is usually surgically removed during the prepubertal period. People with Swyer Syndrome are typically raised as girls and have a female identity. Because they do not have functional ovaries, the affected person usually starts hormone replacement therapy during adolescence to induce menstruation and development of female secondary sexual characteristics such as breast enlargement and uterine growth. Hormone replacement therapy also helps reduce the risk of bone loss (osteopenia and osteoporosis). In typical Swyer Syndrome, women with this disorder do not produce eggs but may remain pregnant with donated oocytes or embryos. However, there are also particular Swyer syndromes. Some people may have complete lack of Mullerian structures (vagina, uterus and fallopian tubes), others may have a fully developed uterus and fully developed uterine tubes. Swyer's syndrome usually only affects sexual development; such a case is called isolated Swyer's syndrome.

Synonyms

- 46, XY CGD
- 46, XY complete gonadal dysgenesis
- 46, XY pure gonadal dysgenesis
- Gonadal dysgenesis, female XY type

Causes

Genes are DNA sequences that are located in a specific location of a chromosome. Genes determine a particular feature or feature of a person. Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. The cells of the human body normally have 46 chromosomes. Pairs of chromosomes in humans are numbered 1 to 22 and called autosomes. The sex chromosomes are X and Y. Male sex is defined by a chromosome X and a Y chromosome (46 X Y), while female sex is defined by 2 X chromosomes (46 X X karyotype). In Swyer's Syndrome, affected individuals with 1 X chromosome and 1 Y chromosome in each cell, typical of male gender, have female external genitalia. In most cases of Swyer's syndrome, the exact cause of the disorder is unknown. Researchers believe that Swyer's syndrome is caused by mutations and deletions in genes involved in sexual fetal differentiation:

1. **SRY gene mutation (15% - 20% of cases of Swyer syndrome):** The SRY gene is considered to be essential in initiating male determination by stimulating undifferentiated gonadal tissue to transform into testicles. Absence or mutation of this gene generates failure of testicles. The SRY gene, located on the Y chromosome, provides data to form the Y protein of the determining sex region. The determining region of sex in the Y protein initiates processes that are involved in male sexual development. These processes cause a fetus to develop male gonads (testis) and prevent the development of female reproductive structures (uterus and fallopian tubes). Mutations of the SRY gene that causes Swyer's syndrome prevent Y-protein production from the sex-determining region or lead to the production of a non-functional protein. A fetus whose cells do not produce the functional sex determinant Y will not develop the testicles, but will develop a hypoplastic uterus and fallopian tubes, despite the fact that it usually has a male karyotype [3].
2. **Map3K1 gene mutation - common cause of Swyer's syndrome (18% of cases):** The MAP3K1 gene provides data for the synthesis of a protein that helps regulate the signaling pathways that control various processes in the body. These include processes for determining sexual characteristics before birth. The mutations in this gene that produce Swyer's syndrome decrease the signal that leads to male sexual differentiation and increase the signaling that leads to female sexual differentiation, preventing the development of the testicles and allowing the development of Uterine hypoplasia and fallopian tube deformation.
3. NROB1 gene mutation on chromosome X.
4. Mutation of the DHH gene on chromosome 12 and mutation of the Steroidogenic factor-1 (SF-1, Ad4BP, encoded by NR5A1).

   The DHH gene provides instructions for synthesizing an important protein for the early development of tissues in many parts of the body.

   The NR5A1 gene provides instructions for producing another transcription factor called Steroidogenic factor-1 (SF1).

   Mutations in the DHH and NR5A1 genes affect the process of sexual differentiation, preventing individuals with a typical male karyotype from developing the testicles and causing them to develop a uterus and fallopian tubes.
5. Mutation of the WNT4 and CBX2 gene.
6. Gene mutation GATA4.
7. Mutation of the WWOX gene.
8. Additional, yet unidentified genes may also be associated with the development of Swyer's syndrome.

