CASE REPORT

Multiorgan system structural malformations associated with Mayer-Rokitansky-Küster-Hauser Syndrome (MRKHS) type 2: avoiding pitfalls in diagnosis, counseling and treatment

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SUMMARY

An 18-year-old virginal woman was referred to the reproductive endocrinology clinic with primary amenorrhoea and secondary sexual development in the absence of pelvic pain. Additionally, she had significant congenital sensorineural hearing loss, autism, bipolar disorder and class III obesity. On physical examination, secondary sexual development was confirmed (Tanner 5 breasts and Tanner 4 pubic hair). She refused further pelvic examination following prior attempts by the referring physicians. Serum leutinizing hormone (LH), follicle stimulating hormone (FSH), prolactin, estradiol and total testosterone values were within normal limits. Karyotype was 46,XX. MRI demonstrated complete uterine agenesis, short vagina, sacral dysgenesis with complete absence of the coccyx and a horseshoe kidney. Diagnosis of Mayer-Rokitansky-Küster-Hauser Syndrome type 2 was established based on clinical, laboratory and MRI findings. The patient and family were counselled regarding the disease process, techniques for vaginal elongation, sexual activity and future reproductive options.

BACKGROUND

Primary amenorrhoea is a distressing condition for adolescent women and their families.¹⁻³ The differential diagnosis in those with evidence of secondary sexual development includes imperforate hymen, transverse vaginal septum, cervical atresia, Müllerian agenesis and 46,XY disorders of sexual development, primarily the androgen insensitivity syndromes.^{2,4} In addition to the perception of being different from peers, women with primary amenorrhoea secondary to congenital absence of Müllerian structures are understandably concerned about the potential for sexual functioning and future fertility. Prompt referral to multidisciplinary centres experienced in the evaluation of primary amenorrhoea is a cost-effective strategy which may ameliorate psychological distress reported by parents and young women alike when the diagnosis is delayed or incomplete or erroneous counselling is rendered.^{5,6} Once a diagnosis is reached, genetic counselling, psychological support, establishment and maintenance of sexual functioning and a discussion of reproductive options are integral parts of patient management.^{1,2,4}

CASE PRESENTATION

An 18-year-old virginal woman was referred to the reproductive endocrinology clinic following evaluation in paediatric and then general gynaecology clinics with primary amenorrhoea and what was described as 'incomplete' secondary sexual development. By history (much of which was supplied by her biological mother), she was the product of an unremarkable term pregnancy. She had bilateral congenital sensorineural hearing loss. Thelarche and adrenarche were reported at age 9. She had one episode of light bleeding on her undergarments at age 9 but was unable to identify whether it originated from the vagina or rectum. She had a 'growth spurt' around ages 10–11. The patient carried the diagnoses of autism and bipolar disorder treated with lurasidone 120 mg, clonidine 0.1 mg two times per day, paroxetine 10 mg and thiothixene 10 mg. Family history was negative for primary amenorrhoea, delayed puberty or androgen insensitivity syndrome. On physical examination, the patient was 150 cm tall (3%ile), obese (body mass index 42.6 kg/m² or 99 percentile) with Tanner 5 breast by palpation and Tanner 4 pubic hair development. The patient refused speculum and bimanual examination, citing frustration and fear following unsuccessful attempts by two prior practitioners. Examination of the neck, spine and extremities suggested no bony abnormalities. Scoliosis was absent.

INVESTIGATIONS

Prior to referral, laboratory included serum FSH 4.7 mIU/mL, LH 4.3 mIU/mL, estradiol 39 pg/mL, and total testosterone 25 mg/dL by gas chromatography dual mass spectrometry (GC/MS/MS). Karyotype was 46,XX. All values were normal for an adolescent girl who had completed the pubertal sequence. Abdominal ultrasound showed a suspected hypoplastic uterus measuring 2.3×2.6×1.6 mm in the midline pelvis with the endometrial lining measuring 1.5 mm. The right and left ovaries were normal in appearance. The images were judged to be of poor quality due to the patient's body habitus (class III obesity). The referring general gynaecologist ordered a CT scan which revealed a horseshoe kidney (figure 1), normal ovaries, and coccygeal absence. No uterus was seen although the quality

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Figure 1 Pelvic MRI. Note short vagina, absence of uterus, sacral dysgenesis and coccygeal agenesis.

of the pelvic images was unsatisfactory to assess for a vagina or vaginal septum.

Given her reluctance to undergo another pelvic examination, MRI scan was ordered to better visualise the internal anatomy and vagina (figure 2). No uterine structure was seen and there was absence of the upper vagina with a rudimentary lower vagina present. In addition, sacral agenesis with complete absence of the coccyx and a horseshoe kidney were identified.

