Endocrinology, Diabetes & Metabolism CASE REPORTS

R Ambachew and others | Gonadal, mullerian, pituitary and thyroid dysgenesis

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A rare case of 46,XX gonadal dysgenesis, Mayer–Rokitansky–Kuster–Hauser syndrome, pituitary and thyroid hypoplasia

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Summary

Mayer–Rokitansky–Kuster–Hauser syndrome is characterized by congenital absence or hypoplasia of the uterus and upper two-thirds of the vagina in both phenotypically and karyotypically normal females with functional ovaries, whereas gonadal dysgenesis is a primary ovarian defect in otherwise normal 46,XX females. An association between these two conditions is extremely rare. We report a 21-year-old female presented with primary amenorrhea and undeveloped secondary sexual characteristics. The karyotype was 46,XX and the hormonal profile revealed hypothyroidism and hypogonadotropic hypogonadism. Pelvic MRI showed class I Mullerian duct anomaly with ovarian dysgenesis. Ultrasound showed bilateral thyroid hypoplasia and brain MRI suggested anterior pituitary hypoplasia. Levothyroxine and hormone replacement therapy were started.

Learning points:

- The simultaneous presentation of 46,XX gonadal dysgenesis, Mayer–Rokitansky–Kuster–Hauser syndrome, hypothyroidism, and pituitary hypoplasia is a Possibility.
- Extensive evaluation should be made when a patient presents with one or more of these features.
- The diagnosis imposes a significant psychological burden on patients and adequate counseling should be provided.
- Hormone replacement therapy remains the only therapeutic option for the development of secondary sexual characteristics and the prevention of osteoporosis.

Background

Disorders of sex development (DSD) are a heterogeneous group of rare conditions characterized by an abnormality of the chromosomal, gonadal, or phenotypic features that typically define sex development (1). According to the Chicago Consensus, DSDs are classified as 46,XX, 46,XY, and sex chromosome DSDs (1). Evaluation and counseling of patients with DSD are important in alleviating the psychosocial stress and fertility concerns of the patients.

One of the DSDs in females with 46,XX karyotype is Mullerian agenesis or Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, characterized by congenital aplasia of the uterus and the upper two-thirds of the vagina in a woman with normal secondary sexual characteristics affecting 1 in 5000 live female births (2). MRKH syndrome often presents with primary amenorrhea during adolescence and is classified as type I (isolated

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uterovaginal aplasia) or type II (associated with extragenital manifestations) (2).

46,XX gonadal dysgenesis is a primary ovarian defect that leads to premature ovarian failure. It is a very rare disorder that occurs in <1 in 10 000 women characterized by underdeveloped ovaries resulting in absence of puberty, primary amenorrhea, and hypergonadotropic hypogonadism (3, 4, 5, 6).

The association between pituitary hypoplasia and primary hypothyroidism is very rare, rather pituitary hyperplasia is seen in patients with severe primary hypothyroidism (7).

Herein, we present a very rare case of a 21-year-old patient who presented with primary amenorrhea. The evaluation showed 46,XX gonadal dysgenesis, class I Mullerian agenesis, hypothyroidism, and hypogonadotropic hypogonadism secondary to pituitary hypoplasia.

Case presentation

A 21-year-old female college student from Ethiopia, presented with primary amenorrhea, short stature, and absence of secondary sexual characteristics. She has no libido and is not sexually active.

She has no family history of similar conditions. She had good developmental milestones and has average educational performance.

She has no history of maternal drug intake during pregnancy except routine immunizations.

On physical examination, her blood pressure was 120/70 mmHg and pulse rate was 70 b.p.m. Her height was 144 cm, weight 49 kg, and BMI 23.6 kg/m^2.

There was no facial dysmorphism, webbing of the neck, high-arched palate, thyroid enlargement, or skeletal deformity found on examination.

Staging of breast development, pubic and axillary hair growth showed Tanner's Stage 1.

Genital examination revealed underdeveloped female external genitalia with no clitoris and localized hypopigmentation of the vulva. Labia minora and majora are underdeveloped. The ureteral opening looks normal. The vaginal canal is premature measuring 3 .5 cm and ends blindly.

The complete blood count, renal, liver function tests, and serum electrolytes were within the normal range. The endocrinological evaluation revealed primary hypothyroidism and hypogonadotropic hypogonadism and the rest of the hormonal parameters were normal (Table 1).

On neck ultrasound, the isthmus measured 0.3 cm in anteroposterior diameter; the right thyroid lobe measured 1.46 × 1.18 × 1.8 cm in size with an estimated volume of 1.63 cm^3 and the left thyroid lobe has a size of 1.54 × 0.88 × 1.66 cm with an estimated volume of 1.19 cm^3 (the normal volume of the thyroid gland in adult females is 10–15cm^3) suggesting bilateral thyroid hypoplasia.