Some cases of Swyer's syndrome are not considered to be inherited, but rather the result of a new genetic mutation (*de novo* mutation) or an anomaly that occurs for unknown reasons (spontaneously). However, some women with Swyer syndrome due to the SRY gene mutation had fathers (and some even brothers) who also had the SRY mutation on the Y chromosome. It is unknown why in these cases, parents and/or siblings do not have Swyer's Syndrome. Researchers speculate that other genes or factors in combination with a mutation of the SRY gene may be needed to develop Swyer's syndrome in these patients. According to specialized medical literature, some cases of Swyer syndrome have autosomal dominant or recessive transmission. Dominant autosomal transmission is related to the mutation of WNT4, MAP3K1 or SF1 (NR5A1) genes. Autosomal recessive transmission is linked to the mutation of the DHH gene. Genetic transmission with dominant transmission occurs when only a single copy of an abnormal gene is required to cause a particular disease. The abnormal gene may be inherited from any of the parents or may be the result of a new mutation (gene change) occurring in the affected individual. The risk of abnormal gene transmission from an affected parent to the child is 50% for each pregnancy. The risk is the same for men and

women. In some people, the disorder is due to a *de novo* genetic mutation that appears in the egg or sperm cell. In such situations, the disorder is not inherited from parents. Genetic recessive disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one copy from each parent. In these cases, if an individual inherits a normal gene and a gene for the disease, the person will be a carrier of the disease, but will usually not show symptoms. In this situation, the risk for two parents bearing the abnormal gene to have an affected child is 25% for each pregnancy. The risk of having a baby carrying the abnormal gene is 50% for each pregnancy. The risk of a child getting normal genes from both parents is 25%. The risk is the same for women and men. Parents who are close (inbred) relatives are more likely to carry the same abnormal gene, than parents who are not. People affected by Swyer Syndrome are encouraged to seek genetic counseling for answers to any questions regarding the genetic factors involved in Swyer's syndrome [4].

Pathophysiology

Pathophysiology: normal development up to the 8th embryonic week → mutation of the SRY gene → gonads do not develop in the testicles → no production of testosterone and anti-mullerian hormone (AMH) → male genital organs do not develop → uterus and vagina develop despite the presence of XY chromosomes

Diagnosis

Instead of having sex gonads, women with Swyer syndrome have "streak gonads," in which the ovaries do not develop properly (aplasia) and are replaced by scar tissue (fibrous connective tissue), which means they are not functional. Because they do not have functional ovaries, people with Swyer syndrome do not produce sex hormones and will not go to puberty (unless they are being treated with hormone replacement therapy). Most people who suffer from Swyer Syndrome have no symptoms until adolescence when they visit a doctor with complaints of primary amenorrhea. This is when the absence of ovaries is usually detected and therefore giving reason to the absence of sex hormones (estrogen or progesterone). People with sexual development disorder with 46 XY karyotype require a multidisciplinary approach from a pediatrician, endocrinologist, geneticist and gynecologist. Initially, the family history, obstetrical history of the patient and a thorough gynecological physical examination should be made. The lab tests show a very high level of follicular stimulating hormone (FSH) and luteinizing hormone (LH) and a low level of estrogen [5].

Methodology and Case Presentation

A 16-year-old patient presents at the endocrinology hospital with a chief complaint of primary amenorrhea and delayed puberty. She had no significant pathological history, no significant family history, she had been referred for consultation by a family doctor for further investigation and treatment. The clinical examination performed revealed a young girl with female features, a height of 1.64 cm, Weight of 70 kg, Tanner PV BlV stage, external genitalia of female phenotype with normal conformity and an intact hymen.

