Familial Müllerian agenesis

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Müllerian agenesis is characterized by the absence of the fallopian tubes, uterus and internal portion of the vagina. Patients have normal female phenotype and genotype, with normal secondary sex characteristics but with amenorrhea. We report a family in which müllerian agenesis was diagnosed in three siblings and their two paternal aunts. This family was ascertained when the proband was evaluated for primary amenorrhea. She had normal secondary sexual development. Her karyotype was 46, XX. Ultrasound examination and magnetic resonance imaging of the pelvis revealed absence of the uterus and vagina. The proband had three sisters and two of them showed similar physical and radiological findings. Two of the proband's paternal aunts had no uterus. Although the pathogenesis of müllerian agenesis is well understood, the etiology and genetics are still unknown. Various forms of inheritance patterns have been suggested by several authors. In conclusion, it would appear that müllerian agenesis is influenced by multifactorial inheritance and polygenic and familial factors.

Key words: müllerian agenesis, familial, genetics.

The normal development of the female reproductive system depends on complete interaction between genetic, hormonal and environmental factors to produce the differentiation of the müllerian and wolffian ducts and urogenital sinus. The female reproductive system develops from the pair of müllerian ducts, which subsequently, in the absence of müllerian inhibiting factor, secreted by the testis, fuse to create the fallopian tubes, the uterus and the upper four-fifths of the vagina[1,2].

Müllerian abnormalities range from minor anatomic changes to total aplasia[1,3]. Müllerian agenesis, also known as Mayer-Rokitansky-Küster-Hauser syndrome, is a syndrome involving the absence of müllerian structures including the fallopian tubes, the uterus and the internal portion of the vagina. The disorder may be associated with other somatic anomalies, most frequently involving the urological and skeletal systems, and rarely the eye and middle ear.

Although the pathogenesis of müllerian abnormalities is well understood, the etiology and the genetics of müllerian agenesis are still unknown. Familial aggregates of müllerian agenesis have been reported[4,5]. But a genetic study of 23 families by Carson et al.[6] revealed no affected relative of the proband. Shokeir[7] concluded that müllerian aplasia was a female-limited autosomal dominant trait.

The syndrome is usually diagnosed in adolescence because of primary amenorrhea. The karyotype is usually 46, XX.

We report a family in which müllerian agenesis was diagnosed in three siblings and their two paternal aunts, and review the literature.

Case Report

This family was ascertained when the proband, 14-years-old, was evaluated for primary amenorrhea. She had the normal onset of thelarche and adrenarche at the age of 11 years. On physical examination she had normal secondary sexual development. Her vaginal introitus appeared rudimentary with a depth of 0.5 cm and a hypoplasia of the hymenal ring. Her karyotype was 46, XX. Ultrasound examination and magnetic resonance imaging of the pelvis revealed absence of the uterus and vagina (Fig. 1). Both ovaries were present and normally located (Fig. 2). Radiographic findings of the spine were normal. Intravenous

pyelogram showed normal renal system. The odiogram and ear examination were normal.

The proband had three sisters, two of whom showed similar findings. Genital examination showed blind vaginal pouch. Their karyotypes were 46, XX. Ultrasound examination and magnetic resonance imaging of the pelves of the two sisters showed absence of the uterus and vagina (Figs. 3, 4). Intravenous pyelogram and spine radiograms were normal.

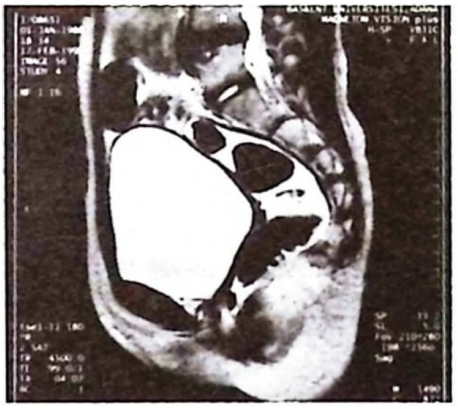

Fig. 1. Midline sagittal section with T2W reveals the absence of the uterus.

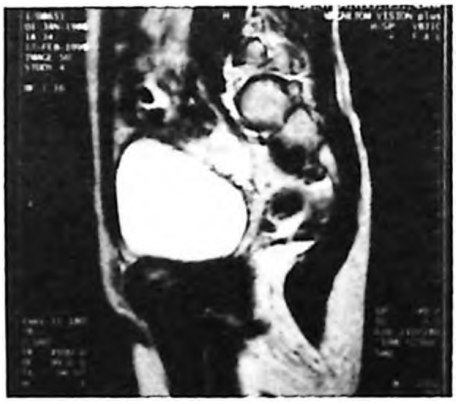

Fig. 2. Right parasagittal T2W image demonstrates the right ovary containing several follicles.

