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Sexual infantilism in a normal karotypic female related to ovarian agenesis associated with Müllerian agenesis – Case report

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Summary

Purpose: To describe an unusual case of Müllerian agenesis associated with gonadal agenesis and thus sexual infantilism. *Materials and Methods:* Pelvic magnetic resonance imaging (MRI) and sonography were performed and MRI of the kidneys. Pelvic sonography and serum follicle stimulating hormone (FSH) were also obtained. *Results:* The only pelvic organ that this 15-year-old girl had was the distal portion of the vaginal canal. The kidneys were normal. *Conclusions:* This case suggests that at least in some cases some possible viral damaging process may lead to damage to both the ovaries and the Müllerian system. If there was a problem with the anti-Müllerian hormone (AMH), the kidney may be affected. Furthermore, AMH has nothing to do with the ovaries and a chance association of these two entities though possible, seems less likely than a common factor causing both problems.

Key words: Müllerian agenesis; Ovarian agenesis; Sexual infantilism; Premature ovarian failure.

Introduction

The most common cause of primary amenorrhea is Turner's syndrome (gonadal dysgenesis) with an incidence between one in 2,500 to one in 5,000 live born girls [1]. Turner's syndrome is generally associated with sexual infantilism in 80-90% of cases [2].

A far less common cause of sexual infantilism is gonadal agenesis where instead of having a missing or defective X chromosome as in Turner's syndrome, the karyotype is XX and there are no physical stigmata, e.g., short stature as in gonadal dysgenesis. There are no definite causes of gonadal agenesis but possibilities include damage to the early gonad from viruses, metabolic issues, or possible undiscovered genetic mutation.

Isolated gonadotropin deficiency or hypopituitary or hypothalamic abnormalities, e.g., craniopharyngioma, can also be a cause of primary amenorrhea with sexual infantilism. In gonadal dysgenesis or agenesis the serum FSH and luteinizing hormone (LH) are elevated at the age of puberty but of course it is low in hypothalamic-pituitary conditions.

Müllerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) signifies a woman with primary amenorrhea and congenital absence of the upper two-thirds of the vagina [3]. It is the second most common cause of primary amenorrhea next to gonadal dysgenesis with an established incidence of one in 5,000 newborn girls [4].

Patients with Müllerian agenesis have the absence or hypoplasia of the internal vagina and usually the absence of the uterus and fallopian tubes. Since the ovaries are not Müllerian structures, in contrast to gonadal dysgenesis, these patients with primary amenorrhea can easily be distinguished from girls with Turner's syndrome because of their normal growth and appropriate sexual development at the typical age of puberty.

Primary amenorrhea and sexual infantilism have been previously reported occurring with Müllerian agenesis [5]. The sexual infantilism was related to the fortuitous and independent presence of isolated gonadotropin deficiency [5].

The authors present another case of Müllerian agenesis associated with primary amenorrhea and sexual infantilism. However, in this case, the cause of the sexual infantilism was not hypothalamus-pituitary related, but was from the much rarer co-existence of gonadal agenesis and Müllerian agenesis.

Case Report

The young woman presented at age 15 with a history of primary amenorrhea and sexual infantilism. A transabdominal ultrasound failed to detect any ovaries but a hypoechoic structure measuring 3.6 x 0.7 x 1.8 cm was seen in the midline of the pelvis which did not look like a uterus but the study suggested that a magnetic resonance imagining (MRI) be performed. The MRI

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failed to identify the uterus, cervix, and the majority of the proximal vagina. However, the MRI did identify a portion of the very distal vagina.

Subsequent chromosome analysis found a normal female karyotype (46xx). Her serum testosterone level was only ten ng/dL. A subsequent kidney MRI showed normal sized kidneys without hydronephrosis or nephrolithiasis. The teenager was placed on conjugated estrogen 0.9 mg daily. Despite the estrogen replacement, her serum FSH at age 16.5 years was very elevated at 27 mIU/mL.

Discussion

If the frequency of gonadal dysgenesis is one in 2,500 and Müllerian agenesis is one in 5,000, one might expect this combination in about one in 12 million female births. Cases reported to date of bilateral or unilateral gonadal agenesis with normal female karyotype did not have typical phenotypic features of Turner's syndrome as in the present patient [6-10].

Gonadal agenesis or "pure gonadal" agenesis is rare. The fortuitous association of these two entities would occur much less frequently than the estimated one in 12 million for the combination of Müllerian agenesis and gonadal dysgenesis.

Back in 1979, a study was published showing that the inappropriate retention of the Müllerian structures in a male in some instances could be related to a mutation of the anti-Müllerian hormone (AMH) receptor causing insensitivity to the AMH [11]. Although AMH is mostly secreted by sertoli cells in the testes beginning at seven weeks, very small amounts of AMH mRNA are present early in life in the ovary. Thus, based on the 1979 study by Imbeaud *et al.* [11] many researchers believe that mutations for the gene for AMH or genes from the AMH hormone receptor would be found that would explain this phenomenon. Theoretically, some mutation would allow the increased expression of ovary derived AMH, or persistence of secretion or a mutation that would increase the sensitivity of the AMH receptor on the Müllerian structure making them susceptible to regression of the Müllerian structures to the small amount of ovarian AMH. A defect in AMH or its receptor would explain why about one-third of females with congenital absence of the uterus and proximal vagina also have urinary tract abnormalities since the kidneys, and the collection system are Müllerian structures.

However, despite 30 years since the publication by Imbeaud *et al.* [11], no mutations causing the absence of Müllerian structures have been identified. As mentioned, one of the proposed mechanisms for ovarian agenesis involves destruction of the fetal ovaries by a virus. Theoretically, a virus effecting the fetal pelvis could destroy not only the ovaries but the nearby structure of uterus, upper vagina, and fallopian tubes. However, similar to this case, the kidney's would already be in another anatomical position and thus protected from the virus. This would explain normal kidney and collection system as seen in this case. Thus, the present authors favor this viral destructive scenario to explain the findings of Müllerian agenesis associated with sexual infantilism which was related to ovarian agenesis in a young lady with a normal female karyotype.

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