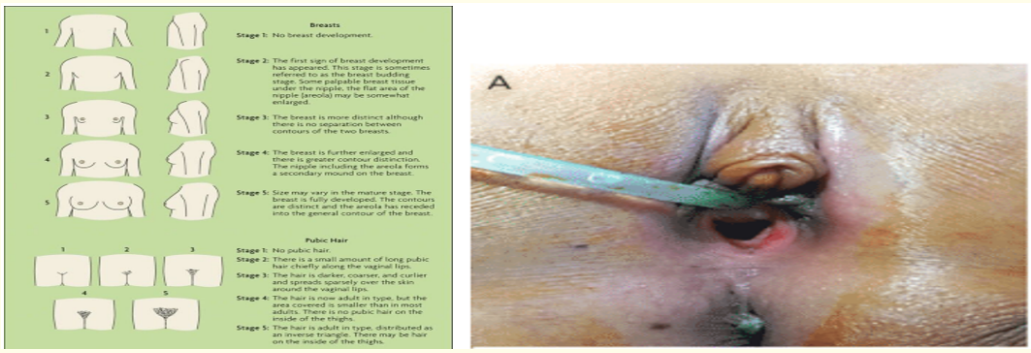

Figure 2

The lab test results showed a very high value of the hormone FSH = 81.4 mUI / mL and LH = 15.8 mUI / mL and a low estradiol level of < 20. The Testosterone level was within normal limits for women. A cytogenetic examination was performed, in which male chromosomal structure was detected, 46, XY, giving the diagnosis of complete androgen insensitivity, hypogonadotropic hypogonadism. The ultrasound exam in the endocrinology clinic detected an absence of the uterus and the presence of two formations with a diameter of 1.81 cm, suspected to be testicles. The patient was redirected to the gynecology obstetrics clinic with the observational diagnosis of Morris Syndrome, which allowed by protocol an assessment using imaging, the exact origin of the intra-abdominal formations and allow the surgeon information for the excision of the intra-abdominal formations. People with sexual development disorder with 46 XY karyotype require a multidisciplinary approach from a pediatrician, endocrinologist, geneticist and gynecologist. We have opted for multidisciplinary investigations in order to establish accurate diagnosis. Diagnosis of Swyer's syndrome may be a challenge, because the visualization of Mullerian structures is sometimes difficult, just as what happened in our case, and genetic mutation analysis is not useful for the differential diagnosis between Swyer's Syndrome and the Androgen's Complete Insensitivity Syndrome.

CT exam performed prior to surgery

- Pulmonary parenchyma at baseline in normal range.
- Liver with normal, homogeneous size range without primary or secondary focal lesions
- Gallbladder with normal appearance, without calculus.
- Spleen, normal appearance adrenal glands.
- Homogeneous pancreas without nodular lesions.
- Normal kidneys (bilateral).
- Urinary Bladder in normal position with normal-looking walls.
- Uterus with small size ~ 15/13 mm - no muscle structure - aspect of uterine hypogenesis.
- Cervical canal and vagina absent
- ovaries - absent.
- Inguinal canal with no continents, bilateral.
- Intestines, sigmoid colon and rectum with normal appearance.

Results of Exploration

Absence of free fluid and Abdomino-pelvic adenopathies.

Dg CT: Normal hepato-spleno-pancreato-renal. Uterine body hypogenesis with cervical and ovarian canal agenesis. No gonads seen on the CT exam.

A decision was made to carry out diagnostic laparoscopy in order to perform the differential diagnosis between Swyer and Morris syndrome. Laparoscopy; -At the introduction of the video camera we discovered: A hypoplastic uterus, about 1.5 cm in diameter :Left adnexa- fibrous with a nodular attachment r 3.5 / 3.8 cm in diameter, white in colour, compact in appearance with consistency ; left Fallopian tube 5 cm, in length, with macroscopic changes, right adnexa: Fallopian tube of 7 cm long, with adipose tissue attached but showing to macroscopic likeness to a gonad.

Extemporaneous examination; left gonadal tissue - hyalinated connective tissue without histopathological organ diagnostics is performed.

Laparoscopic ablation of gonads with bilateral salpingectomy was performed.