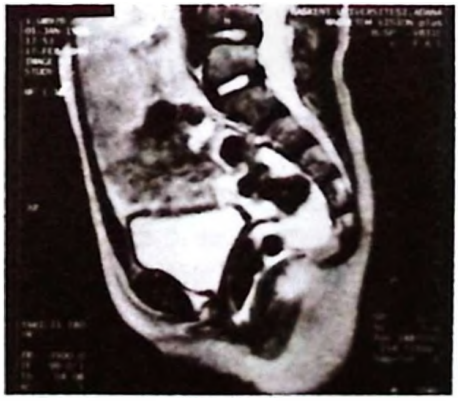

Fig. 3. T2W midline sagittal image demonstrates the bladder and rectum. The uterus is absent.

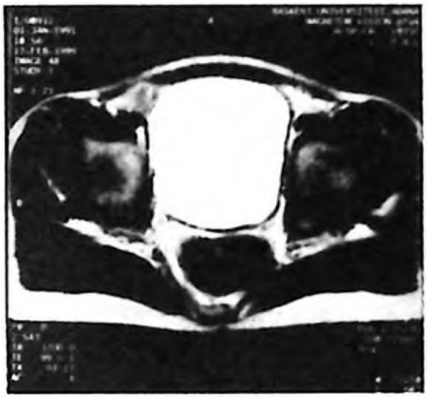

Fig. 4. T2W transverse image reveals the absence of the uterus between the bladder and rectum.

The pedigree of the family is shown in Fig. 5. The mother and father were second-degree relatives. The father had eight siblings and the mother ten. Two of the proband's paternal aunts were infertile and had been told by their gynecologist that they had no uterus. The paternal grandfather and grandmother were not relatives. There were seven other female cousins, but the family refused to bring them in for diagnostic investigations.

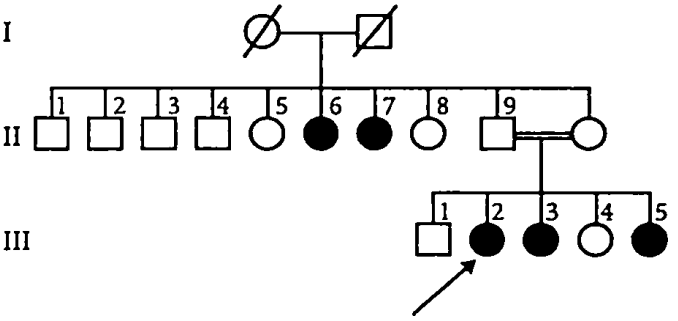

Fig. 5. The pedigree of the family.

Discussion

Müllerian agenesis is characterized by the absence of the fallopian tubes, uterus, and internal portion of the vagina. Patients have normal female phenotype and genotype and normal secondary sex characteristics, but with amenorrhea.

Müllerian agenesis is accompanied by renal abnormalities in approximately one-third of the cases[8-11]. Spinal and skeletal anomalies may occur with a frequency ranging from 10 to 12 percent[12,13]. Anomalies involving the eye and middle ear can also occur[14,15].

Strubbe et al.[16], in a study including 100 women with congenital absence of the vagina and uterus, performed various diagnostic investigations to

establish whether there were any associated congenital anomalies. His findings suggested that there might be two different syndromes in this patient group, namely an isolated form of congenital agenesis of the vagina and uterus and a more generalized condition. In the family we report here no other abnormalities involving the other systems were detected, thus suggesting an isolated form of congenital absence of the vagina and uterus.

The etiology and genetics of müllerian agenesis is unknown. Activating mutations of either the gene for antimüllerian hormone or of the gene for the antimüllerian hormone receptor are proposed as possible factors[17].

Familial aggregates of müllerian aplasia have been reported by Sarto and Simpson[5,18] and suggested a polygenic or a multifactorial inheritance. Families with affected siblings have been documented by several investigators[19]. These familial aggregates raise the formal possibility of an autosomal recessive gene. But Lischke et al.[20] observed three affected individuals who each had a normal monozygotic twin. Thus, autosomal recessive inheritance is an unlikely explanation for all cases. In this study, Schokeir[7] believed that a sex limited autosomal dominant gene might be responsible for some of the cases of müllerian aplasia. The study of Petrozza et al.[21] suggested that congenital absence of the uterus and vagina is not inherited commonly in a dominant fashion and that it is likely a polygenic, multifactorial, or possibly a recessive trait.

Although the family we report here and other reports of families characterized by multiple affected siblings and relatives raise the possibility of an autosomal recessive gene or female limited autosomal dominant inheritance, other earlier reports in the literature suggested various forms of inheritance. In conclusion, it would appear that müllerian agenesis is influenced by multifactorial inheritance and polygenic and familial factors.

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