Müllerian Aplasia: A Genetic Perspective

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Abstract

In this review, we explore müllerian aplasia, a structural abnormality in the female reproductive tract originating from a genetic abnormality that affects the müllerian duct in-utero. Previous research has found the pathology and etiology of the condition, and genetics components have been found to influence the presentation of the condition. The purpose is to give an overall understanding of the condition and its genetic influences to spread awareness about a more common condition that one would think. The main findings include symptoms, process of diagnoses, treatments (surgical and nonsurgical options), and genetics components affecting the presentation of the condition. This condition is one that is present in more people than previously thought, and it is important to understand the significance of the condition on those females' lives.

Introduction

Developmental disorders affect millions of Americans each year, and several limits an individual's ability to live a normal life. One such disease is mullerian aplasia, also referred to as mullerian agenesis, a condition defined by the incomplete development of the Mullerian duct. The Mullerian duct refers to the female tract that exists in utero prior to a completely assigned sex. If the zygote is female, a cascade of hormones will be released, promoting the müllerian duct to form into a female reproductive tract, and suppress any male specific hormones. The incomplete development or complete absence of the Mullerian duct defines mullerian aplasia. Most cases consist of the absence or underdevelopment of the uterus, fallopian tubes, cervix and parts of the vagina. One in 4,500-5,000 females are affected by mullerian aplasia, with them normally being identified with the condition around the normal pubertal development stages (ACOG).

Symptoms and Signs of Mullerian Aplasia

Primary symptoms of mullerian aplasia include: primary amenorrhea, hyperandrogenism, and kidney issues (NIH, “Mullerian Aplasia and Hyperandrogenism”). To diagnose the condition, ultrasound technology and magnetic resonance imaging (MRI) can be used to accurately identify the condition in a patient. Treatments for mullerian aplasia mostly are used for preserving fertility and quality of life. Many patients have compromised ovarian function, yet still have viable eggs. Alternatively, ovarian function and structure can be normal, but the ovaries are present in an abnormal location. Thus, patients are still able to have biological children, but would not be able to carry those children due to lack of a uterus. Surrogacy is one intervention that restores a patient’s ability to have biological children (ACOG).

Surgical and Non-surgical Treatments for Mullerian Aplasia

The quality of life can also be compromised, which a few treatments can improve. Since many patients can have an absent vaginal canal, non-surgical dilators can be used to construct one. Using different size dilators, a patient is instructed to sit on a chair to put pressure on the area where a vaginal opening should have developed to construct a vagina. Consistent use is needed to maintain a partially dilated vaginal canal. Approximately 87% to 91% of patients choose to take this course of treatment over the surgical option. Vaginoplasties are given to

patients who prefer a more permanent solution to vaginal abnormalities; around 10% of patients with mullerian aplasia choose to undergo surgery. Although the physical toll is substantial, the mental toll on patients can be detrimental to their day-to-day lives. Regular measures with mental health specialists can be required for those who feel that they are struggling, along with different medications to suppress the symptoms of any psychological issues (Lee).

Introduction of WNT4 and Body Systems

Multiple families of genes are involved in the etiology of mullerian aplasia. The two genes that affect the presentation the most are WNT4 and PAX8 (Herlin et al.). Having a critical role in development prior to birth, the WNT family of genes controls sex determination (NIH, “WNT 4 Gene”). When determining the fetal sex, the WNT genes suppress the male lineage and promote the female sex characteristics. These genes have an important role in female development while in males, they regulate and produce androgens, or male sex hormones (NIH, “WNT 4 Gene”)Some disturbances in this gene create irregular distinctions between male and female physical traits, such as hyperandrogenism or primary amenorrhea (NIH, “Chromosome 1”).

WNT4 is one of nineteen in the WNT family of genes, and it is present on the first chromosome. The gene plays an important role in cell differentiation during embryonic development. Some of the regulators of the WNT4 gene are EGR1, PAX2, and FOXC2. WNT4 has many different roles and is expressed in many cell types: osteoclasts, pancreatic beta cells, neural stem cells, dendritic cells, and myofibroblasts. Alongside this,WNT4 also activates beta-catenin-dependent and beta-catenin- independent pathways. When the WNT4 gene is disrupted, in certain situations, sex-reversal can occur in the embryonic period, specifically in the male-to-female direction. While loss-of-function mutations in WNT4 can cause mullerian aplasia, decreased WNT4 expression later in adult life can cause premature skeletal aging, endometriosis, and gynecological cancers (Quanlong Zhang et al.).

Introduction of PAX8 and Body Systems

PAX8, on the other hand, is found on the second chromosome (NIH, “Chromosome 2”). The PAX family of genes plays important roles in embryonic development. Specifically, it plays a key role in kidney and thyroid development (NIH, “PAX8 Gene”). This supports the involvement of PAX8 in mullerian aplasia, as these organ systems are often affected by PAX8 loss (NIH, “PAX8 Gene”). Mutations in PAX8 can result in restricting fetal length, malformed external or internal structures, and neurological disabilities. The clinical manifestation of PAX8-mediated mullerian aplasia can be differentiated from other causes by the involvement of kidney and thyroid issues (NIH, “Chromosome 2”). PAX8 is 1 of 9 genes in the paired-box gene family and has an important role in the development of thyroid follicular cells. It regulates thyroid-specific genes and is expressed in the thyroid, metaphors, and müllerian duct. Disturbances to the PAX8 gene sometimes may cause gynecological problems, like that of mullerian aplasia. PAX8 specifically, however, has a strong effect on proliferation and cell survival. It has an important role in epithelial cell survival and affects parts of the cell cycle that have to do with apoptosis. The expression of the PAX8 gene is directly proportional with the proliferation rate of the epithelial cells (T Di Palma et al.). Given that PAX8 is intimately involved in mullerian duct cell survival, it then follows that without this key gene, the mullerian duct is absent as well.

Conclusion

Given the genetic basis of this condition, more research is needed to fully understand the biological implications of the absence of PAX8 and WNT4. Disruptions to these important factors can cause mullerian aplasia, as well as male-to-female sex reversal, causing issues in sexual development in-utero. Affecting almost 1 in every 5000 females, the key symptoms of mullerian aplasia include primary amenorrhea and some hallmark kidney issues. As discussed in this paper, mullerian aplasia is a condition in which the female reproductive tract is only partially developed *in-utero* due to a disruption in the müllerian duct from fully developing. In conclusion, mullerian aplasia is a psychological affecting condition, hurting thousands of females in the world. Through proper treatments, physicians can help these people have a better quality of life.

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