CASE REPORT

Müllerian anomaly in a woman with Hirschsprung's disease

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SUMMARY

Müllerian anomalies are usually isolated or found in association with abnormalities of the renal tract. Rarely, they are encountered with coexisting gastrointestinal anomalies. Similarly, Hirschsprung's disease may coexist with additional somatic abnormalities, yet only a single case report has reported a müllerian anomaly coexisting with Hirschsprung's. A 35-year-old woman with long-standing dysmenorrhoea and infertility and history of Hirschsprung's disease and some components of VATER syndrome (vertebral anomalies, anal atresia, tracheoesophageal fistula, renal anomalies) underwent operative laparoscopic exploration for pelvic pain and was found to have an incidental finding of a unilateral segmentally hypoplastic uterine horn (variation of an ASRM (American Society for Reproductive Medicine) type 2C müllerian anomaly). The genetics of müllerian anomalies and Hirschsprung's disease have been extensively studied with certain loci and candidate genes theorised as being causative. An established familial relationship and heritability exists with both syndromes; however, no genetic foci have been found to connect müllerian abnormalities and Hirschsprung's disease.

BACKGROUND

Müllerian anomalies encompass a variety of lower female genital tract abnormalities that may involve the uterus, fallopian tubes, cervix and upper vagina.^{1 2} These organs are formed upon fusion of the müllerian ducts, and failure of this process can produce a broad array of isolated anomalies within the female genital tract and other extragenital organs, specifically renal anomalies.¹⁻³ Congenital uterine anomalies are present in 6.7% of fertile women, 7.3% of infertile women and 16.7% of women with recurrent pregnancy loss, suggesting that these anomalies may play a significant role in reproduction.^{3 4}

Hirschsprung's disease is a unique lower gastrointestinal tract anomaly in which there is an absence of enteric neurons from the myenteric and submucosal plexuses.⁵ Hirschsprung's disease has been linked to many different medical conditions, including trisomy 21, multiple endocrine neoplasia type 2 and Waardenburg syndrome, to name only a few.⁶

We examine a case of a woman with a long history of dysmenorrhoea and primary infertility and known medical history of Hirschsprung's disease and components of VATER syndrome who was found to have a segmentally hypoplastic left uterine horn

and fallopian tube on laparoscopic inspection of the pelvis.

CASE PRESENTATION

A 35-year-old nulligravid woman presented to the reproductive endocrinology clinic with severe dysmenorrhoea and primary infertility. Her dysmenorrhoea caused her to miss work 2 days per month despite use of ibuprofen. She had increasing deep dyspareunia with premenstrual diarrhoea.

At birth, she was diagnosed with imperforate anus, tracheoesophageal fistula and ultimately Hirschsprung's disease. Her medical records as a child indicate concern for a possible VATER syndrome. She had undergone distal colon resection, colostomy, colostomy reversal and proctotomy to form an anus. Her last GI surgery was at age 14. Prior imaging demonstrated two normal kidneys. She denied a family history of gastrointestinal or genitourinary anomalies.

Imaging with three-dimensional transvaginal and saline infusion sonohysterography reported a single uterine cavity, but no flow could be identified through either fallopian tube with a *FemVue* device. On laparoscopic exploration of the pelvis with chromotubation, normal left uterine horn, patent fallopian tube and normal ovary were identified. The right horn did not fill, and a segmental portion of the right uterine horn and ipsilateral fallopian tube appeared hypoplastic (*figure 1*). The right ovary (a non-müllerian structure) was present distally (*figure 2*). The hypoplastic portion of the right uterine horn was resected, and histological examination revealed no endometrial tissue (variation of an ASRM 2C müllerian anomaly). Endometriosis was present on the bladder and in the cul-de-sac, which was surgically resected and verified pathologically. Six months since surgery, her dysmenorrhoea and dyspareunia have entirely resolved.

DISCUSSION

Our understanding of the genetic causes and associations with diseases is at the forefront of modern clinical medicine. In one such example, it has been found that müllerian anomalies coexist in higher rates among monozygotic twins compared with dizygotic twins with a 12-fold increase in risk among first-degree relatives.^{1 4} Genes that have been implicated in this wide possibility of abnormalities include HNF1B, HOX genes and WNT pathways.¹ The extragenital system most strongly

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Figure 1 Unilateral segmental hypoplasia of the right uterine horn with an ipsilateral atretic tube. Transvaginal ultrasound did not demonstrate an endometrial echo in the right uterine horn. On pathological examination, no endometrial cavity was found in the hypoplastic right uterine segment.

Figure 2 Isolated right ovary proximal to a very thin, hypoplastic right fallopian tube.

associated with müllerian anomalies is the renal system, including urogenital dysplasia and hypoplasia of the urogenital ridge.¹⁻³ This woman was born with an imperforate anus, a finding that has been associated with both upper and lower müllerian tract anomalies.⁷

Hirschsprung's disease is a disorder with multifactorial inheritance associated with isolated genetic mutations, with special focus on the RET gene located on chromosome 10. Over 100 mutations have been described.⁸⁻¹⁰ Both autosomal recessive and autosomal dominant inheritance, with incomplete penetrance, have been described, and there has been a reported 30%

association of Hirschsprung's disease with other genetic malformations. Only a single case of Hirschsprung's disease with a müllerian anomaly has been previously published.² Given the variety of single gene mutations associated with Hirschsprung's disease and müllerian anomalies, this case suggests that there could be a unifying mutation linking both abnormal findings, although it may be purely happenstance that two single gene mutations are present.

At present, there is no known reported genetic or epigenetic focus connecting müllerian anomalies and Hirschsprung's disease (or any other gastrointestinal tract abnormality). Future research of the human genome will enhance and clarify our understanding of these diseases and their genetic foundations, and it is possible that a relationship may be found between these two seemingly unconnected disorders.

Learning points

- ▶ A previously unreported case of Hirschsprung's disease coexisting with unilateral müllerian segmental atresia is presented, verifying that more than one anatomic anomaly may be found in a single patient.
- ▶ Continued genetic study is needed to elicit a possible genetic association between Hirschsprung's disease and müllerian duct abnormalities.
- ▶ Clinicians should look for extragenital associations, particularly within the renal system, when a müllerian anomaly is detected.

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