Based on these MRI, clinical and laboratory findings, the diagnosis Mayer-Rokitansky-Küster-Hauser Syndrome (MRKHS) type 2 was established.

DIFFERENTIAL DIAGNOSIS

The major differential diagnoses in young women with congenital uterine absence with secondary sexual development and normal external genitalia are (1) isolated outflow anomalies (imperforate hymen, transverse vaginal septum and cervical atresia) and (2) androgen insensitivity syndrome. Complete androgen insensitivity syndrome (CAIS) accounts for 90% of the androgen insensitivity syndromes and is manifested by adult male-level serum testosterone levels, 46,XY karyotype, breast development and scant pubic hair.^{2,4} Uterine absence is explained by normal production of Müllerian inhibitory factor by the testes which are often located intra-abdominally. Differentiation from MRKHS is established by an elevated serum testosterone level with definitive verification by karyotype.² Gonadectomy following completion of skeletal height growth may be considered on a case-by-case basis. The risk of invasive germ cell tumour is lower than previously thought in CAIS and partial AIS (PAIS). New data suggest a lifetime risk of 10% in both groups in contrast to higher rates published in older literature (20% for CAIS and 60% for PAIS). Armed with this information, many will elect expectant management by various imaging modalities as opposed to gonadectomy.^{7,8} In the absence of a Y-chromosome, gonadectomy is unnecessary for women with MRKHS. MRKHS, CAIS and congenital isolated outflow obstruction are each associated with normal skeletal height.^{2,4}

OUTCOME AND FOLLOW-UP

Extensive counselling and disease information were provided to the patient and her family that included sexual functioning and fertility options. The putative genetic origins of her anomalies were discussed as well as her specific variant of MRKHS. She was informed of potential obstacles she might encounter while engaging in vaginal intercourse due to a short vagina. At assessment, we felt she was not emotionally ready to pursue vaginal dilation or consider intercourse. Techniques for future vaginal dilation were outlined, and surgical construction of a vagina was addressed as an alternative if conservative measures failed. Lastly, in vitro fertilisation (IVF) with a gestational carrier (or perhaps uterine transplantation when the technique matures beyond an experimental procedure) would allow for family formation.

DISCUSSION

MRKHS (Müllerian agenesis) is a heterogeneous condition found in approximately 1 in 4500–5000 women.^{2,9,10} This condition usually goes unrecognised until an investigation is undertaken for primary amenorrhoea with normal secondary sexual maturation during adolescence. The diagnosis of MRKHS is based on partial or complete absence of the Müllerian structures (congenital aplasia or hypoplasia of the uterus, fallopian tubes and upper two-thirds of the vagina) with a normal female (46,XX) karyotype.^{2,4,11} In many cases, the fallopian tubes are preserved intact or in a hypoplastic form. Normal ovarian and adrenal function is manifested by successful secondary sexual development.⁴

There are, however, various phenotypic presentations of MRKHS, and two subtypes of MRKHS have been described. Type I, reported in 44% of all MRKHS cases, is characterised by isolated Müllerian aplasia or hypoplasia (uterus, fallopian tubes and upper vagina) with intact ovaries. Type II MRKHS has been found in 56% of reported cases and has type I characteristics as well as extragenital anomalies including renal, skeletal, cardiac and sensorineural hearing deficits. Renal anomalies are the most common abnormality occurring in 40% (unilateral renal agenesis, horseshoe kidney, ectopia of one or both kidneys and renal hypoplasia). Skeletal anomalies described in MRKHS include scoliosis, isolated

Figure 2 CT with intravenous contrast demonstrating fused 'horseshoe' kidney (arrow).

vertebral anomalies, Klippel-Feil association (fusion of two or more cervical segments), spina bifida, facial asymmetry and bony abnormalities of the hand. Auditory malformations are less common, but can include middle ear developmental defects, sensorineural deficits or dysplasia of the auditory meatus. Lastly, cardiac malformations may be present including an aortopulmonary window, atrial septal defects, conotruncal anomalies, pulmonary valve stenosis and Tetralogy of Fallot.^{2 4 11 12}

The MURCS association (Müllerian agenesis, Renal agenesis, Cervicothoracic Somite abnormalities) is the most severe form of MRKHS type II, presenting with Müllerian aplasia, renal dysplasia and cervicothoracic somite abnormalities.⁴ Bipolar disorder and autism, present in the case presented, are not components which have been described as part of the syndrome hereunto.