Ultrasound of the abdomen and pelvis showed normal kidneys with a non-visualized uterus and ovaries.

Pelvic MRI showed a small (rudimentary) vestigial uterus seen between the bladder and rectum. The normal morphology of the uterus is absent. The lower vaginal canal is seen and well developed. The ovaries were not visualized. The findings suggest class I Mullerian duct anomaly, MRKH with ovarian dysgenesis (Fig. 1A and B).

Brain MRI showed a small pituitary gland measuring 3 × 4 × 4 mm (normal range 6.2 × 11.6 × 10.6 for her age) with homogenous contrast enhancement. The pituitary stalk is not visualized and the posterior pituitary gland is small and ectopically located on the hypothalamus (Fig. 2A and B).

Multiplex ligation-dependent probe amplification (MLPA) assay was performed to describe the karyotype and investigate copy number variation due to deletions or duplications in the *TBX6*, *LHX1*, *HNF1B*, and *TBX1* genes, which are associated with MRKH and on several genes that are associated with various forms of DSD. The results showed a 46,XX karyotype, with no significant copy number change on the sex chromosomes, and the Y chromosome targeting probes did not show signals indicating its absence. Several exons of the genes (*TBX1* on 22q11 and *TBX6* on 16p11) that are associated with MRKH syndrome show significant copy number changes (increase), which appear to be heterozygous duplication.

The diagnosis of type 1 MRKH syndrome with 46,XX gonadal dysgenesis, hypothyroidism, and hypogonadotropic hypogonadism secondary to pituitary hypoplasia was

Table 1 Hormonal profile.

Hormone	Level	Normal range
TSH	12.72	0.34–5.6 µIU/mL
Free T4	0.33	0.6–1.2 ng/dL
FSH	1.07	3.9–8.8 mIU/mL
LH	1.21	2.1–10.9 mIU/mL
Estradiol	< 5.0	20–88 pg/mL
Progesterone	1.0	0.3–1.5 ng/mL
Testosterone	0.46	0.1–0.75 ng/mL
Basal cortisol	13.6	8.7–22.4 µg/dL
Prolactin	12.3	3.3–26 ng/mL

FSH, follicle-stimulating hormone; LH; luteinizing hormone; TSH,thyroid-stimulating hormone.

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made and she was started on L-thyroxine and conjugated estrogen and counseling therapy was done. Her hypothyroid symptoms improved but there is no change with regards to her secondary sexual characteristics as expected considering her age unlike the response in younger cases.

Discussion

Primary amenorrhea is defined as failure of menses to appear by age 14 in the absence of secondary sexual characteristics or the absence of menses by age 16 regardless of the presence of normal growth and development of secondary sexual characteristics (5).

Gonadal dysgenesis is the most common cause of primary amenorrhea and absent secondary sexual characteristics and the second most common cause of primary amenorrhea is MRKH syndrome, characterized by uterovaginal atresia in 46,XX female (6).

In our case ovarian dysgenesis, MRKH syndrome, hypogonadotropic hypogonadism, and hypothyroidism all can be the cause of primary amenorrhea.

The concomitance of gonadal dysgenesis and MRKH syndrome is extremely rare with very few cases reported. From such cases in the literature, 46,XX gonadal dysgenesis and Mullerian agenesis patients presented with normal female phenotype, primary amenorrhea, absence of puberty, and hypergonadotropic hypogonadism with or without somatic malformations, the latter being extremely rare (3, 4, 5, 6, 8).

In our patient the pelvic MRI finding is suggestive of type 1 MRKH syndrome with non-visualized ovaries, the latter attributed to 46,XX gonadal dysgenesis, explaining the absence of secondary sexual characteristics. The increased copy number changes of the several exons of the genes TBX1 on 22q11 and TBX6 on 16p11 that are associated with MRKH syndrome appear to be additional evidence (9, 10).

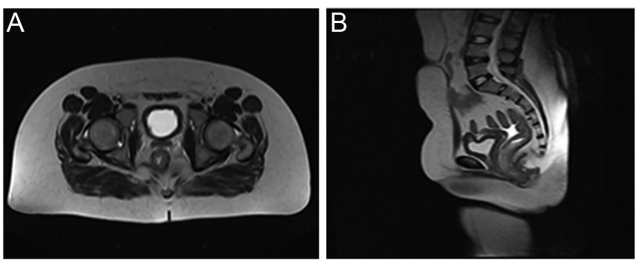

Figure 1
(A) Pelvic axial T2 image at the level of the femoral heads. There is a small rudimentary uterine vestigium seen between the bladder and rectum. The lower vaginal canal is seen well developed. The ovaries were not visualised. (B) Pelvic sagittal T2 image. The normal morphology of the uterus is absent with a small rudimentary uterine remnant seen between the bladder and rectum. The lower third of the vagina is normal. The ovaries were not visualizsd.