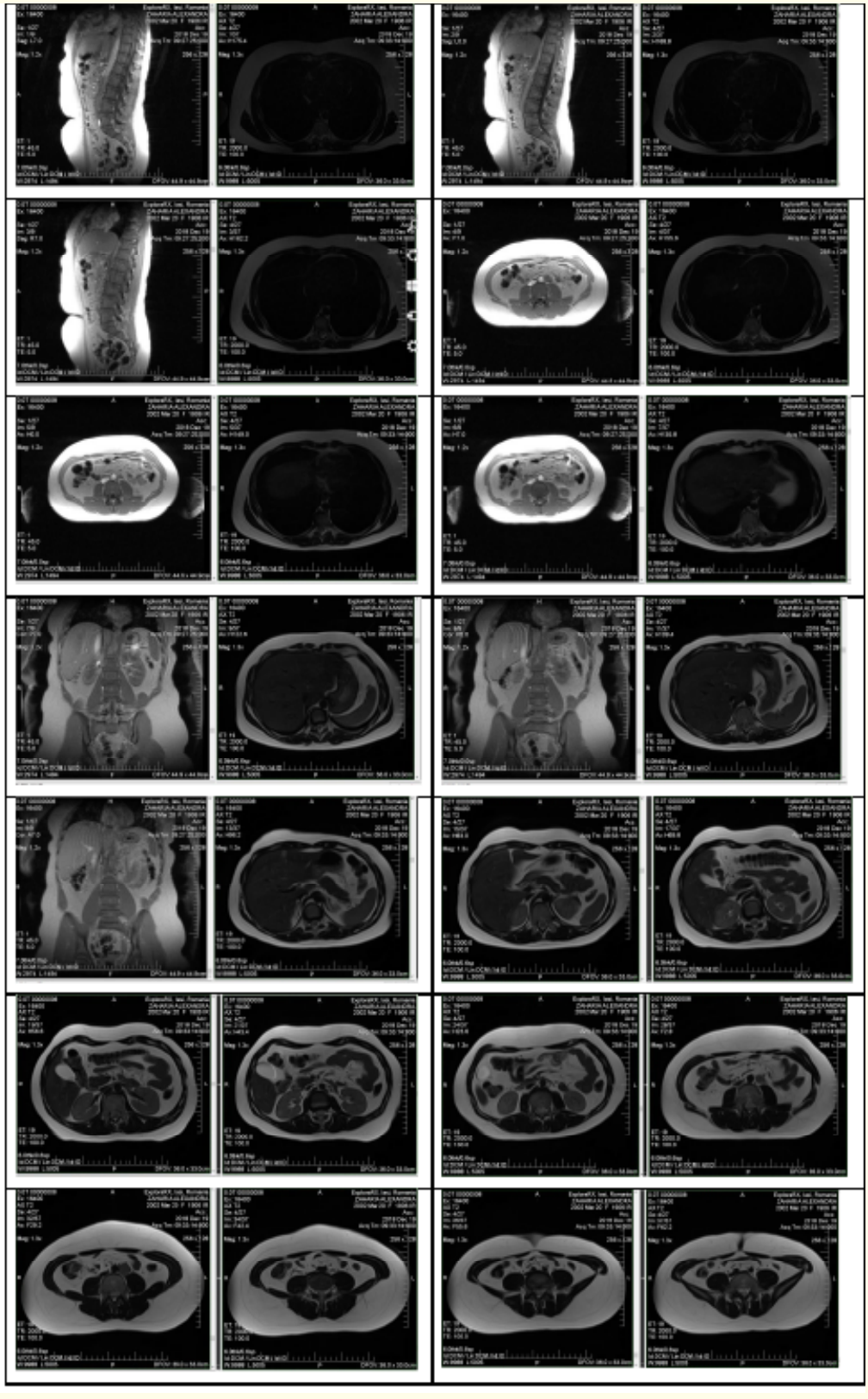

Figure 2

Favorable post-interventional progression under treatment with Clexane 20 mg/day, Refen vial/day, Algocalmin vial/da. General status; Supple abdomen, mobile with respiratory movements, intestinal transit present for gas and faeces, physiological spasms. A recommendation to the Endocrinology Clinic for hormone replacement therapy was made.