MRKHS seems to be sporadic with occasional familial clustering noted. The latter suggests an inherited pattern in an autosomal dominant mode with variable expressivity and incomplete penetrance. Array comparative genomic hybridisation and multiplex ligation-dependent probe amplification analysis have suggested chromosomal microdeletions, duplications and sequence aberrations in different chromosomal regions.^{4 11} A number of gene candidates could play a potential role in the development of MRKHS. WNT4 is one potential candidate as it has been proven to be a vital gene in both Müllerian duct and renal development, but mutations identified within this gene do not implicate it as a sole cause of MRKHS. A number of other genes have been implicated as well including WNT9B, HOX genes (HOXA9-13 and HOXB9-13), LHX1, TBX6, GALT, CFTR, MH and MHR. X-chromosome deletions have also been described in case reports.^{4 12 13}

The patient and her family expressed frustration and dismay concerning the circuitous route to establishing a diagnosis and receiving proper counselling and treatment. Management of patients with MRKHS is complex and multidisciplinary and is best relegated to physicians, counsellors and centres with expertise in dealing with primary amenorrhoea or congenital Müllerian anomalies. When a young patient allows pelvic examination, a seasoned clinician with knowledge of genital anomalies should perform physical examination. By the time she had reached the reproductive endocrinology clinic, she feared further attempts at internal (speculum and bimanual) examination. Transvaginal or transperineal ultrasound is relatively inexpensive and is free from radiation exposure; hence, ultrasound is a reasonable first step in pelvic imaging. However, as in this case, pelvic structures may be identified erroneously, especially compared with MRI imaging which gives optimal assessment of pelvic structures.² Our adolescent patient underwent CT scanning by a referring physician which yielded inadequate visualisation of the vagina as well as extra costs and avoidable radiation exposure to her care.

From a psychological viewpoint, women with uterine absence may suffer considerably with depression/anxiety and diminished self-esteem. Parents may express guilt.^{6 14} Disclosure to a romantic partner may prove troublesome. Accordingly, women with MRKHS should be offered psychological counselling and access to peer groups.^{2 6}

Because of a short vagina, most women will encounter difficulty with penetrative intercourse. Non-surgical intervention with vaginal dilators is usually the first line of treatment and carries a 90%–95% success rate with proper instruction and patient motivation.^{15 16}

Unfortunately, many gynaecologists are poorly trained on the use of vaginal dilators.² The treating physician should also assess psychological maturity and readiness to proceed with

dilation.^{2 17 18} Self-dilation also offers women a sense of control over their physical condition. Regular office follow-up will allow the physician to monitor progress and assess for problems such as bleeding or pain. Regular sexual activity or intermittent dilation is required to maintain the vaginal length. Surgical construction of a neovagina by a host of techniques may be required for those unsuccessful with mechanical dilation. Referral to surgical centres experienced with vaginal lengthening procedures is the best option for these patients, as the initial surgical procedure is the most likely to be successful.^{2 19 20}

Another item for concern in MRKHS is childbearing. Due to their absence of a uterus, patients with MRKHS are unable to have children by the traditional route. Adoption or use of a gestational carrier (surrogacy) are currently the best options available for patients with MRKHS.^{2 21} Uterine transplantation, at least at this time, is considered experimental but holds promise for women with MRKHS desiring to carry a pregnancy.²² Oocyte function is usually intact, and live birth rates using gestational carriers using gametes from women with MRKHS are as high as matched controls undergoing routine IVF.²³ Pregnancy by gestational carrier does not appear to impact negatively parenting or child development. Although a genetic origin to MRKHS has been postulated, there is no large collaborative reporting characterising the offspring derived from oocytes from mothers with MRKHS. Finally, women with MRKHS, including those with the MURCS variant, can live a normal lifespan despite developmental abnormalities present.^{4 23}

Learning points

- ▶ Women with primary amenorrhoea are best evaluated in centres familiar with the workup and treatment of such disorders. Prompt referral diminishes fear and frustration associated with the diagnosis and improves participation in the medical system.
- ▶ Mainstay of Mayer-Rokitansky-Küster-Hauser Syndrome treatment is multifaceted and involves psychological support, education, counselling and individualised initiation of vaginal dilation. Reproductive counselling should include adoption, in vitro fertilisation with gestational carrier, and perhaps uterine transplantation in the future as the technique becomes refined.
- ▶ Genetic screening may play a role in future management; however, further studies are required to establish possible inheritance patterns and the efficacy of this methodology.

Contributors RPK was responsible for seeing the patient in the reproductive endocrinology clinic, counseling the patient concerning vaginal dilation and future fertility, made referral to a psychologist, obtained consent from the mother and assisted in manuscript preparation. NG, JHM and JAH did background research and each participated in manuscript preparation in a meaningful way. NG authored the first draft of the manuscript.

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