As a limitation, laparoscopic evaluation should have been done to completely exclude the presence of ovaries, though MRI has good sensitivity in evaluating ovarian morphology. Anti-müllerian hormone as a measure of the ovarian reserve was not done.

The hypogonadotropic hypogonadism despite gonadal dysgenesis seen in our patient can be explained by the anterior pituitary hypoplasia.

The presence of high TSH, low free T4, and hypoplastic thyroid gland on ultrasound suggests primary hypothyroidism. Although central hypothyroidism is a possible differential diagnosis in our patient as some patients with central hypothyroidism may have slightly high TSH levels and can have small thyroid gland because of insufficient stimulation by TSH.

Further MLPA reactions were done in our patient to investigate deletions and duplications in the *TPO*, *PAX8*, *FOXE1*, *NKX2*-1, and *TSHR* genes that are associated with thyroid dysgenesis, accounting for most cases of congenital hypothyroidism (11), did not show significant copy number changes in any of these genes.

From our literature review, we found very few case reports of primary hypothyroidism and MRKH syndrome (8, 12). It was primary nonautoimmune hypothyroidism with a structurally intact thyroid gland, unlike our case which is associated with a hypoplastic thyroid gland; though thyroid autoantibodies were not done. One of the cases reported the co-presentation of primary hypothyroidism, gonadal dysgenesis, and MRKH syndrome (8), with some resemblance to our case.

In a few other case reports, microdeletion involving the PAX8 gene associated with Mullerian agenesis in an MRKH I and hypothyroidism has been reported; but in our patient, PAX 8 deletion was not found on genetic testing (13).

Evaluation of anterior pituitary and thyroid function could be of paramount importance in patients with MRKH syndrome to determine whether they have a higher prevalence of these hormone deficiencies or a coincidental finding.

Our patient has proportionate short stature with possible etiologies include; long-standing hypothyroidism and probable growth hormone deficiency as a consequence of the pituitary hypoplasia. Human growth hormone therapy is recommended for short stature cases due to growth hormone deficiency at a younger age.

Hormone substitution therapy remains the only therapeutic option for the development of secondary sexual characteristics and the prevention of osteoporosis.

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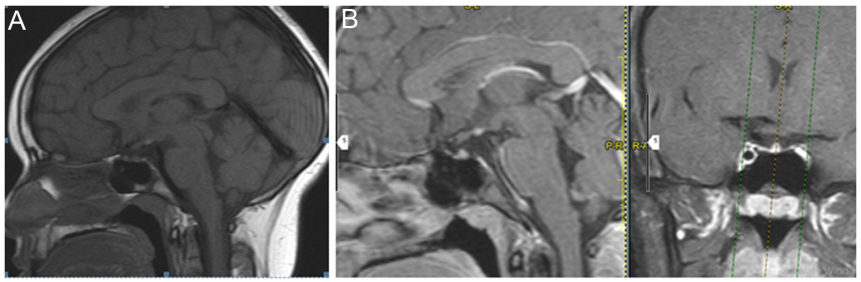

Figure 2
(A) Sagittal precontrast T1WI brain MRI showing a hyper-intense ectopic posterior pituitary. (B) T1WI sagittal and coronal post-contrast pituitary MRI showing a hypoplastic anterior pituitary gland and a non-visualised pituitary stalk.

The diagnosis of MRKH syndrome imposes a significant psychological burden on patients because of the associated medical, psychological, and infertility issues (6). Assisted reproductive techniques and surrogacy can be options concerning fertility (6). Counseling and management of psychosocial issues should be well addressed.

In conclusion, we report a rare association between a 46,XX gonadal dysgenesis, class I Mullerian agenesis, hypothyroidism, and hypogonadotropic hypogonadism secondary to pituitary hypoplasia. To our knowledge, this is the first case reported of such a combination. The etiopathogenesis of these associations needs to be investigated.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement
Rediet Ambachew: major contributor in writing and editing the manuscript. Amare Gulilat and Tewodros Aberra: compiled and edited the patient data. Ahmed Reja and Getahun Tarekegn reviewed the manuscript. Wubalem Bedilu reported the radiologic findings. Zewdu Terefework analyzed and reported the MPLA assay. All authors read and approved the final manuscript.

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