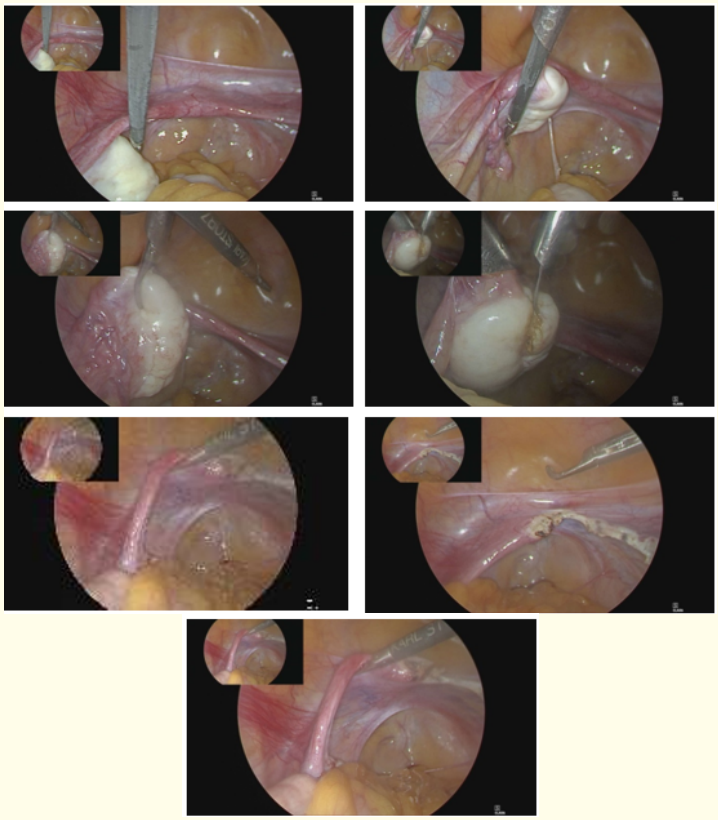

Figure 3

Sections considered

- A subcapsular nodular formation, in place of the Normal ovaries, with a thin ovarian stromal band without ovarian follicles but with a small tubular cavity wall structure, the cystic formations present with variation some with eosinophilic intratubular content, others with calcifications (inclusion cysts) and sclero-hyalinosis areas. Serial sections do not identify sertoli cells or Leydig cells.
- Left tube with tubal sclera-hyalinosis
- Right tube with paratubercular serum cysts
- Do not identify the right microscopic gonad.

The genetic test performed reveals the mutation of the SRY gene.

The particularity of the case. We present a Swyer syndrome case where Mullerian structures could not be visualized by imaging, the differential diagnosis between Swyer syndrome and the complete androgen insensitivity syndrome was difficult. Analysis of genetic mutations is not useful for the differential diagnosis between these 2 syndromes. We demonstrate the importance and utility of laparoscopy for the diagnosis of Swyer syndrome. We present a particular case of Swyer syndrome in which the total absence of Mullerian structures (vagina), hypoplasia of other Mullerian structures (uterus hypoplasia), and the complete development of other Mullerian structures (Fallopian tubes) have been identified. Since the patient has uterus hypoplasia, it is not possible for her to be impregnated with donated oocytes. Early diagnosis, as has been the case here, is very important for several reasons: firstly because of the risk of gonadal malignancy, secondly because of the importance of early hormonal replacement therapy for the induction of puberty, and thirdly, the importance of prevention of osteoporosis.

Discussions

In patients with Swyer syndrome, the risk of developing tumors is significant. Approximately 20% -30% of affected individuals develop tumors. The frequent tumor in these cases is represented by gonadoblastoma. Cases of dysgerminoma or embryonic carcinoma have also been reported. Due to the increased risk of developing tumors, excessive screening and identification of rudimentary gonads is required and bilateral gonadectomy is recommended. As shown in this case, individuals with Swyer's syndrome should be investigated excessively for gonads. Sometimes it is difficult to visualize the imagery of Mullerian structures, but this should not prevent the practitioner from extensive searching of these structures, and in this case, we present the importance of laparoscopy in the complete diagnosis of Swyer's syndrome [6]. This case demonstrates the importance of continuing medical education with a permanent updating of scientific knowledge for the early and correct diagnosis of sexual development disorders with appropriate treatment and timing to improve the prognosis of these individuals as well as lifestyle.

Conclusion

This case demonstrates that cytogenetic analysis is not sufficient for the differential diagnosis between these 2 syndromes and that visualization of Mullerian structures is difficult. We demonstrate the importance and utility of laparoscopy for the diagnosis of Swyer syndrome.

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